# FAIR INCLUSION OF PREGNANT WOMEN IN CLINICAL RESEARCH

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**Fair Inclusion of Pregnant Women in Clinical Research**
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# CHAPTER 1

## GENERAL INTRODUCTION

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## BACKGROUND

Historically, there has always been a reluctance to include pregnant women in clinical research due to a fear of harming the foetus. Often mentioned in this respect are the diethylstilboestrol (DES) and thalidomide tragedies. From 1938 to 1971, DES was prescribed to an estimated 1.5 to 3 million women during pregnancy to prevent miscarriage. Only in 1971 was it realised that the drug did not prevent miscarriage and was linked to several adverse complications for the offspring, including vaginal and cervical carcinomas in young women, and malformation of reproductive organs in both male and female children[1,2]. In the late 1950s, thalidomide was prescribed for nausea during pregnancy without prior testing in pregnant women, which resulted in unforeseen teratogenic effects with severe birth defects in over 10,000 children[3]. Even though neither tragedy involved clinical research, these events had a great impact on the research community which at the time was already characterised by a determination to protect allegedly vulnerable populations, including pregnant women, from research participation. The protectionist approach has been one of the reasons for the existing precautionary attitude with regard to including pregnant women in clinical research today[4].

Although concerns about foetal well-being are valid, at the same time there is a need for evidence-based information on medications and treatments for pregnant women, because sick women get pregnant, and pregnant women get sick[5]. In the absence of evidence-based knowledge, clinicians may have to prescribe off-label medications without evidence or based on contradictory evidence[6], or clinicians or pregnant women themselves may choose to discontinue medically important medications. The result of underrepresentation of pregnant women in clinical research is a harmful situation, leaving pregnant women at risk for potentially avoidable therapeutic incidents[7–9]. For example, poorly treated asthma and untreated depression is problematic for pregnant women and foetuses: it is associated with premature birth, low birth weight and foetal growth restriction and, in case of asthma, a higher risk of hypertension and preeclampsia[7,10].

Physiological changes during pregnancy alter the way that drugs are processed by the body and the ways that drugs act on the body in a fashion difficult to predict from the pharmacokinetics (PK) and pharmacodynamics (PD) in men and non-pregnant women. Moreover, teratology and toxicity is often difficult to extrapolate and interpret from pre-clinical data or studies in non-pregnant humans[11,12]. Gathering conclusive data to enable evidence-based therapeutic decisions for pregnant women therefore requires research in the population of pregnant women in order to develop effective treatments for pregnant women with acute or chronic obstetric or non-obstetric illnesses[13–17]. For this reason, inclusion of pregnant women has been promoted in the last decades by bioethicists, pharmacologists, regulators and researchers. For example, in the United States, the Office of Research on Women's Health (ORWH) of the Department of Health and Human Services (DHHS) endorsed the view that pregnant women are to be

presumed eligible for participation in clinical research (1994). This view was later adopted by the Council for International Organizations of Medical Sciences (CIOMS) in their *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), and recently updated in their new guideline which states that research designed to obtain knowledge relevant to the health needs of pregnant women must be promoted[18]. Furthermore, the Second Wave Initiative was launched in 2009, a collaborative academic initiative to find ethically and scientifically responsible solutions to increase the knowledge base for the treatment of pregnant women with medical illness[10,19]. Another (indirect) example is the new Pregnancy and Lactation Labelling Rule (PLLR) of the US Food and Drug Administration, designed to improve risk versus benefit assessment of drugs used in pregnant and nursing mothers. The PLLR is applauded by many for its effort to improve maternal care and help healthcare professionals to adequately treat pregnant women[20–22].

## CURRENT STATE OF THE DEBATE: OPEN ISSUES

Despite all efforts to include pregnant women in clinical research, they are still underrepresented. A 2011 study on all medications approved by the FDA from 1980 to 2010 found that 91% of the medications approved for use by adults did not have sufficient data on safety, efficacy and foetal risk of medications taken during pregnancy[23]. At the same time, the number of pregnant women that take medications, as well as the number of medications in itself, has increased. The total percentage of pregnant women who take medications including off-label medications may currently be as high as 84-99%[17,24–27] and the number of pregnant women taking four or more medications more than tripled over the last three decades, common ones being antibiotics, asthma medications and anti-nausea medications[9,28]. Although these data reinforce the need to study safety and efficacy of drugs in pregnant women specifically, pregnant women generally remain excluded from clinical research. To illustrate, exclusion of pregnant women is common practice in industry-sponsored phase IV research[29,30], and a recent review demonstrated that between 1960 and 2013 less than 1.29% of pharmacokinetic clinical trials were conducted for pregnant women, and the ones that were undertaken had a strong focus on acute labour and delivery issues[9]. Changing the status-quo in which pregnant women are systematically underrepresented requires their inclusion in clinical research. Presumably there are ethical reasons underlying the underrepresentation of pregnant women and these reasons need to be discussed in order to change to a situation of inclusion. There are at least four open ethical issues that need to be addressed relative to the inclusion of pregnant women in clinical research.

First, the level of acceptable risk for inclusion of pregnant women in clinical research needs to be defined. With regard to acceptable levels of risk, there is limited empirical evidence on the considered moral judgements of stakeholders who are directly involved

with clinical research in pregnant women, including pregnant women themselves. Empirical data is needed to obtain practical insights on the topic, which is essential for ethical evaluation on practice. Furthermore, ethical guidelines that attempt to stipulate an acceptable level of risk for pregnant women are ambiguous and often differ in their guidance[31,32], and there is only one guideline that has recently proposed a standard of acceptable levels of risk[18]. The ambiguity on the acceptable level of risk for pregnant women in clinical research hinders Research Ethics Committees (RECs) in their assessments of clinical research. For instance, RECs sometimes base their judgments on emotional motivations instead of rational deliberation, which may lead to inaccurate risk assessments often resulting in conservative risk interpretations because of a precautionary attitude[33,34]. As such, at the level of RECs and day-to-day risk-benefit analyses, further ethical reflection on the concept of the precautionary principle proved appropriate. The precautionary principle may play an essential role as a decision-making strategy which can underlie risk-benefit decisions during the assessment of clinical trials. The precautionary principle, in its "better safe than sorry"-formulation has a specific appeal relative to clinical research in pregnant women, because potential foetal harm as a result of research participation is considered to be serious and irreversible, one of the prerequisites to invoke the precautionary principle. Yet it is unclear whether and if so how the precautionary principle should apply to pregnant women in clinical research.

Second, pregnant women are often labelled as a vulnerable study group. However, it is conceptually unclear what is meant with vulnerability in relation to pregnant women, which may sometimes lead to categorical exclusion from clinical research. In the past decades, questions about what constitutes vulnerability have led to animated debate among bioethicists. While entire groups were traditionally labelled as being vulnerable, this approach has been criticised as being too narrow and too broad because it excluded entire groups while the notion was at the same time so broad that it could be applied to everyone[35]. As a result, it is now agreed that mere characteristics of a group alone are not sufficient to deem them vulnerable.

Third, it is unclear whether or when the inclusion of pregnant women in clinical research may count as fair. Therefore we need to establish when pregnant women should be included and excluded and what the methodological limitations are. Some scholars argue that we should not only justify inclusion of pregnant women, but also justify their exclusion. And some bioethicists even argue for a type of routine inclusion of pregnant women in clinical studies of drug safety and effectiveness including research targeting the non-pregnant population, except when there are compelling scientific or ethical reasons to exclude them[36,37]. Moreover, there is limited empirical data on the willingness of healthcare professionals to include pregnant women in clinical research and there is uncertainty as to whether pregnant women *themselves* would be interested in participation and inclusion, even if they were found to be eligible. Current literature

on stakeholders' views is scarce and the majority of the studies that are employed either conduct retrospective or hypothetical methods, which are problematic due to their recall bias and the gap between reported and actual behaviour.

Fourth, we need to study what counts as an ethically and strategically optimised design for the inclusion of pregnant women. Because of additional risks associated with including pregnant women in clinical research and the altered ways in which drugs are processed by the pregnant body, pregnant women cannot be treated as an ordinary subgroup in the various phases of traditional drug development.

By addressing these four open ethical issues, we aim to encourage the responsible inclusion of pregnant women in clinical research. As such, **the main objective of this thesis is to challenge the underrepresentation of pregnant women by developing a normative framework specifying the conditions under which pregnant women could be included in clinical research.**

## RESEARCH QUESTIONS

This thesis firstly explores the preliminary question about underrepresentation of pregnant women and subsequently identifies and evaluates four ethical issues relative to the inclusion of pregnant women in clinical research. The research questions for this thesis are:

Preliminary question

1. What are the reasons for the underrepresentation of pregnant women from clinical research? (Chapter 2)

Theme: acceptable level of risk

2. What are the views of pregnant women and stakeholders on the acceptable level of risk for pregnant women in clinical research? (Chapter 3)
3. When and how should the precautionary principle be applied to pregnant women in clinical research? (Chapter 4)

Theme: vulnerability

4. To what extent are pregnant women in clinical research vulnerable and in need of special protections? (Chapter 5)

Theme: fair inclusion

5. What constitutes fair inclusion of pregnant women in clinical research? (Chapter 6)

Sub-questions

6. What is the willingness of pregnant women to participate in clinical research? (Chapter 7)

7. What are the views of pregnant women and stakeholders on the inclusion of pregnant women in clinical research? (Chapter 8)

Theme: research design

8. To what extent can research designs be ethically and strategically optimised for clinical research in pregnant women? (Chapter 9)

## METHODS AND DEFINITIONS

In this thesis we used an empirical-ethical approach, combining empirical data with normative reflection. Empirical study of established ethical issues may clarify real and perceived barriers to inclusion of pregnant women in clinical research. Normative evaluation of these barriers may contribute to fair inclusion of pregnant women in research. The idea that empirical findings can complement normative reflection, as well as the supported use of empirical methods to obtain insights into issues of ethical interest is increasingly common in the field of bioethics. The mixed-methods approach is supported by the sound methodology of the Normative-Empirical Reflective Equilibrium[38]. The method of reflective equilibrium provides a model for moral reasoning that can facilitate the integration of moral experience and empirical data. As such, the empirical and normative findings are put into a reflective equilibrium in order to reach a coherent normative view. The empirical elements of this thesis comprise (systematic) literature reviews and interpretative qualitative interview studies using an inductive thematic analysis. The normative elements of this thesis are normative reflections on moral principles, such as vulnerability and the precautionary principle.

In this thesis we are concerned with the pregnant woman and the foetus. There is debate on the moral status of the foetus. While some regard the foetus as a patient[39,40], others regard the foetus as a participant[10,41]. Moreover, some argue that the interest of the pregnant woman and the foetus are distinct, whereas others label the conflict between the pregnant woman and the foetus as a false dichotomy. Despite this debate about the moral status of the foetus, we can reasonably agree that actions that would unjustifiably harm a future child should be avoided[42]. Moreover, we underwrite the reasoning that even though it could be argued that the interests of the mother and the foetus may be conceptually separable, in practice, the notion of maternal-foetal conflict poses a "false dichotomy" because risks and benefits are entwined and it is impossible to completely separate the pregnant woman and the foetus[14,43]. We thus assume that benefit or harm to the mother is almost always linked to benefit or harm to the foetus. Following such a holistic approach, this thesis holds that pregnant women and foetuses should be treated as a complete unit.

## OUTLINE

In **Chapter 2** we examine the reasons for exclusion of pregnant women, by way of a systematic review of the literature.

Following, we address the theme of acceptable levels of risk. In **Chapter 3** we present our qualitative study on stakeholders' (pregnant women; healthcare professionals; REC members; and regulators) views on acceptable levels of risks for pregnant women in clinical research. **Chapter 4** conceptually examines the often invoked precautionary principle and aims to explore whether and if so when it should be applied to pregnant women in clinical research.

**Chapter 5** encompasses a conceptual analysis of the notion of vulnerability, which we apply to pregnant women.

In **Chapter 6** we examine when inclusion of pregnant women in clinical research may count as fair from an ethical and methodological perspective. In **Chapters 7 and 8** we present the views of pregnant women and healthcare professionals on the inclusion of pregnant women in clinical research. Chapter 7 constitutes a systematic review on the willingness of pregnant women to participate in clinical research. Chapter 8 regards our qualitative study on stakeholders' (pregnant women; healthcare professionals; REC members; and regulators) views on the inclusion of pregnant women in the APOSTEL VI study, a low-risk obstetrical randomised controlled trial.

In **Chapter 9** we address the challenge of research design by proving a practical framework for responsible inclusion of pregnant women in drug research. The framework includes suggestions for different design options in order to prompt ethical and strategic discussion on the topic of research design.

Finally, we present the General Discussion of our findings in **Chapter 10**, by way of a normative framework. In this normative framework, we present the normative considerations and overall recommendations for practice that are drawn from this thesis.

## REFERENCES

1. Allesee. Pregnancy and Protection: The Ethics of Limiting a Pregnant Woman's Participation in Clinical Trials. J. Clin. Res. Bioeth. 2011;2.
2. Swan SH. Intrauterine exposure to diethylstilbestrol: long-term effects in humans. APMIS. 2000;108:793–804.
3. Macklin R. Enrolling pregnant women in biomedical research. Lancet. 2010;375:632–3.
4. Langston L. Better Safe Than Sorry: Risk, Stigma and Research During Pregnancy. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
5. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
6. F Baylis, R MacQuarrie. Why Physicians and Women Should Want Pregnant Women Included in Clinical Trials. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
7. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
8. Buhimschi CS, Weiner CP. Medications in pregnancy and lactation: part 1. Teratology. Obstet. Gynecol. 2009;113:166–88.
9. McCormack S a, Best BM. Obstetric Pharmacokinetic Dosing Studies are Urgently Needed. Front. Pediatr. 2014;2:9.
10. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
11. Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, Van Den Anker JN. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. Am. J. Obstet. Gynecol. 2014. p. 690.e1-690.e11.
12. Services H. Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies Reviewer Guidance Evaluating the Risks of Drug Exposure in Human Pregnancies. Epidemiology. 2005.
13. Little BB. Pharmacokinetics during pregnancy: Evidence-based maternal dose formulation. Obstet. Gynecol. 1999. p. 858–68.
14. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. Elsevier Inc.; 2013;23:e39–45.
15. Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. Clin. Pharmacol. Ther. 2008;83:181–3.
16. Sheffield JS, Siegel D, Mirochnick M, Heine RP, Nguyen C, Bergman KL, et al. Designing drug trials: Considerations for pregnant women. Clin. Infect. Dis. 2014;59:S437–44.
17. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
18. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-Related Research Involving Humans. Geneva, Switzerland: Council for International Organizations of Medical Sciences. [Internet]. 2016. Available from: http://www.cioms.ch/ethical
19. The Second Wave Initiative [Internet]. [cited 2017 Mar 20]. Available from: http://secondwaveinitiative.org/
20. Danesh MJ, Murase JE. The new US Food and Drug Administration pregnancy and lactation labeling rules: Their impact on clinical practice. J. Am. Acad. Dermatol. American Academy of Dermatology, Inc.; 2015;73:310–1.

21. ACOG Statement on FDA Pregnancy Labeling Final Rule - ACOG [Internet]. [cited 2016 May 24]. Available from: http://www.acog.org/About-ACOG/News-Room/Statements/2014/ACOG-Statement-on-FDA-Pregnancy-Labeling-Final-Rule
22. Ramoz LL, Patel-Shori NM. Recent changes in pregnancy and lactation labeling: Retirement of risk categories. Pharmacotherapy. 2014. p. 389–95.
23. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am. J. Med. Genet. C. Semin. Med. Genet. 2011;157C:175–82.
24. EMA. Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned With an Adaptive Design. Reproduction. 2007;
25. Noah BA. The inclusion of pregnant women in clinical research barbara a. noah* a. 2014;353–89.
26. Lupattelli a, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby a C, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4:e004365.
27. Mitchell A a., Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am. J. Obstet. Gynecol. Elsevier Inc.; 2011;205:51.e1-51.e8.
28. Parisi MA, Spong CY, Zajicek A, Guttmacher AE. We don't know what we don't study: The case for research on medication effects in pregnancy. Am. J. Med. Genet. Part C Semin. Med. Genet. 2011. p. 247–50.
29. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
30. Scaffidi J, Mol B, Keelan J. The pregnant women as a drug orphan: A global survey of registered clinical trials of pharmacological interventions in pregnancy. BJOG An Int. J. Obstet. Gynaecol. 2016;
31. Secretariat on Responsible Conduct of Research. Tri-Council Policy Statement (TCPS-2): Ethical conduct for research involving humans. [Internet]. [cited 2016 Mar 25]. Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf
32. OHRP, DHHS. Code of Federal Regulations - Title 45: Public Welfare and Title 46: Protection of Human Subjects. 45 CFR 46. 2009;1–14.
33. Levine RJ. IRB perspective on inclusion of pregnant women in clinical research. ORWH Work. Enrolling pregnant women Issues Clin. Res. An ORWH 20th Anniv. Event. Bethesda, MD: National Institutes of Health; 2011. p. 37–43.
34. Minkoff H, MF M. Fetal Risks, Relative Risks, and Relatives' Risks. Am. J. Bioeth. 2016;16:3–11.
35. Luna F. Elucidating the concept of vulnerability: Layers not labels. Int. J. Fem. Approaches Bioeth. 2009;2:121–39.
36. Baylis F, Kaposky C. Wanted: inclusive guidelines for research involving pregnant women. J. Obstet. Gynaecol. Canada. 2010;32:473–6.
37. Halperin SA. Research involving pregnant women : trials and tribulations. 2012;2:139–46.
38. Van Thiel GJMW, Van Delden JJM. Reflective Equilibrium as a Normative Empirical Model. Ethical Perspect. 2010;17:183–202.
39. Chervenak F a, McCullough LB. The fetus as a patient: an essential ethical concept for maternal-fetal medicine. J. Matern. Fetal. Med. 1996;5:115–9.
40. McCullough LB, Coverdale JH, Chervenak F a. A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. Am. J. Obstet. Gynecol. 2005;193:901–7.

41. Liaschenko J, DeBruin D, Marshall MF. The two-patient framework for research during pregnancy: a critique and a better way forward. Am. J. Bioeth. 2011;11:66–8.

42. Strong C. Minimal risk in research involving pregnant women and fetuses. J. Law. Med. Ethics. 2011;39:529–38.

43. ORWH (United States. Department of Health and Human Services, Public Health Service, National Institutes of Health O of R on WH. Enrolling pregnant women: Issues in clinical research. 2011.

# CHAPTER 2

## FAIR INCLUSION OF PREGNANT WOMEN IN CLINICAL RESEARCH: A SYSTEMATIC REVIEW OF REPORTED REASONS FOR EXCLUSION

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## ABSTRACT

We provide a systematic review of literature relevant to the inclusion of pregnant women in clinical trials. In particular, we address barriers to fair inclusion that we identified within the literature. The 31 articles that were reviewed discuss the exclusion of pregnant women from clinical trials. Reasons given for such exclusion were grouped under several themes, including: foetal safety, collective memory or social controversies, liability, regulations, research ethics committee interpretations, research design, willingness to participate and consent. The discussion reviews arguments in the literature relating to ways to solve these barriers to fair inclusion. We find that barriers to fair inclusion of pregnant women in clinical research interact. While there are practical solutions for surmounting some barriers, others require further discussion.

## BACKGROUND

In the last decade, fair inclusion of pregnant women in clinical research has been widely promoted[1–3]. This is motivated by the need to produce evidence-based knowledge concerning medications that are prescribed to women during pregnancy for both obstetric and non-obstetric illnesses[4]. Currently, the percentage of pregnant women who take medications – for which there is not substantial data on safety, efficacy, and foetal risk evaluation – may be as high as 84–99 %[5–8]. While protection of the foetus is commonly cited as a reason for the exclusion of pregnant women from research, maternal as well as foetal well-being can be promoted by more frequent inclusion of pregnant women in clinical research as this may provide more information on prevention and treatment options[2,9,10]. Lack of a sound evidence base leads to suboptimal care or even under- treatment of pregnant women[11]. Poorly treated asthma, for example, places pregnant women at higher risk of hypertension, preeclampsia, and uterine haemorrhage. As well, asthma is associated with foetal growth restriction, premature birth, and low birth weight[2]. In contrast, when asthma is well-controlled by medication, maternal and perinatal outcomes are as good as comparable groups without asthma[12]. Creating a more solid evidence base can lead to consensus in treatment guidelines, and ultimately result in better health outcomes for pregnant women and their foetuses.

The research community has not ignored the call for fair inclusion of pregnant women in clinical research, and there have been various efforts to take on the challenge. In the United States, the Office of Research on Women's Health (ORWH) of the Department of Health and Human Services (DHHS) has endorsed the view that pregnant women are to be presumed eligible for participation in clinical research (1994). This view was later adopted by the Council for International Organizations of Medical Sciences (CIOMS) in its *Ethical Guidelines for Biomedical Research Involving Human Subjects*[13]. And in 2009, the Second Wave Initiative was launched – a collaborative academic initiative to find ethically and scientifically responsible means to increase the knowledge base for the treatment of pregnant women with medical illness[1,14].

Despite multiple attempts to challenge the status quo, the under-representation and exclusion of pregnant women in clinical research remains common practice[4,15]. Many people have hypothesised about the reasons for the current situation, often with a focus on the diethylstilboestrol (DES) and thalidomide tragedies. From 1938 to 1971, DES was prescribed to an estimated 1.5–3 million women during pregnancy to prevent miscarriage. Only in 1971 was it realised that the drug did not prevent miscarriage and was linked to several adverse complications for the offspring, including vaginal and cervical carcinomas in young women, and malformation of reproductive organs in both male and female children[16,17]. In the late 1950s, thalidomide was prescribed for nausea during pregnancy without prior testing in pregnant women, and resulted in unforeseen teratogenic effects with severe birth defects in over 10,000 children[18].

These tragic events had a great impact on the research community, even though neither tragedy involved clinical research[19]. Although the memory of the events that took place over 40 years ago likely contributes to the exclusion of pregnant women from clinical research today, additional barriers to fair inclusion may be at play.

Understanding the barriers to fair inclusion of pregnant women in clinical research (i.e., understanding the putative reasons for the exclusion of pregnant women from clinical research), and the way in which these barriers intersect is important relative to the goal of promoting fair inclusion. With this systematic review, we first identify the barriers to fair inclusion. We then briefly discuss those barriers that, in our estimation, can easily be addressed. Other barriers to fair inclusion, such as those that relate to the level of acceptable research risk for pregnant women, and the protection owed to alleged vulnerable populations are not easily addressed, and are discussed elsewhere.

## DESIGN

We conducted a systematic review of reasons for the exclusion of pregnant women loosely based on the review of reasons as developed by Strech and Sofaer and the thematic synthesis methods for the categorisation of reasons[20,21]. Sofaer and Strech incorporate the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and allow for analytical strategies that are typically used in qualitative research[22]. Instead of the comprehensive approach for categorisation of reasons we relied on the thematic synthesis of Barnett et al., because it is helpful to identify key themes among different article types.

### Search Strategy

A search of PubMed, EMBASE, and Philosopher's Index was conducted to identify relevant articles in May 2015. These databases were selected for their comprehensive coverage of biomedical and ethics research journals and articles. Additional articles were retrieved through cross-referencing by way of manually searching the reference lists. A broad search strategy that included the following keywords was applied: ((pregnan* OR expecting wom*) AND (research)) AND ((challeng* OR reason* OR motivation* OR view* OR decision*OR attitude* OR willing* OR consideration* OR concern* OR barrier* OR issue*) AND (exclu*)). Table 1 contains the detailed search strategy.

### Study Selection and Inclusion Criteria

One researcher (IvdZ) independently reviewed all titles and/or abstracts to select articles eligible for review, while a second reviewer (JB) subsequently checked a sample from the PubMed results for consistency (n = 55; 8 %). Articles were included in which

the exclusion of pregnant women from clinical research was a specific topic or aspect discussed, determined on the basis of references to the topic in either the title or the abstract. Articles from which it was apparent from the title that the content was out of the research question's scope, were excluded. When this could not be determined based on the title, the abstract was consulted. We excluded articles that were not in English, only reported on primary research reports of trials, or did not include pregnant research participants.

### Data Extraction and Analysis

Our first strategy was to collect the contextual data of the included articles, such as the aim and scope, the country of origin, and the article type. We categorised each article as a: (i) systematic review, (ii) qualitative analysis, (iii) case study/ies, (iv) reasoned opinion, or (v) consensus document, where a reasoned opinion is an article written in an argumentative style and a consensus document is an article of the same type issued by an organisation or institution. We then collated all of the reasons for the exclusion of pregnant women from clinical research mentioned in the articles, and categorised them into themes determined by consensus within our study team.

## RESULTS

### Search and Selection

After removing duplicate references, we screened 669 unique references on the basis of the title and the abstract. Subsequently, 63 articles were assessed in full text, of which 38 met the inclusion criteria. After further assessment for eligibility, seven articles were excluded because they did not provide specific reasons for the exclusion of pregnant women from clinical research. Consequently, 31 articles were included in the final review (Figure 1. PRISMA flow diagram).

### Study Characteristics

Table 2 summarises the characteristics of included articles and the reasons given in these articles for the exclusion of pregnant women. The majority of the articles originate from North America, especially from the United States (n = 22). Most of the articles in the review are reasoned opinions (n = 22). Others are systematic reviews (n = 4), consensus documents (n = 3), a case study (n = 1) and a qualitative analysis (n = 1).

### Synthesis of the Reasons for Exclusion

Table 3 provides an overview of reported reasons for exclusion of pregnant women in clinical research as identified in the articles. This includes articles that explored a single

reason for exclusion (for example, foetal protection is the only reason for exclusion in: Schonfeld and Gordon 2005; Beran 2006 and Goldkind et al. 2010), as well as articles that mentioned multiple reasons. There was considerable consistency among the reported reasons and we were able to identify nine discrete themes: foetal safety (n = 22), liability (n = 15), regulations/wording (n = 15), research design (n = 13), institutional review board (IRB) interpretation (n = 9), collective memory/social controversies (n = 7), willingness to participate (n = 7), vulnerability (n = 4), and consent (n = 4). We then clustered closely related themes into four groups (see Table 4). These groups are briefly described below.

## Foetal Safety, Collective Memory/Social Controversies, and Liability

Protecting the foetus from harm was most frequently cited as a reason for exclusion (n = 22). Since medications can cross the placenta, this can affect the foetus with possibly profound implications, leading to reluctance on the part of many to expose the foetus to clinical research[10,23]. One article mentioned that concern about research involving pregnant women was complicated by social controversies in the United States that influenced the research community, such as the abortion debate in the 1970s which highlighted maternal-foetal conflicts[24]. More frequently, however, there was mention of the collective memory of several historical tragedies, primarily DES and thalidomide (n = 6). In addition to the direct catastrophic health outcomes with these drugs, there were a large number of liability claims resulting in huge financial losses for manufacturers. Many stakeholders, including manufacturers, research ethics review committees, sponsors and researchers, were mentioned as among those worried about legal liability claims (n = 15), possibly explaining the number of times liability was identified as a reason for exclusion.

## Regulations/Wording and IRB Interpretation

Research regulations and guidelines (hereafter collectively referred to as regulations)[1] governing clinical research with pregnant women are among the reasons given for the exclusion of pregnant women (n = 15). A difference can be found between reasons relating to the actual content and meaning of the regulations (n = 9) and reasons relating to the wording, i.e. the comprehensiveness and phrasing of the regulations (n = 6). International and national guidelines provided a mixed picture. For example, the *Declaration of Helsinki* (applicable in most European countries), does not make any reference to research involving pregnant women[25]. Meanwhile, according to the CIOMS

[1] Because most of the articles originate from the United States where there are regulations, the term 'regulations' is used to refer to both regulations and guidelines except when there is specific reference to an identifiable guideline.

guidelines, pregnant women are presumed eligible for research participation[13]. According to the *Common Rule* in the United States, pregnant women are a vulnerable population. In Canada, the *Tri-Council Policy Statement* (*TCPS2)* says "researchers and REBs (Research Ethics Boards) shall take into account foreseeable risks and potential benefits for the woman and her embryo, fetus or infant"[26]. Furthermore, according to some authors, if clinical research in pregnant women is mentioned in regulations, the wording is sometimes restrictive and sometimes vague[18,27,28]. Some authors also noted that since most research regulations do not require researchers to justify the exclusion pregnant women, it is simpler not to include pregnant women in clinical research[1,29].

While research regulations establish relevant norms, research ethics review committees are entrusted to apply them. Since the articles included in this review are mostly about the United States, the comments below focus on Institutional Review Boards (IRBs). Several authors pointed out that IRBs and their members vary in their interpretation of the federal regulations and relevant international guidelines, or interpret these in a conservative or overcautious manner (n = 4)[27]. In addition, some authors noted a tendency for IRBs to almost automatically exclude pregnant women or impose criteria limiting participation in clinical research (n = 4). The practice of exclusion occurred even in studies where there were no additional risks for the foetus and there were costs associated with the exclusion for both the women and their foetuses. One article identified IRBs as the gatekeepers for access to research[1]. Lastly, one article mentioned documentation required by IRBs as a bureaucratic barrier to research involving pregnant women without providing further explanation.

## Research Design

There are unique design challenges with research involving pregnant women that are not experienced with the design of research involving other populations. Among these challenges are research set-up, the recruitment of research participants, and the use of placebo-controlled designs (n = 4). Another reason cited for the routine exclusion of pregnant women from research was their alleged physiological complexity. Physiological changes that occur during pregnancy can potentially alter a drug's pharmacokinetics and pharmacodynamics, and make clinical research within this population more difficult (n = 4). As an example, pregnancy research may require greater numbers of research participants across gestational ages to clearly identify and define optimal treatment regimens[30].

A third reason found to contribute to the difficulty of designing clinical research with pregnant women related to the costs of research (n = 3). As with all population-specific research, data can only be gathered through additional research, which makes conducting research in pregnancy more expensive. Since pregnant women only make up a small percentage of the population likely to use a certain medication, and possibly only take the medication during the nine months of pregnancy, pharmaceutical companies lack

financial incentives to investigate the safety of drugs in pregnant women or develop post-marketing studies[31]. Lastly, one article mentioned that pregnant women were excluded from research either due to the low prevalence of the condition under study in pregnant women (n = 1) or because the researchers wanted to control for risk (n = 1). Regarding the latter, upon asking the researchers about their motivations, the authors found that researchers excluded pregnant women because the drug included in the research had not been approved for use in pregnant women (because of a lack of safety data).

### Willingness to Participate, Vulnerability, and Consent

The last three themes that emerged were willingness to participate (n = 7), vulnerability (n = 4), and consent (n = 4). Concerns relating to the recruitment of participants for clinical research had to do with both the presumed unwillingness of pregnant women to participate in research (n = 5), as well as the unwillingness of clinicians to enrol them in research (n = 2). It appeared that clinicians' willingness to promote research to their pregnant patients was hampered by a lack of resources and time constraints, among other things[32,33]. As concerns the themes of vulnerability and consent, the exclusion of pregnant women from clinical research resulted from their classification as a vulnerable population in regulations (n = 2). Nevertheless, some articles mentioned that the concept of vulnerability had shifted over time, and noted that vulnerability was primarily a historical reason for exclusion (n = 2). Finally, the fact that a foetus is legally unable to consent was cited as another potential reason for exclusion (n = 3).

## DISCUSSION

### Foetal Safety, Collective Memory/Social Controversies, and Liability

Unsurprisingly, the most frequently mentioned reason for the exclusion of pregnant women from research related to the potential harm to foetuses. Although the 1970s social controversy surrounding the abortion debate has lessened in most jurisdictions (except perhaps the United States), our collective memory of the DES and thalidomide tragedies remains, and this has had an impact on clinical research[19]. Changing the current perception of research as an unacceptably risky activity may be particularly difficult. Nevertheless, highlighting dangers to the foetus from routine interventions for which safety evidence is lacking could be an effective way to address this barrier. In addition, advancements in research technologies may contribute to decreasing certain risks for foetuses which in turn might shift the assumption that the best way to protect the foetus from harm is to exclude pregnant women from clinical research. To illustrate this point, placental perfusion experiments can be used to predict placental drug transfer and could facilitate the assessment of the risks and potential benefits of drug therapy in pregnancy in the pre-clinical phases of research[34,35]. An underlying unresolved ethical

issue is what counts as an acceptable level of risk for the foetus in clinical research with pregnant women. Certainly, foetal safety should always be considered when conducting research with pregnant women; however, with realistic assessment of the risks, this barrier to research participation need not be as solid as it is often portrayed.

With regard to clinical research in the United States there is fear regarding potential liability claims since all who are involved in the design of clinical research in pregnant women could potentially be sued under tort law if foetuses are injured as a result of research participation[27,36,37]. The risk of legal liability notwithstanding, the likelihood that anyone would be held liable is actually fairly low (which explains the limited existing litigation)[10,37,38]. Demonstrating the predicted low occurrence of tort liability claims could be a first step towards overcoming this obstacle to research participation. There could be other solutions, however. For example, Chris Kaposy and Lorraine Lafferty note that in both the United States with the 2011 H1N1 influenza vaccine trial, and in Canada with the Pertussis Maternal Immunization Study, the manufacturers were protected from tort liability. In the United States this was through the US Federal Government's *Public Readiness and Vaccine Trials Involving Pregnant Women Emergency Preparedness Act*. In Canada, liability was shifted to the research institute and its insurance providers[39]. The authors propose that such strategies could be extended to enhance further clinical research with pregnant women. Additionally, Wendy Mariner proposes that in some instances tort law could be avoided by introducing a compensation system where responsibility for research injuries is shifted from the manufacturer to society as a whole. She argues that, since research participants take on risks for society's sake, in return society has a moral obligation to compensate those who are harmed[40]. In short, even though legally liability is a very real concern, there might be ways to work around this barrier.

## Regulations/Wording and IRB Interpretation

While liability concerns may influence IRBs (and research ethics review committees more generally) in their overcautious interpretation of regulations[4,27,30,41], providing training and guidance for IRB members on the harms of exclusion and possible liability risks because of *exclusion* might help to increase fair inclusion[1,30,38,42]. Further clarification of the regulations and explications of certain wording is needed in order to facilitate practical implementation. For example, despite the fact that several ethicists have tried to define minimal risk[43,44], the wording remains ambiguous and there is no consensus on how to weigh risks and potential benefits. A workable notion of what constitutes an acceptable risk for the foetus or the pregnant woman is needed. Currently, as a result of ambiguity concerning acceptable research risks, pregnant women have been excluded from clinical research that did not pose any risks or where risks were negligible. Consider, for example, observational research or research on physiologic processes involving FDA approved drugs already used by pregnant women[2,15,45].

Another proposal concerns a change in the language of regulations: not leaving inclusion of pregnant women in clinical research optional, but instead requiring a justification for the exclusion of pregnant women from clinical research. Such a formulation would not only take away the perception that pregnancy is always a reason for exclusion, or that pregnant women should simply be ignored in clinical research, but would also ensure that potential benefits are distributed more equally[2,3,23]. The idea of requiring justification for the exclusion of pregnant women from research is grounded in a notion of justice as equity or as corrective justice[46]. Justice as equity calls for equal treatment and precludes exclusion for arbitrary reasons. On this view, pregnant women should be included in clinical research in the same way as other populations. According to corrective justice, justifying exclusion is essential to restore differences between trial populations.

To illustrate, the lack of research on the pharmacokinetics and pharmacodynamics of medications in pregnancy has a negative impact on the health of pregnant women and their foetuses which results in class injustice for this particular group. Considered from a corrective justice point of view, one could, for example, require the prioritisation of pregnant women in clinical research until they are more equally represented. However, there are methodological limitations to the routine inclusion of pregnant women in clinical research. For instance, when it is unknown whether an intervention's effect differs between pregnant women and non-pregnant women, the inclusion of pregnant women in a clinical trial in which this intervention is tested should have a favourable harm-benefit ratio that is either proportional or substantial in order to be methodologically meaningful. Thus, justice as equity and corrective justice will not necessarily make inclusion of pregnant women as a study population more fair[46].

## Research Design

There is an urgent need for clinical research on safety, efficacy, and dosing of medications that pregnant women take either due to chronic medical conditions, or because of acute pregnancy problems. As long as the risks for the pregnant woman and her foetus are acceptable, which is implied by the use of specific medications in clinical treatment, it is imperative that there be research in the population that is actually taking the medications, i.e., in pregnant women[9]. Besides, numerous studies with pregnant women in randomised clinical trials and observational studies demonstrate that the perceived barriers of costs and physiological complexity in clinical research with pregnant women can be overcome[28]. In addition, innovative research designs, such as specialised cohort registries, may be able to strike a favourable balance between minimising the risks and burdens of research procedures and interventions, while maintaining scientific validity[3]. Moreover, the inclusion of pregnant women in Phase IV clinical trials could increase the knowledge base on the risks and potential benefits of certain medications[47]. Systematically collecting data from post-marketing studies is the least that can be done to enhance evidence-based medicine for pregnant women[2,3]. Next, in order to determine

whether the recruitment of pregnant women and the motivation of clinicians to enrol them in clinical research constitute an actual barrier for which possible solutions might be found, more information is needed. This can only be established by adding to the existing empirical data on the views of pregnant women and clinicians.

### Willingness to Participate, Vulnerability, and Consent

Vulnerability is generally on the agenda in relation to the exclusion of pregnant women from clinical research[28,30,48]. For a long time, the concept has been connected to the capacity to give informed consent and to the anticipated exposure to potential harm. Obviously, pregnant women are capable of decision-making and not automatically vulnerable in this aspect[49–52]. However, potential exposure to the harms of research cannot be negated and risks must be taken into account when talking about vulnerability. As such, vulnerability may play a more implicit role, primarily conceived of as risks for the foetus which we found to be the most frequently cited reason for exclusion. Since we can express risks through risk-benefit assessments, the classification of pregnant women as a vulnerable group might no longer be needed. Indeed, some authors have challenged the utility of traditional uses of the concept of vulnerability and argued that it needs to be reconceptualised in order to regain its usefulness as a concept in relation to pregnant women in clinical research[49,51,53–56]. This may explain why vulnerability was only mentioned four times in our review of the literature.

Although pregnant women are capable of giving informed consent, foetuses are not and this inability to give consent was another area where barriers to fair inclusion were mentioned[1,57]. This relates in particular to the moral status of the foetus. With research involving pregnant women, the interests of the pregnant woman might be in conflict with the interests of the foetus, and whose interests should prevail depends on whether the foetus has independent moral status. There is scarce literature on conflicting maternal-foetal interests in clinical research. Some regard the foetus as a patient[58], while others consider the foetus a research participant[1]. In addition, some regard the interests of the pregnant woman and the foetus as distinct[58,59], whereas others label the conflict between the pregnant woman and the foetus as a false dichotomy since research participation can benefit both the pregnant woman and the foetus[30]. To better understand and evaluate the potential conflict between pregnant women and their foetuses, the moral status of the foetus needs to be clarified, indicating the duties that various stakeholders have.

## LIMITATIONS

This systematic review has some limitations. First, there is no tool available to perform an adequate quality assessment of the different reasons for exclusion. Therefore, we were

unable to determine whether the most frequently mentioned reasons for the exclusion of pregnant women from clinical research correspond to the strongest arguments in support of this view. In addition, the systematic review primarily included articles from North America, probably depicting a narrow scope of the issues. We tried to increase the number of articles by authors outside of North America by conducting a small search on English-language articles authored by Europeans, however, we were not successful in identifying any additional sources. Finally, since we were specifically looking for articles in which the reasons for exclusion of pregnant women from clinical research was a major subject (and not a mere mention as part of exclusion criteria in a trial), we chose to exclude a large number of articles based on title and abstract. In part, our ability to do so is a reflection of a broad search strategy in which the term 'research' as a keyword was included instead of more narrow synonyms like 'study' or 'trial' or 'method*' in the two biomedical databases (PubMed and EMBASE) that we searched. As such, it is possible that we might have excluded relevant articles.

## CONCLUSIONS

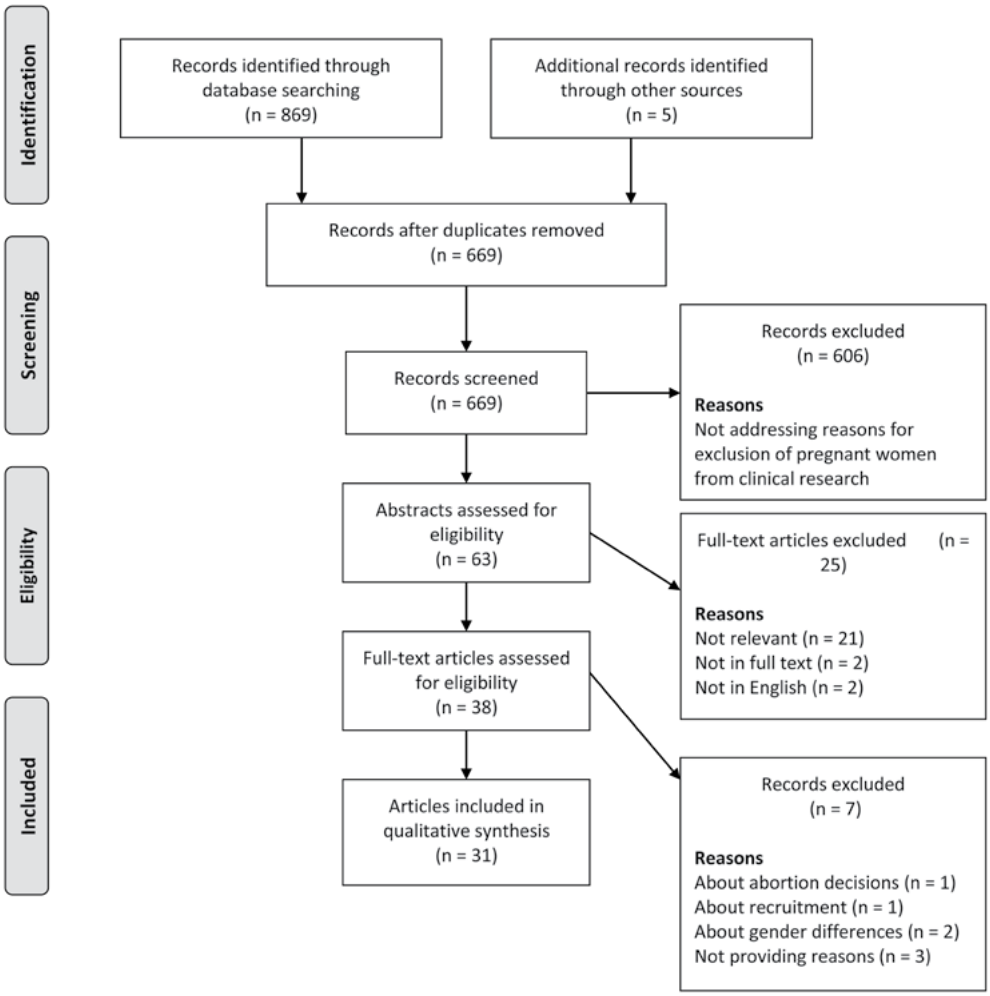
The systematic review of reasons for the exclusion of pregnant women from clinical research indicates that there are a number of interacting barriers hindering the fair inclusion of pregnant women. These include issues surrounding foetal safety, collective memory/social controversies and liability; ambiguity regarding regulations/ wording and IRB interpretation; the unique challenges of research design; and questions concerning the willingness to participate, vulnerability and consent. While there are practical solutions to some of these barriers, there are also a number of barriers that need further discussion. In particular, barriers associated with claims/ concerns about acceptable levels of risks, and claims about vulnerability of pregnant women remain important ethical challenges.

# FIGURES AND TABLES

**Table 1.** Searches

| Search | Terms | Hits |
|---|---|---|
| **PUBMED**<br>**Date of search: May 18th, 2015** | | |
| 1 | ((((((((((challeng*[Title/Abstract]) OR reason*[Title/Abstract]) OR motivation*[Title/Abstract]) OR view*[Title/Abstract]) OR decision*[Title/Abstract]) OR attitude*[Title/Abstract]) OR willing*[Title/Abstract]) OR consideration*[Title/Abstract]) OR concern*[Title/Abstract]) OR barrier*[Title/Abstract]) OR issue*[Title/Abstract] | 2312595 |
| 2 | exclu*[Title/Abstract] | 380158 |
| 3 | #1 AND # 2 | 60360 |
| 4 | ((pregnan*[Title/Abstract]) OR expecting wom*[Title/Abstract]<br>AND<br>research* [Title/Abstract])) | 19792 |
| 5 | #3 AND #4 | 387 |
| **EMBASE**<br>**Date of search: May 18th, 2015** | | |
| 1 | (challenge*:ab,ti OR reason*:ab,ti OR motivation*:ab,ti OR view*:ab,ti OR decision*:ab,ti OR willing*:ab,ti OR attitude*:ab,ti OR consideration*:ab,ti OR concern*:ab,ti OR barrier*:ab,ti OR issue*:ti,ab) | 2,792,242 |
| 2 | Exclu*:ti,ab | 530,749 |
| 3 | #1 AND #2 | 90,193 |
| 4 | ((pregnan*:ti,ab OR expecting wom*:ti,ab) AND research*:ti,ab) | 14,891 |
| 5 | #3 AND #4 | 365 |
| **Philosophers Index**<br>**Date of search: May 20th, 2015** | | |
| 1 | (research* or trial* or stud*).mp. [mp=abstract, title, heading word] | 57827 |
| 2 | pregnan*.mp. [mp=abstract, title, heading word] | 695 |
| 3 | 1 and 2 | 138 |
| 4 | limit 3 to (english) | 117 |

**Figure 1.** PRISMA Flow Diagram




From: Moher D., A. Liberati, J. Tetzlaff, D.G. Altman, and The PRISMA Group. 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prismastatement.org

**Table 2.** Summary of papers selected for the review

| | Reference | Country | Paper type | Scope of paper | Aim of paper | Mentioned reason(s) for exclusion* |
|---|---|---|---|---|---|---|
| 1 | ACOG 2007 | USA | Consensus document | Clinical research | To update previous committee opinion on earlier publication on pregnant women in research | Pregnant women were viewed as a vulnerable population and there was concern that trial participation would result in harm to the foetus and increased liability risk for researchers |
| 2 | Alexander 2010 | USA | Reasoned opinion | Clinical research | To provide a historical overview of the Federal regulations (45 CFR46, Subpart B) and discuss the revision | Fears of legal liability and social controversies (abortion debate in the USA) have led to exclusion |
| 3 | Allesee and Gallagher 2011 | USA | Reasoned opinion | Clinical research | To examine the ethics of the exclusion or inclusion of pregnant women in clinical trials | It is too dangerous for the baby if a pregnant woman participates; liability considerations of manufacturers and IRBs; IRB concerns with inherent and unknown danger to the foetus; reticence manufacturers due to historical tragedies |
| 4 | Battino 2001 | Italy | Reasoned opinion | Antiepileptic drug trials | To promote the inclusion of inclusion women in AED trials | Historically pregnant women were considered as a vulnerable population in relation to foetus |
| 5 | Baylis 2010 | CAN | Reasoned opinion | Clinical research | To argue that routine exclusion is unethical and unscientific and regulators must mandate change | Pregnant women are routinely excluded because of the harm the intervention might do to the developing foetus |
| 6 | Baylis and Kaposy 2010 | CAN | Reasoned opinion | Guidelines | To illustrate the negative ethical implications of excluding pregnant women in guidelines | The Tri-Council Policy Statement takes into account potential harms instead of having to give reasons for exclusion; existing fear of exposing foetuses to substances of unknown teratogenicity |
| 7 | Beran 2006 | AUS | Reasoned opinion | Anti-epileptic medications | To provide arguments for inclusion of AEM trials based on a review of existing information | Non-maleficence supports exclusion due to potential teratogenicity and protection of the potential offspring remains mandatory from the perspective of the non-malevolence principle |

**Table 2.** (continued)

| | Reference | Country | Paper type | Scope of paper | Aim of paper | Mentioned reason(s) for exclusion* |
|---|---|---|---|---|---|---|
| 8 | Blehar et al. 2013 | USA | Reasoned opinion | Clinical research | To further analyse three major interrelated scientific and science regulatory issues that emerged as important concerns at the 2010 ORWH meeting | Fear of harm to the foetus, threat of legal liability, concern about the complicated physiology of pregnant women, uncertainty whether pregnant women would be willing to participate, regulations which classify pregnant women as a vulnerable population and vague and restrictive wording of regulations which IRBs in turn interpret conservatively for pregnant subjects |
| 9 | Brandon et al. 2013 | USA | Qualitative analysis | Perinatal mental health research | To describe existing perspectives held by investigators (n=15) and IRB members (n=6) on acceptable perinatal mental health research | Semi-structured interviews indicate study design/ methodology; safety concerns (risk mother, foetus, minimal risk interpretation); participant selection and recruitment and autonomy (competency informed consent, need for parental consent) |
| 10 | Cain et al. 2000 | USA | Systematic literature review | Clinical protocols | To survey the contraceptive requirements in clinical trial protocols which were presented to an IRB (n = 410 ) | "[T]he near complete exclusion of pregnant women found in this review illustrates the impact that legal and economic concerns of sponsors about fetal outcome have (beyond issues of teratogenicity)." |
| 11 | Foulkes et al. 2011 | USA | Consensus document | Clinical research | To summarise a NIH workshop on barriers and opportunities enrolling pregnant women | pregant women are physiologically complicated, they will complicate our research, and they would be difficult to recruit. There are also challenges concerning legal liability and regulatory obscurity |
| 12 | Frew et al. 2014 | USA | Systematic literature review | Clinical research | To synthesize the body of literature that details challenges, facilitators, and best practices toward recruitment and retention through the socioecological model of health promotion | Public scandals, federal guidelines, IRB provisions and liability issues. In addition there are community/social level factors (i.e. willingness clinicians) and individual level factors (i.e. willingness participants) |

**Table 2.** (continued)

| | Reference | Country | Paper type | Scope of paper | Aim of paper | Mentioned reason(s) for exclusion* |
|---|---|---|---|---|---|---|
| 13 | Godlovitch 2003 | CAN | Reasoned opinion | Clinical research | To explore some of the ethical issues, the implicit ageism and sexism in the exclusion of seniors. | t Exclusion can be rationalised because babies are legally incapable of consenting, and pharmaceutical companies might not want potential exposure to later legal claims |
| 14 | Goldkind et al. 2010 | USA | Reasoned opinion | H1N1 influenza pandemic | To argue that it is not only permissible but also imperative that pregnant women be judiciously included in research | The effort to protect the fetus from research related risks is generally a reason for exclusion |
| 15 | Hurlimann et al. 2011 | CAN | Systematic literature review | Nutrigenetics clinical research | To examine inclusion in nutrigenetics clinical research and its scientific and ethical challenges | Challenges are the obtainment and quality of informed consent of vulnerable populations (i.e. ethical questions in terms of benefit and protection of future autonomy children), the notion of minimal risk and acceptable burden in research with vulnerable populations is controversial |
| 16 | Kaposy and Lafferty 2012 | CAN | Reasoned opinion | Vaccine trials | To argue that vaccine research in pregnancy can be ethical and to explore methods for overcoming vaccine manufacturers' fear of liability | Vaccine manufacturers' fear of liability is a primary force behind the exclusion |
| 17 | Kornblum 1994 | USA | Reasoned opinion | Clinical research | To discuss whether pregnant women should be research subjects | "During a recent exchange, some NIEHS [National Institute of Environmental Health Sciences] scientist argued that existing federal rules against experimenting on pregnant women are beneficial to protect a fetus and prevent exploitation." |
| 18 | Levine RJ 2010 | USA | Reasoned opinion | IRBs and policies | To review the development of policies and discuss current guidelines | Apparent IRB reasons: Subpart B of the Federal Code presents challenges, guidelines are restrictive, conservatism, exposure to legal liability, influenced by frightening history, and a documentation focus |

**Table 2.** (continued)

| | Reference | Country | Paper type | Scope of paper | Aim of paper | Mentioned reason(s) for exclusion* |
|---|---|---|---|---|---|---|
| 19 | Little et al. 2009 | USA | Reasoned opinion | Clinical research | To outline reasons for inclusion and outline possible steps to advance responsible inclusion | Researchers/IRBs view pregnancy as near-automatic cause of exclusion; no (legal) incentives to design studies; studies are more costly; there is a concern for the foetus, resistance due to thalidomide tragedy; vagueness leads to excluding interpretations |
| 20 | Lyerly 2010 | USA | Reasoned opinion | Clinical research | To provide a brief background of the need for research with pregnant women | Historical reasons for exclusion: complicated physiologies of pregnant women; the need to protect women and foetuses from potential risks of the drug; Thalidomide which led to an almost universal exclusion of pregnant women from research. |
| 21 | Lyerly et al. 2008 | USA | Reasoned opinion | Clinical research | To outline resulting knowledge gaps and their costs and then highlight the ethical obligation to confront the challenges of including pregnant women in clinical research | Challenges concerning exclusion: safety of medication for the foetus; capacity to consent; cultural anxiety to place any risk on the foetus for sake of woman; liability concerns; IRBs are the gatekeepers of access to research; no legislation concerning justification of exclusion |
| 22 | Lyerly et al. 2007 | USA | Reasoned opinion | Medical decision making around pregnancy | To outline three patterns in risk perception and reasoning that affect medical decision making around pregnancy | Many researchers and IRBs continue to regard pregnancy as a virtually automatic cause for exclusion due to the tendency to notice risks of intervening to the exclusion of risks of not intervening |
| 23 | Macklin 2010 | USA | Reasoned opinion | Biomedical research | To provide a perspective on the enrolment of pregnant women in biomedical research | Exclusion exist because researchers took the wrong message from thalidomide, ethical guidelines provide a mixed picture, and foetal safety concerns |
| 24 | Madan et al. 2014 | AUS | Case study/ies | Randomised trial methods | To explore difficulties in recruitment to improve future trial participation using a case-study of an RCT on cervical ripening | Clinicians are gatekeeping ("patients are not to be approached for the trial") "because of time constraints, lack of resources and a lack of equipoise |

**Table 2.** (continued)

| | Reference | Country | Paper type | Scope of paper | Aim of paper | Mentioned reason(s) for exclusion* |
|---|---|---|---|---|---|---|
| 25 | Merkatz 1998 | USA | Reasoned opinion | Clinical research | To outline a historical overview of exclusion and discuss reasons for current policy changes | Research practice shows that protection of the foetus remains an essential priority in research and that liability fears are still germane in present day research |
| 26 | Merton 1993 | USA | Reasoned opinion | Biomedical research | To catalogue ways in which women have been disadvantaged by exclusion; recent developments to redress them; dissect underlying rationales | Researcher's commitment to quality science (physiology and expenses); moral duty to avoid infliction of fetal harm; dictates of the law (government regulations) and tort phobia: the risk of liability to the offspring |
| 27 | Noah 2014 | USA | Reasoned opinion | Clinical research | To describe the current status of inclusion and discuss the FDA-related regulatory barriers to collecting safety and efficacy information | Current regulations discourage inclusion in a "misguided attempt to avoid challenging ethical issues, possible injuries to research participants and fetuses, and potential liability." |
| 28 | Sahin 2011 | USA | Consensus document | Clinical research | To present the FDA Perspective on the ethical barriers of conducting research in pregnant women in relation to recent publications | Pregnant women are an understudied population due to the ethical and medical-legal considerations of harming the foetus and in the effort to protect the foetus, institutional review boards' interpretation of the regulation may be overly cautious. |
| 29 | Schonfeld and Gordon 2005 | USA | Reasoned opinion | Contraception in research | To give a policy suggestion on contraception requirements in research | "[m]any investigators and sponsors are reluctant to include women of childbearing potential in research because of the risk of fetal harm should subject become pregnant during the study." |
| 30 | Shields and Lyerly 2013 | USA | Systematic literature review | Phase VI trials | To measure the current exclusion of pregnant women from industry sponsored clinical trials as a baseline for future comparison | Condition has low prevalence in pregnant women; not enough safety data/not approved in pregnant women; considered vulnerable by FDA; pregnancy is always an exclusion criteria. In addition they hypothesise |

**Table 2.** (continued)

| | Reference | Country | Paper type | Scope of paper | Aim of paper | Mentioned reason(s) for exclusion* |
|---|---|---|---|---|---|---|
| | | | | | | that the desire not to do harm, over interpretation of federal guidelines and the presumption that women might not be willing to participate are reasons as well |
| 31 | Theiler 2009 | USA | Reasoned opinion | Antimicrobial therapy | To provide a perspective on evidence-based antimicrobial therapy in pregnancy | Reasons are concerns for foetal well-being; current drug approval mechanisms (X labelling without tests in humans); legal environment; profit driven drug pipeline: post marketing studies are expensive and there are liability issues |

* N.B.: authors often report on reasons for exclusion but do not actually promote or endorse these reasons

**Table 3.** Overview of Reasons for Exclusion

| General Theme | Article |
|---|---|
| **Foetal Safety (n=22)** | |
| Concern that trial participation would result in harm to the foetus* | 1 |
| Too dangerous for the baby if a pregnant woman participates | 3 |
| IRB concerns with inherent and unknown danger to the foetus | 3 |
| The harm the intervention might do to the developing foetus | 5 |
| Existing fear of exposing foetuses to substances of unknown teratogenicity | 6 |
| Non-maleficence supports exclusion due to potential teratogenicity | 7 |
| Protection of the potential offspring remains mandatory | 7 |
| Fear of harm to the foetus | 8 |
| Protect the foetus from research related risks | 14 |
| Existing federal rules against experimenting on pregnant women are beneficial to protect a foetus and prevent exploitation | 17 |
| Concern for the foetus | 19 |
| The need to protect women and foetuses from potential risks of the drug* | 20 |
| Worries about the safety of medication for the foetus | 21 |
| Cultural anxiety to place any risk on the foetus for sake of woman | 21 |
| Foetal safety concerns | 23 |
| Protection of the foetus remains an essential priority in research | 25 |
| Moral duty to avoid infliction of foetal harm | 26 |
| Ethical and medical-legal considerations of harming the foetus | 28 |
| Effort to protect the foetus | 28 |
| Risk of foetal harm | 29 |
| Desire not to do harm | 30 |
| Concerns for foetal well-being | 31 |
| **Regulations/Wording (n=15)** | |
| Tri-Council Policy Statement takes into account potential harms instead of having to give reasons for exclusion | 6 |
| Existing regulations are somewhat ambiguous | 8 |
| Safety concerns (risk mother, foetus, minimal risk interpretation) | 9 |
| Language of minimal risk relative to the foetus is unclear (Subart B Federal Code) | 11 |
| Federal guidelines | 12 |
| Notion of minimal risk/ acceptable burden for vulnerable populations is controversial | 15 |
| Subpart B of the Federal Code presents challenges | 18 |
| Guidelines are restrictive | 18 |
| Vagueness leads to excluding interpretations | 19 |
| There is no legislation concerning justification of exclusion | 21 |

**Table 3.** (continued)

| General Theme | Article |
|---|---|
| Ethical guidelines provide a mixed picture | 23 |
| Dictates of the law (government regulations) | 26 |
| The current regulations discourage inclusion in a "misguided attempt to avoid challenging ethical issues, possible injuries to research participants and foetuses, and potential liability." | 27 |
| Current drug approval mechanisms (X labelling without tests in humans) | 31 |
| Legal environment | 31 |
| **Liability (n=15)** | |
| Increased liability risk for researchers* | 1 |
| Fears of legal liability | 2 |
| Liability considerations of manufacturers and IRBs | 3 |
| Threat of legal liability | 8 |
| Legal concerns of sponsors about foetal outcome | 10 |
| Economic concerns of sponsors about foetal outcome | 10 |
| Challenges concerning legal liability | 11 |
| Liability issues | 12 |
| Pharmaceutical companies might not want potential exposure to later legal claims | 13 |
| Vaccine manufacturers' fear of liability | 16 |
| IRB exposure to legal liability | 18 |
| Liability concerns | 21 |
| Liability fears are still germane | 25 |
| Tort phobia: the risk of liability to the offspring | 26 |
| Liability issues | 31 |
| **Research Design (n=13)** | |
| Concerns about the complicated physiology of pregnant women | 8 |
| Study design/methodology | 9 |
| Pregnant women are physiologically complicated | 11 |
| Pregnant women complicate our research | 11 |
| There are no (legal) incentives to design studies | 19 |
| Studies are more costly | 19 |
| Complicated physiologies of pregnant women* | 20 |
| Researcher's commitment to quality science (physiology) | 26 |
| Condition has low prevalence in pregnant women | 30 |
| There is not enough safety data/not approved in pregnant women | 30 |
| Pregnancy is always an exclusion criteria | 30 |
| Pharmaceutical companies have little incentive to investigate the safety of drugs | 31 |
| Profit driven drug pipeline: postmarketing studies are expensive | 31 |

**Table 3.** (continued)

| General Theme | Article |
|---|---|
| **IRB Interpretation (n=9)** | |
| Vague and restrictive wording of regulations which IRBs in turn interpret conservatively for pregnant subjects | 8 |
| IRB provisions (stringent regulation of protocols) | 12 |
| IRB conservatism | 18 |
| IRB documentation focus | 18 |
| Researchers/IRBs view pregnancy as near-automatic cause of exclusion | 19 |
| IRBs are the gatekeepers of access to research | 21 |
| Researchers and IRBs continue to regard pregnancy as a virtually automatic cause for exclusion due to the tendency to notice risks of intervening to the exclusion of risks of not intervening | 22 |
| Institutional review boards' interpretation of the regulation may be overly cautious | 28 |
| Overinterpretation of federal guidelines | 30 |
| **Willingness to Participate (n=7)** | |
| Uncertainty whether pregnant women would be willing to participate | 8 |
| Participant selection and recruitment | 9 |
| Pregnant women would be difficult to recruit | 11 |
| Individual level factors (i.e. willingness participants) | 12 |
| Community/social level factors (i.e. willingness clinicians) | 12 |
| Clinicians are gatekeeping ("patients are not to be approached for the trial") "because of time constraints, lack of resources and a lack of equipoise | 24 |
| There is a presumption that women might not be willing to participate | 30 |
| **Collective memory/Social Controversies (n=7)** | |
| Social controversies have led to exclusion* | 2 |
| Reticence of manufacturers due to historical tragedies | 3 |
| Public scandals | 12 |
| IRBs are influenced by frightening history in the field | 18 |
| Resistance due to thalidomide tragedy | 19 |
| Thalidomide led to an almost universal exclusion of pregnant women from research* | 20 |
| Researchers took the wrong message from thalidomide | 23 |
| **Consent (n=4)** | |
| Autonomy (competency informed consent, possible need for parental consent) | 9 |
| Babies are legally incapable of consenting | 13 |
| Challenges are the obtainment and quality of informed consent of vulnerable populations (i.e. ethical questions in terms of benefit and protection of future autonomy children) | 15 |

**Table 3.** (continued)

| General Theme | Article |
|---|---|
| Capacity to consent | 21 |
| **Vulnerability (n=4)** | |
| Pregnant women were viewed as a vulnerable population* | 1 |
| Pregnant women were considered as a vulnerable population in relation to foetus* | 4 |
| Regulations which classify pregnant women as a vulnerable population | 8 |
| Pregnant women are considered vulnerable by FDA | 30 |

* Mentioned as an earlier existing reason which might have lost its relevance

**Table 4.** Categorisation of reasons for exclusion

| General Theme | Article* |
|---|---|
| **Foetal Safety (n=22)** | 1, 3, 3, 5, 6, 7, 7, 8, 14, 17, 19, 20, 21, 21, 23, 25, 26, 28, 28, 29, 30, 31 |
| **Collective memory/Social Controversies (n=7)** | |
| Social controversies | 2 |
| Reticence of manufacturers due to historical tragedies | 3, 12, 18, 19, 20, 23 |
| **Liability (n=15)** | |
| Concerns liability (general) | 2, 8, 11, 12, 21, 25, 26, 31 |
| Liability considerations of researchers, manufacturers, sponsors and IRBs | 1, 3, 10, 10, 13, 16, 18 |
| **Regulations/Wording (n=15)** | |
| Regulations | 6, 8, 12, 18, 21, 26, 27, 31, 31 |
| Formulation ambiguity | 9, 11, 15, 18, 19, 23 |
| **IRB Interpretation (n=9)** | |
| Conservatism/caution in interpretation | 8, 18, 28, 30 |
| Pregnancy as near-automatic cause of exclusion | 12, 19, 21, 22 |
| IRB documentation focus | 18 |
| **Research Design (n=13)** | |
| Study design/methodology | 9, 11, 19, 30 |
| Complicated physiology | 8, 11, 20, 26 |
| Studies are more costly | 19, 31, 31 |
| Low prevalence of a condition | 30 |
| Control for risk | 30 |

**Table 4.** (continued)

| General Theme | Article* |
|---|---|
| **Willingness to Participate (n=7)** | |
| (Presumed) unwillingness pregnant women | 8, 12, 30 |
| Recruitment difficulties | 9, 11 |
| Unwillingness clinicians | 12, 24 |
| **Vulnerability (n=4)** | |
| Pregnant women were viewed as a vulnerable population | 1, 4, 8, 30 |
| **Consent (n=4)** | |
| Capacity to consent foetus | 9, 13, 21 |
| Obtainment/quality consent vulnerable populations | 15 |

*Several articles mentioned multiple reasons, in that case the number of the article is repeated

## REFERENCES

1. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
2. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
3. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
4. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
5. EMA (European Medicines Agency). Guideline of the exposure to medicinal products during pregnancy: need for post-authorisation data. [Internet]. 2005 [cited 2016 Mar 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf
6. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
7. Lupattelli a, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby a C, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4:e004365.
8. Noah BA. The inclusion of pregnant women in clinical research barbara a. noah* a. 2014;353–89.
9. Zajicek A, Giacoia GP. Obstetric clinical pharmacology: coming of age. Clin. Pharmacol. Ther. 2007;81:481–2.
10. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. Clin. Infect. Dis. 2014;59 Suppl 7:S400-7.
11. F Baylis, R MacQuarrie. Why Physicians and Women Should Want Pregnant Women Included in Clinical Trials. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
12. Tan KS, Thomson NC. Asthma in Pregnancy. 1970;9343.
13. CIOMS & WHO. International ethical guidelines for biomedical research involving human subjects. [Internet]. 2002. [cited 2016 Mar 25]. Available from: http://www.cioms.ch/publications/layout_guide2002.pdf.
14. The Second Wave Initiative [Internet]. [cited 2017 Mar 20]. Available from: http://secondwaveinitiative.org/
15. Cain J, Lowell J, Thorndyke L, Localio a R. Contraceptive requirements for clinical research. Obstet. Gynecol. 2000. p. 861–6.
16. Swan SH. Intrauterine exposure to diethylstilbestrol: long-term effects in humans. APMIS. 2000;108:793–804.
17. Allesee. Pregnancy and Protection: The Ethics of Limiting a Pregnant Woman's Participation in Clinical Trials. J. Clin. Res. Bioeth. 2011;2.
18. Macklin R. Enrolling pregnant women in biomedical research. Lancet. 2010. p. 632–3.
19. Langston L. Better Safe Than Sorry: Risk, Stigma and Research During Pregnancy. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
20. Strech D, Sofaer N. How to write a systematic review of reasons. J. Med. Ethics. 2012;38:121–6.
21. Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: a critical review. BMC Med. Res. Methodol. 2009;9:59.

22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J. Clin. Epidemiol. 2009. p. e1-34.

23. Lyerly AD, Mitchell LM, Armstrong EM, Harris LH, Kukla R, Kuppermann M, et al. Risks, values, and decision making surrounding pregnancy. Obstet. Gynecol. 2010;109:979–84.

24. Alexander D. Global health issues and US regulation 45 CFR46, Subpart B. In: ORWH, editor. ORWH Work. Enrolling pregnant women Issues Clin. Res. An ORWH 20th Anniv. Event,. Bethesda, MD: National Institutes of Health.; 2011.

25. Assembly G. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2013;1–8.

26. Secretariat on Responsible Conduct of Research. Tri-Council Policy Statement (TCPS-2): Ethical conduct for research involving humans. [Internet]. [cited 2016 Mar 25]. Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf

27. Levine RJ. IRB perspective on inclusion of pregnant women in clinical research. ORWH Work. Enrolling pregnant women Issues Clin. Res. An ORWH 20th Anniv. Event. Bethesda, MD: National Institutes of Health; 2011. p. 37–43.

28. Foulkes MA, Grady C, Spong CY, Bates A, Clayton JA. Clinical research enrolling pregnant women: a workshop summary. J. Womens. Health (Larchmt). 2011;20:1429–32.

29. Baylis F, Kaposky C. Wanted: inclusive guidelines for research involving pregnant women. J. Obstet. Gynaecol. Canada. 2010;32:473–6.

30. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton J a. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. 2013;23:e39-45.

31. Theiler RN. Evidence-based antimicrobial therapy in pregnancy: long overdue. Clin. Pharmacol. Ther. Nature Publishing Group; 2009;86:237–8.

32. Brandon AR, Shivakumar G, Inrig SJ, Sadler JZ, Craddock Lee SJ. Ethical Challenges in Designing, Conducting, and Reporting Research to Improve the Mental Health of Pregnant Women: The Voices of Investigators and IRB Members. AJOB Empir. Bioeth. 2014;5:25–43.

33. Madan A, Tracy S, Reid R, Henry A. Recruitment difficulties in obstetric trials: a case study and review. Aust. N. Z. J. Obstet. Gynaecol. 2014;54:546–52.

34. Myren M, Mose T, Mathiesen L, Knudsen LE. The human placenta--an alternative for studying foetal exposure. Toxicol. In Vitro. 2007;21:1332–40.

35. Hutson JR, Garcia-Bournissen F, Davis a, Koren G. The human placental perfusion model: a systematic review and development of a model to predict in vivo transfer of therapeutic drugs. Clin. Pharmacol. Ther. Nature Publishing Group; 2011;90:67–76.

36. Merkatz RB. Inclusion of women in clinical trials: a historical overview of scientific, ethical, and legal issues. J. Obstet. Gynecol. Neonatal Nurs. 1998;27:78–84.

37. Clayton EW. Liability exposure when offspring are injured because of their parents' participation in clinical trials. In: A.C. Mastroianni, R. Faden, D. Federman ., editor. Women Heal. Res. Ethical Leg. Issues Incl. Women Clin. Stud. Vol. 2, Work. Comm. Pap. Washington, D.C.: National Academies Press.; 1999. p. 103–12.

38. Merton V. The exclusion of pregnant, pregnable, and once-pregnable people (a.k.a. women) from biomedical research. Am. J. Law Med. 1993;19:369–451.

39. Kaposy C, Lafferty L. Overcoming liability concerns in vaccine trials involving pregnant women. Account. Res. 2012;19:156–74.

40. Mariner W. Compensation for Research Injuries. In: A. Matroianni, R. Faden, D. Federman ., editor. Women Heal. Res. Ethical Leg. Issues Incl. Women Clin. Stud. Vol. 2 Work. Comm. Pap. Washington, D.C.: National Academies Press; 1999.

41. Sahin L. The FDA Perspective on the Ethical Barriers of Conducting Research in Pregnant Women. AJOB Prim. Res. 2011;2:13–4.

42. Flannery, E., Greenberg S. Liability exposure for exclusion and inclusion of women as subjects in clinical studies. In: A.C. Mastroianni, R. Faden, D. Federman ., editor. Women Heal. Res. Ethical Leg. Issues Incl. Women Clin. Stud. Vol. 2, Work. Comm. Pap. Washington, D.C.: National Academies Press; 1999. p. 91–102.

43. Binik A, Weijer C, Sheehan M. Minimal Risk Remains an Open Question. Am. J. Bioeth. 2011;11:25–7.

44. Strong C. Minimal risk in research involving pregnant women and fetuses. J. Law. Med. Ethics. 2011;39:529–38.

45. Westreich D, Rosenberg M, Schwartz S, Swamy G. Representation of women and pregnant women in HIV research: a limited systematic review. PLoS One. 2013;8:e73398.

46. van der Graaf, Rieke; Groenwold, Rolf H. H.; Kalkman, Shona; Grobbee, Diederick E.; Van Delden JJM. From Justifying Inclusion to Justifying Exclusion of Study Populations: Strengths and Limitations. World Med. J. 2013;59:192.

47. Briggs GG, Polifka JE, Wisner KL, Gervais E, Miller RK, Berard A, et al. Should Pregnant Women be Included in Phase IV Clinical Drug Trials? Am. J. Obstet. Gynecol. Elsevier Ltd; 2015;

48. OHRP, DHHS. Code of Federal Regulations - Title 45: Public Welfare and Title 46: Protection of Human Subjects. 45 CFR 46. 2009;1–14.

49. Levine C, Faden R, Grady C, Hammerschmidt D, Eckenwiler L, Sugarman J. The limitations of "vulnerability" as a protection for human research participants. Am. J. Bioeth. 2004;4:44–9.

50. Gynecologists. AC of O and. Research involving women. ACOG Committee opinion No. 377. Obs. Gynecol. 2007;110:731–6.

51. Hurst S a. Vulnerability in research and health care; Describing the elephant in the room? Bioethics. 2008. p. 191–202.

52. Luna F, Vanderpoel S. Not the usual suspects: Addressing layers of vulnerability. Bioethics. 2013;27:325–32.

53. Macklin R. and Protection. 2003;17.

54. Luna F. Elucidating the concept of vulnerability: Layers not labels. Int. J. Fem. Approaches Bioeth. 2009;2:121–39.

55. Schroeder D, Gefenas E. Vulnerability: too vague and too broad? Camb. Q. Healthc. Ethics. 2009;18:113–21.

56. Ballantyne A, Rogers W . Pregnancy, Vulnerability, and the Risk of Exploitation in Clinical Research. In: Clinical Research Involving Pregnant Women. In: F Baylis, A Ballantyne ., editor. Clin. Res. Involv. Pregnant Women. Springer. Switzerland; 2016.

57. Godlovitch. Age discrimination in trials and treatment: old dogs and new tricks. Monash Bioeth. Rev. 2003;22:66–77.

58. Chervenak F a., McCullough LB. An Ethically Justified Framework for Clinical Investigation to Benefit Pregnant and Fetal Patients. Am. J. Bioeth. 2011;11:39–49.

59. Macklin R. Maternal-fetal conflict: An ethical analysis. Women's Heal. Issues. 1990;1:28–30.

# CHAPTER 3

## A QUALITATIVE STUDY ON ACCEPTABLE LEVELS OF RISK FOR PREGNANT WOMEN IN CLINICAL RESEARCH

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## ABSTRACT

**Background:** There is ambiguity with regard to what counts as an acceptable level of risk in clinical research in pregnant women and there is no input from stakeholders relative to such research risks. The aim of our paper was to explore what stakeholders who are actively involved in the conduct of clinical research in pregnant women deem an acceptable level of risk for pregnant women in clinical research. Accordingly, we used the APOSTEL VI study, a low-risk obstetrical randomised controlled trial, as a case-study.

**Methods:** We conducted a prospective qualitative study using 35 in-depth semi-structured interviews and one focus group. We interviewed healthcare professionals, Research Ethics Committee members (RECs) and regulators who are actively involved in the conduct of clinical research in pregnant women, in addition to pregnant women recruited for the APOSTEL VI case-study in the Netherlands.

**Results:** Three themes characterise the way stakeholders view risks in clinical research in pregnant women in general. Additionally, one theme characterises the way healthcare professionals and pregnant women view risks with respect to the case-study specifically. First, ideas on what constitutes an acceptable level of risk in general ranged from a preference for zero risk for the foetus up to minimal risk. Second, the desirability of clinical research in pregnant women in general was questioned altogether. Third, stakeholders proposed to establish an upper limit of risk in potentially beneficial clinical research in pregnant women in order to protect the foetus and the pregnant woman from harm. Fourth and finally, the case-study illustrates that healthcare professionals' individual perception of risk may influence recruitment.

**Conclusions:** Healthcare professionals, RECs, regulators and pregnant women are all risk adverse in practice, possibly explaining the continuing underrepresentation of pregnant women in clinical research. Determining the acceptable levels of risk on a universal level alone is insufficient, because the individual *perception* of risk also influences behaviour towards pregnant women in clinical research. Therefore, bioethicist and researchers might be interested in changing the perception of risk, which could be achieved by education and awareness about the actual benefits and harms of inclusion and exclusion of pregnant women.

## BACKGROUND

Underrepresentation of pregnant women in clinical research has led to a lack of evidence-based knowledge on drugs and treatments, resulting in suboptimal care or even under-treatment of pregnant women and their foetuses[1–4]. In recent years, bioethicists, pharmacologists and regulators have therefore argued that research participation of pregnant women is essential in order to achieve fair healthcare opportunities for pregnant women and their future children[2,5–10]. Various stakeholders have taken up the challenge of inclusion, for example by endorsing the view that pregnant women are presumed to be eligible for participation in clinical research[5,9,11]. Another (indirect) example can be found in the US Food and Drug Administration (FDA). Previously, it used the five pregnancy categories for drug-use in pregnant women, but after much critique that the categorisation was both over-simplistic and ambiguous[12,13], it has now been replaced by the Pregnancy and Lactation Labelling Rule (PLLR), designed to improve risk versus benefit assessment of drugs used in pregnant and nursing women. Although the Final Rule is applauded by many for its effort to improve maternal care and help healthcare professionals to adequately treat pregnant women[12,14,15], it is also likely to further expose how little human data exist for most drugs that are available in the United States (92.9% of pharmaceutical drugs obtain pregnancy data from animal studies; 5.2% have human pregnancy data)[12,16,17]. Some have articulated the hope that the new labelling will provide added incentives for the development and conduction of more clinical research in pregnant women[14].

However, research participation of pregnant women is a complex matter and certain difficulties remain unresolved. One of these issues concerns the ambiguity with regard to what counts as an acceptable level of risk in clinical research in pregnant women. Currently, what may count as an acceptable level of risk can often not clearly be deduced from ethical guidelines or regulations, or the information that is provided is conflicting. The US Code of Federal Regulations (CFR) is one of the few places in which the risks to pregnant women are addressed. According to the Common Rule, the risk to the foetus should be "the least possible for achieving the objectives of the research" (minimising risk) and in research that has no potential individual benefit the risks should "not be greater than minimal" (45 CFR 46). Contrarily, the new CIOMS draft guideline proposes that when the social value of the research for pregnant or lactating women or their foetus or infant is compelling, a minor increase above minimal risk might be permitted in research that has no potential for individual benefit (CIOMS draft 2015). One could expect that the proposed broader phrasing of the CIOMS draft guideline might allow for more clinical research than was previously conceivable.

At the same time, the literature indicates that stakeholders such as Research Ethics Committees (RECs) or researchers or clinicians might be hesitant to conduct research in pregnant women [18,19]. For example, it has been suggested that RECs often interpret

guidance on research in pregnant women in an overly cautious manner and act as gatekeepers to research[5,20,21]. In the scarce literature on the willingness of pregnant women to participate in research it is seems that they themselves are willing to participate for different reasons, for example because of altruistic or personal motives[22–25]. However, these assumptions about pregnant women's willingness are often based on hypothetical or retrospective research, while prospective research on their willingness is lacking. Moreover, there is no data on stakeholder's views relative to research risks, while their input is essential in order to create clarity about acceptable levels of risk. Gaining an understanding of existing views in the field is not only of interest to the research community, it could also direct guideline committees and researchers in their development of general strategies on acceptable levels of risk in pregnant women. The aim of our paper was therefore to explore what stakeholders who are actively involved in the conduct of clinical research in pregnant women deem an acceptable level of risk for pregnant women in clinical research, by way of a qualitative approach.

# METHODS

## Study design

We employed a qualitative study design using semi-structured interviews and one focus group to explore stakeholders' views on the topic of acceptable risks for pregnant women in clinical research.

## Sample and Setting

We sought to reach maximum variation in context and conducted the study among a variety of stakeholders whom were contacted by the researcher. We explored the topics through interviews with four groups: healthcare professionals, REC members, regulators and pregnant women. The healthcare professionals and REC members were recruited from two academic hospitals in the Netherlands, the University Medical Center Utrecht (UMC Utrecht) and the Academic Medical Center (AMC) in Amsterdam. We interviewed gynaecologists (n=3), gynaecologists-in-training (n=6), (research)midwifes (n=5), and REC members (n=5). Of the five REC members, two were also gynaecologists themselves. We also organised one focus group with regulators (n=5) from LAREB, a Dutch pharmacovigilance centre where we spoke with employees from the Teratogenic Information Service (TIS) department. The focus group lasted 1:15h. In addition, we interviewed two regulators from the Dutch Medicine Evaluation Board (MEB).

Finally, we recruited pregnant women (n=14) from the two previously mentioned academic hospitals in our qualitative study. Pregnant women were eligible when they were recruited for the APOSTEL VI study and had made their decision about enrolment in that study (see Box 1).

**Box 1. Case-study: APOSTEL VI**

The APOSTEL studies are a series of studies in the field of treatment of preterm labour within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (NVOG Consortium 2.0.). The APOSTEL VI study in particular assesses whether a cervical pessary prolongs pregnancy in women who have been admitted for threatened preterm birth but remained undelivered after 48 hours (http://www.studies-obsgyn.nl/apostel6). Women are randomly allocated to receive either a cervical pessary or no intervention. Women participating in the study were not perceived to be at an increased risk since previous studies using the pessary had shown no foetal adverse effects and the cervical pessary was not associated with increased neonatal or maternal morbidity and mortality (APOSTEL VI Research Protocol).

The APOSTEL VI study took place from November 2013 until September 2016, when the study was prematurely stopped following the advice of the Data and Safety Monitoring Board (DSMB). The premature cancellation was due to the fact that after interim analysis the intervention was unlikely to improve outcome, and maternal side effects were often present in the intervention arm.

Our qualitative study took place from March 2015 till September 2016 and we reached saturation before the APOSTEL VI itself was cancelled. In all our interviews it was therefore assumed that the APOSTEL VI would be completed.

We selected the APOSTEL VI study because it was the only obstetrical study in the Netherlands that at the time provided us access to the purposive sample of pregnant women recruited for a clinical study and the possibility to prospectively interview them. Accordingly, shortly after the women had decided about enrolment in the primary study, they were approached by research midwifes at the study sites. When they indicated an interest in our qualitative study they were later contacted by the researcher of the qualitative study and asked to participate in an interview. We interviewed the respondents after they were randomised to either perceive the pessary or no intervention. See Table 1 with characteristics of participants and Figure 1 with the flowchart of inclusion. The REC of the UMC Utrecht assessed the qualitative research proposal and issued a waiver for the project.

## Data collection

All participants were interviewed by one researcher (IvdZ). The focus group was conducted by two researchers (IvdZ and RvdG). Verbal informed consent and written informed consent in case of the pregnant women was obtained from all participants. Initial interview topics and questions were formulated after examination of the relevant literature and discussion with members of the team (see Table 2 for the general topic list and the Appendix for examples of extended topic lists). The semi-structured in-depth interviews were conducted according to a predefined topic list, however, according to the technique of constant comparative analysis, the interview topics evolved as the interviews progressed through an iterative process where the desired results is reached by repeating rounds

of analysis[26]. In case of healthcare professionals and pregnant women, we used the APOSTEL VI study as a starting point to ask respondents about acceptable levels or risks, however, we then extended the conversation to cover questions about acceptable levels of risk in clinical research in pregnant women in general. Interviews took place at the workplace or the home of the respondents. Thematic saturation was reached after 20 interviews. Data collection took place from March 2015 to September 2016.

### Data analysis

The analysis was carried out according to the thematic analysis method[27,28]. The focus group and the interviews were transcribed verbatim and the data was imported in the software programme Nvivo 10[29]. IvdZ independently coded the transcripts and through comparison across transcripts higher order themes were found. RvdG checked codes for consistency and the found themes were discussed at team meetings until a consensus was reached. To enhance the validity of our findings, we organised an expert meeting in the last phase of data collection. In the expert meeting we discussed our preliminary results and validated the data concerning the APOSTEL VI study.

## RESULTS

Based on the responses of the respondents, we were able to identify three main themes characterising the stakeholders' views on acceptable levels of risk in clinical research in pregnant women in general. Additionally, we identified one theme with respect to the APOSTEL VI case-study specifically. These themes emerged consistently within and across all interviews. Per theme, the views of the regulators, REC members, healthcare professionals and pregnant women are respectively presented. The first three themes concern observations based on the views of all respondents, while the theme relative to the APOSTEL VI study is based on the views of healthcare professionals and pregnant women specifically. Representative quotations were chosen in order to illustrate the identified themes (Table 3).

## ACCEPTABLE LEVELS OF RISK IN GENERAL

### I. Continuum of acceptable risks in general

The interviews demonstrated that regulators, REC members and pregnant women all start from the presumption of zero risk to the foetus. Nevertheless, the regulators from the pharmacovigilance centre were the ones most strongly adhering to the presumption. They said that clinical research that poses any risk should not be conducted and argued that when something is 'research', it automatically means that zero risk for the foetus cannot be unconditionally guaranteed and that risks should therefore be classified as high.

Interviews with regulators from the Medicine and Evaluation Board (MEB) and REC members demonstrated that they were willing to extend the level of acceptable research risks in case of research that has potential individual benefit, depending on the severity of the problem and the potential benefit. For example, REC members said that when zero risk is not attainable, the level of acceptable risk could be extended to "extremely low", "below 1%" or "1:1.000.000". Moreover, regulators from the MEB mentioned that inclusion of ill pregnant women in phase III trials with non-pregnant participants with a severe illness (such as rheumatic patients) would be acceptable because there would at least be knowledge about the effectiveness. Additionally, inclusion in phase IV post-authorisation studies (with medication originally labelled for different populations) was also suggested as an acceptable form of research in pregnant women with severe illnesses.

Pregnant women mentioned that they found the specific topic of weighing research risks very complex, but when further probed the initial answer "zero risk" changed in relation to different scenario's concerning research that has potential individual benefit and research that has no potential individual benefit. In scenarios where clinical research could potentially benefit the foetus, pregnant women mentioned that on behalf of the foetus they would consider participating in clinical research with higher risks ('higher' not further specified) than in clinical research with no potential personal benefit or than they would normally consider participating in.

During the interviews with healthcare professionals, it became clear that they, in their role as researchers, start from the presumption that pregnant women should be included in clinical research if there is a possibility for improvement of the current situation (for themselves or their group). Healthcare professionals specified the prerequisite for both observational and interventional research as follows: risks demonstrated to be to some extent foreseeable and low; a medication or intervention that is presumably safe and without long-term harmful effects; and a guarantee that women are not exposed to higher risks. The respondents mentioned that the prerequisites could be proven based on for example pre-clinical information, case-studies or database research. The basic assumption appeared to be that pregnant women in clinical research will either be better off, or that there is no effect. The tipping point of clinical research becoming unacceptable is when pregnant participants would have a chance of being *worse off.*

## II. Desirability of clinical research in pregnant women in general

The interviews with regulators and REC members showed that they generally understood the reasons why pregnant women are often excluded from all clinical research. These respondents actually questioned the need for inclusion. Concerns about potential risks as well as financial, ethical and methodological challenges were mentioned as underlying reasons. To illustrate, REC members explicated that although research that poses zero

or negligible risks for the foetus would not be unacceptable, they still prefer not to conduct it because it is deemed unnecessary. Moreover, the interviews showed that REC members did not recognise a responsibility to ask researchers about exclusion of pregnant women, or they found such questions irrelevant. Some said they would advise the exclusion of pregnant women since, in their words, it is the easiest way to exclude such vulnerable groups. Instead, both regulators and REC members argued that investing in observational database research through registration systems is the preferred way to gather the necessary scientific knowledge.

The interviews with healthcare professionals demonstrated that they believed that clinical research in pregnant women is desirable in order to increase the evidence-base, although they did mention that researchers should in principle be more careful with pregnant women in comparison with non-pregnant research participants. When asked about inclusion of their own patients, healthcare professionals appeared to be more reluctant. Reasons that were mentioned were both practical (acute care has priority over clinical research) but also motivational, for example not believing a study is in the best interest of a patient or not believing in the intervention. Moreover, the healthcare professionals (as well as the regulators form the MEB) noticed that the lack of scientific knowledge concerning pregnant women is sometimes overrated or could be gathered in another way.

From the interviews with pregnant women, it became evident that their starting point in daily life was risk avoidance. For example, the women were careful with their food intake, they were extra cautious in traffic, and they would avoid taking any medication (including painkillers or natural vitamin supplements). The desire to avoid any risk for the foetus also extended to participation in clinical research, relative to which women reported that they would generally not participate in invasive clinical research because of potential risks. Research that would only pose risks to themselves and not to their foetus would be less problematic, similar to research that would encompass potential gain for themselves or the foetus. In relation to non-invasive research which posed no risks to the foetus (such as blood pricks or questionnaires), women reported an interest in participation in order to help other pregnant women.

## III. Interest in an upper limit of acceptable risk

Particularly in relation to acceptable risks in research that has potential individual benefit, the topic of an upper limit of risks emerged throughout the interviews. All respondents recognised the need for an upper limit of risks in light of possible harm to the foetus and potential misconceptions in research that has potential individual benefit, however, no one could explicitly stipulate a maximum. An example of an upper limit that was given was that in pregnant women one would never test a medication for safety. When respondents talked about potential misconceptions, they referred to their belief of pregnant women's trust in the system and their idea that pregnant women would be

willing to take excessive risks for their child. For instance, the healthcare professionals said that women appeared to have a somewhat excessive degree of intrinsic trust that their physician would never ask anything potentially harmful or not beneficial. And most women believed that research for which they as pregnant women were recruited or would be recruited for in the Netherlands would never actually expose them to any real risk in clinical research.

## ACCEPTABLE LEVELS OF RISKS IN APOSTEL VI SPECIFICALLY

### I. Perceived risks of APOSTEL VI study

The interviews demonstrate that although the REC of the UMC Utrecht classified the APOSTEL VI study as a low-risk study, healthcare professionals' opinions on the risk that the APOSTEL VI posed differed. Most healthcare professionals classified the APOSTEL VI as no risk (n=4) or extremely low or low risk (n=4), because the intervention is not a medication and the device is proven to be safe for the foetus and does not lead to increased risk during pregnancy. Other healthcare professionals classified the APOSTEL VI as a potential high risk study (n=3), because there is not enough knowledge and the cervical pessary could actually affect the uterus in a negative way (e.g. by creating an inflammation which would then lead to preterm birth), thus comprising an increased risk. Others were unsure or had no opinion (n=3). Furthermore, an overall scepticism with regard to the actual working mechanism of the pessary; concerns about the pessary itself ("it's not nothing"/"it's quite a thing"); and the extra internal exam (only for UMC Utrecht) surfaced throughout the conversations. But despite concerns about the study, the respondents mentioned that there was a distinction between "pointless" or "harmful" studies. Since the APOSTEL VI was not perceived to be harmful, in light of the current lack of knowledge on preventing preterm birth, most healthcare professionals were generally positive about inclusion of pregnant women in the APOSTEL VI study.

The interviews with pregnant women indicated that most perceived the APOSTEL VI to pose zero risk (n=12) because enrolment would not negatively impact the development or growth of their child. The reasoning was that a pessary would not reach and therefore not affect the foetus (in contrast to e.g. a medication in the bloodstream), and that the device was safe because it was already used by other (pregnant) women. Moreover, the pregnant women mentioned that they found the burdens such as pain during the placement of the pessary and increased vaginal discharge relatively small. Two women who did not enrol in APOSTEL VI mentioned potential risk for the foetus as one of the reasons for not participating (because of the extra internal exam which they believed might cause a preterm birth), while one woman who did enrol also considered the risks to the foetus but ultimately decided to enrol because it would always be possible to remove the pessary.

## DISCUSSION

Our qualitative study shows that among stakeholders who are actively involved in the conduct of clinical research in pregnant women in the Netherlands, risk-adversity is the main characteristic dominating the discourse on acceptable levels of risks. Risk-adversity is demonstrated in two ways. First, the risk-adverse attitude is so fundamentally present among stakeholders (including pregnant women themselves), that the need for the conduct of clinical research in pregnant women is questioned altogether. This possibly explains why pregnant women have even been excluded from research that posed no risk at all[2,30,31]. Correspondingly, stakeholders indicate a preference for zero risk for the foetus if research does take place. And, when zero risk is not achievable, stakeholders propose to establish an upper limit (not further specified) in potentially beneficial research in order to protect the foetus from harm and the pregnant woman from potential misconceptions about research participation. Currently, upper limits of risk are primarily set in particular types of research that has no potential individual benefit, with persons who are incapable of giving informed consent. However, for research with children and incompetents, no upper limits of risk are set when the research has the potential for individual benefit[32]. The interest in an upper limit for research that has the potential to benefit pregnant women is thus even more stringent for pregnant women than for research with persons who are incapable of giving informed consent. Since there is no immediately obvious reason why pregnant women would be incompetent to make a decision about research participation[33], the interest in an upper limit might be another illustration of stakeholder's risk adversity towards clinical research in pregnant women.

Second, the risk-adverse attitude also influences the actual conduct of clinical research in pregnant women. At first, there appeared to be a difference between regulators, pregnant women and REC members on the one hand, and healthcare professionals on the other, where the latter seem more willing to include pregnant women for potential group benefits for their population. However, while healthcare professionals in their role as researcher report a willingness to advance inclusion of pregnant women in clinical research, in practice they are also reluctant to include their patients and sometimes even resort to gatekeeping, the fashion where eligible participants are prevented from entering research[4,34,35]. It appears that healthcare professionals make their individual judgements about risks and that they sometimes perceive minimal risk as high risk. The personal opinion of a study combined with the perception of risk seems to influence behaviour, as illustrated by our case-study. The now prematurely cancelled APOSTEL VI was originally classified as a low risk study, but it was actually rejected by a number of academic centres due to the perceived high risks that the intervention would pose. Moreover, healthcare professionals from centres where the case-study was approved made individual judgements on the risk and voiced various concerns with regard to the study, in our case doubts about the pessary as an intervention. A lack of equipoise concerning an intervention has been suggested earlier as a reason for hampering recruitment[36]

(also suggested in relation to the APOSTEL IV study[37]). Moreover, it could also explain why even minimal risk studies often get cancelled. Cancellation can happen because of various reasons such as financial or safety issues, but also because of disappointing patient recruitment rates which might be traced back to gatekeeping by healthcare professionals[36] (APOSTEL IV study[37] and possibly also the APOSTEL VI study).

Bioethicists believe that more regulatory clarity on accepted levels of risk in clinical research in pregnant women may result in fair inclusion of pregnant women[5,38]. While a universally accepted risk standard might indeed contribute to fair inclusion by taking away ambiguity with regard to what kind of research would be acceptable, our analysis shows that a classification of risk alone is not sufficient since the *perception* of risk also strongly influences behaviour. In order for universal risk standards to be applied in practice, bioethicists might therefore be interested in stimulating an alteration in the framework of thought on risk for pregnant women. A possibility would be to address the feasibility of a study beforehand, by aligning the risk classification between RECs and healthcare professionals. Additionally, educating REC members and healthcare professionals to internalise the content of present guidelines (most guidelines already allow for certain risks) and to equally focus on research benefits, next to risks, and on the need for evidence-based clinical care and treatment could be worthwhile[5,19,39]. Moreover, raising awareness about the actual need for clinical research in pregnant women could stimulate patient advocacy, which, as demonstrated by the increased conduct of research in children or certain orphan diseases after active involvement of patients, could be an effective method[40], also taking into consideration that pregnant women reported altruistic motives to participate in non-invasive studies with no risk to the foetus. Finally, guideline committees and researchers may want to take notice of the discrepancies about risk acceptability and the reigning precautionary principle when they develop further guidance on clinical research in pregnant women.

## LIMITATIONS

This qualitative study has a number of limitations. First, we interviewed stakeholders regarding only the Dutch situation and from an academic setting, it is possible that the results are different in other countries and other settings, thus challenging the generalizability of the findings. Second, we did not include any pharmaceutical companies in our stakeholder list. Since we realise that pharmaceutical companies are an important stakeholder we contacted seven organisations with a request to participate, but unfortunately we were unable to conduct any interviews since they did not respond or did not want to participate in our study. Third, the saturation number of twenty interviews was reached on a group level, but not always on sub-group level. For example, regarding the case-study we only interviewed healthcare professionals and pregnant women. As such, our inter-group comparisons are less valid than our group analyses. Finally, we only

included pregnant participants who were enrolled in the APOSTEL VI study, a group that consists of women that become sick during their pregnancy. We selected the APOSTEL VI study because it was the only obstetrical study in the Netherlands that at the time provided us access to the purposive sample of pregnant women recruited for a clinical study and the possibility to prospectively interview them. Future research should also aim to include research subjects from the group of sick women who become pregnant and participants recruited for non-obstetrical studies. We attempted to include women from the latter group, but all three trials we collaborated with were unfortunately cancelled.

## CONCLUSIONS

Stakeholders generally deem clinical research in pregnant women only acceptable when the risks to the foetus are zero or very close to zero. Although there seems to be a conflict between healthcare professionals in their role as researchers (wanting to advance the interest of the group) and RECs, regulators and pregnant women (wanting to safeguard the interest of the individual), in practice everybody acts risk-adverse in the context of research. The risk-adverse attitude probably explains the continuing underrepresentation of pregnant women in clinical research. Consequentially, fair inclusion of pregnant women may not be achieved by determining the acceptable levels of risk alone, because the *perception* of risk also influences stakeholders' behaviour. Therefore, bioethicists and researchers might be interested in changing the perception of risk, for example by education of professionals and by stimulating patient advocacy amongst pregnant women. In addition, guideline committees and researchers may want to take notice of the discrepancies about risk acceptability when they develop further guidance on clinical research in pregnant women.

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## FIGURES AND TABLES

**Table 1a.** Demographic characteristics professionals

| Characteristics professionals | (n=26)[a] |
|---|---|
| **Gender** | |
| Male | 11 |
| Female | 15 |
| **Age** | |
| 25–40 | 13 |
| 41–55 | 7 |
| > 55 | 6 |
| **Experience at present job (years)** | |
| <5 | 13 |
| 5–10 | 6 |
| 11–15 | 4 |
| 16–20 | 3 |
| **Profession** | |
| Gynaecologist | 3 |
| Gynaecologist-in-training[b] | 6 |
| Midwife[c] | 5 |
| REC member[d] | 5 |
| Regulator/knowledge centre | 7 |

[a] 5 regulators from the focus group, 21 interviewees
[b] 1 gynaecologist-in-training was a gynaecologist-not-in-training (ANIOS)
[c] 3 research midwifes from academic hospitals
[d] 2 REC members were also gynaecologists

**Table 1b.** Demographic characteristics pregnant women

| Characteristics pregnant women | (n=14) |
|---|---|
| **Age** | |
| <25 | 1 |
| 25–30 | 5 |
| 31–40 | 8 |
| **Parity** | |
| Nulliparous | 9 |
| Primiparous | 2 |
| Multiparous | 3 |

**Table 1b.** (continued)

| **Characteristics pregnant women** | **(n=14)** |
|---|---|
| **Gestational age (weeks)** | |
| 25–30 | 5 |
| 31–35 | 9 |
| **Education** | |
| Highschool | 3 |
| Lower vocational (MBO) | 3 |
| College (HBO/WO) | 4 |
| Graduate degree | 4 |
| **Partner** | |
| Married | 5 |
| Living together | 9 |
| Single | 0 |
| **Enrolment in study** | |
| Participating in Apostel VI | 8 |
| *Recruited from UMC Utrecht* | *3* |
| *Recruited from AMC* | *5* |
| Not participating in Apostel VI | 6 |
| *Recruited from UMC Utrecht* | *6* |
| *Recruited from AMC* | *0* |

**Table 2.** General Topic List

| |
|---|
| Balancing risks and potential benefits in general; |
| Whether there is a potential conflict between the mother and the foetus; |
| Whose interests should prevail; |
| Acceptable level of risks in certain types of research or in different phases; |
| Societal benefit versus therapeutic benefit; |
| Suggestions how to assess acceptability of risks; |
| Relation with acceptable research risks for children; |
| Balancing risks and potential benefits in the APOSTEL VI study; |
| Perceived risks of the APOSTEL VI study. |

**Figure 1.** Flowchart of Inclusions

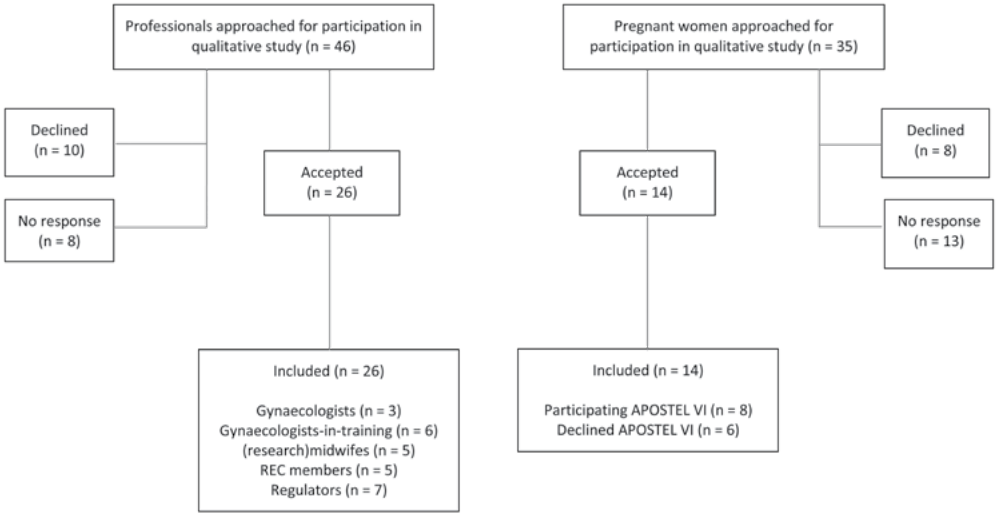


**Table 3.** Representative quotations

| Theme | Quotations* |
|---|---|
| **3a. Acceptable levels of risk in general** | |
| Continuum of acceptable risks in general | **REG00, focus group LAREB:** But with regard to the foetus you want to accept nothing, risks have to be zero and you cannot guarantee that [..]. |
| | **PW07, participating in APOSTEL VI:** There is never an acceptable risk for the foetus, never. |
| | **REC05, gynaecologist:** A pregnant woman is very much protected in our society. After all, a pregnant woman is a little sacred. I can understand that. |
| | **HCP09, gynaecologist:** You should at least demonstrate that you have no reason to assume that it [research] is unsafe. |
| | **HCP12, gynaecologist-in-training:** If you run the risk that if you stop with that medication the mother dies, that's a different story than when you want an alternative for a very safe medication simply because the pills taste bad or they are big or whatever. |
| | **PW08, not participating in APOSTEL VI:** If you face a huge growth retardation and it will not change during the course of your pregnancy and you can participate in a study that potentially offers a remedy, then I think that I would also be more willing to go further […]. |
| | **PW11, participating in APOSTEL VI:** The most important thing is whether there are risks for the baby. The baby needs to be able to grow optimally and survive the pregnancy. And as a mother I would accept quite a lot for that myself. Unless the risks are really dangerous [e.g. resulting in serious illness or death]. |

**Table 3.** (continued)

| Theme | Quotations* |
|---|---|
| Desirability of clinical research in pregnant women in general | **REC01, legal expert:** When a researcher has already decided that he doesn't want to expose a certain category of research subjects to the intervention or the medication or the risks of a study, well, then who am I as a REC member to tell him that maybe he should do that? |
| | **REC03, gynaecologist:** If it's unnecessary than of course it's always more sensible… Because that is something you notice, pregnancy always raises extra questions that make you think longer about whether it is acceptable or not. So for me I would say, let's just keep them out if it is not strictly necessary to include them. |
| | **REG02, MEB member:** And it's a question whether it always needs to be proven, because gathering the evidence requires a lot of pregnant women, with all the risks that entails. |
| | **HCP06, gynaecologist-in-training**: There is often so much happening when someone comes in and then you think, "oh yes, the trial. That is really the last priority. |
| | **HCP10, research midwife:** I said that I wouldn't counsel for this study [...]. You shouldn't go beyond your own limits. I'm really not going to do something that I cannot support. |
| | **PW12, not participating in APOSTEL VI:** Why would you take a risk if you don't have to, or if there is nothing to gain? I would not take such a risk for science. |
| Interest in an upper limit of acceptable risk | **HCP05, gynaecologist:** There should be a maximum risk for the foetus, but where do you draw the line? |
| | **HCP10, research midwife:** It worries me because if you as a caregiver offer this, and that woman is desperate enough and she thinks my child is going to die this is my last resort, then maybe she doesn't look beyond delivering a child that is alive. |
| | **PW05, participating in APOSTEL VI:** They won't allow you to take the big risks anyway. There are laws and regulations for that. […] It is offered for a reason and if they offer it, well than I guess that the risks won't be so high. |
| | **PW11, participating in APOSTEl VI**: I trust that most studies are to some extend safe, they won't allow you to take a lot of risk here [in the Netherlands]. That is a consideration that initially makes me say yes quite fast. Because if there is too much risk than it wouldn't be conducted here. |
| **3b. Acceptable levels of risk in APOSTEL VI specifically** | |
| Perceived risks of APOSTEL VI study | **HCP06, gynaecologist-in-training:** A pessary is low risk, because you don't have the connection with the child. |
| | **HCP03, gynaecologist-in-training:** We insert a device that is foreign to the body of which we know that it gives a local reaction, and if that is an inflammatory reaction it might just as well result in premature birth. So therefore it could also actually be a higher risk. |

**Table 3.** (continued)

| Theme | Quotations* |
|---|---|
| | **HCP04, gynaecologist-in-training:** Why would you do an intervention, why would we do something that has not been proven? I also wonder what the working mechanism of the pessary is, nobody can tell me, not even the big advocates. |
| | **HCP14, gynaecologist:** I don't believe in the intervention at all, and luckily I don't have to counsel for the study, but I do think that if you don't know if something works the best way to find out is to conduct a study. |
| | **PW03, participating in APOSTEL VI:** They just don't know if it [the pessary] results in an extended gestational time. But real risks, no I don't think those were described. |
| | **PW14, participating in APOSTEL VI:** It's very clear in the study that the risks are really very low, and that it won't result in a premature birth which is the most important thing. |

* Quotations are sometimes slightly modified in order to enhance readability.

**Table 4.** Overview of risk continuum

| Stakeholder | What level of research risk? (for the foetus) | What type of research is acceptable? | When is research acceptable? |
|---|---|---|---|
| Regulators (LAREB) | Zero | None | Never |
| | Zero | Observational | Registries |
| | Close to zero | Phase IV | Post-authorisation studies with off-label medications already used by pregnant women |
| Regulators (MEB) | Zero | Observational | Registries |
| | Low but with exceptions | Phase III and/or Phase IV | Research that has potential individual benefit with high potential direct benefit for severely ill pregnant woman |
| RECs | Extremely low (below 1%) | Observational | Research that is not too demanding |
| | | Intervention | Research that has potential individual benefit with high potential direct benefit for severely ill pregnant woman |
| Pregnant women | Zero | Observational | Not too demanding/useful for other women |
| | Minimal | Intervention | Research that has potential individual benefit with high potential direct benefit for the child |
| | More than minimal | | |
| Healthcare professionals | Low, at least not higher in comparison to not participating | Observational | Research that has no potential individual benefit and research that has potential individual benefit |
| | | Intervention | |
| | | Phase II | |
| | | Phase III | Benefit for individual or group |
| | | | "no harm in trying principle" |

## REFERENCES

1. Zajicek A, Giacoia GP. Obstetric clinical pharmacology: coming of age. Clin. Pharmacol. Ther. 2007;81:481–2.
2. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
3. Macklin R. Enrolling pregnant women in biomedical research. Lancet. 2010. p. 632–3.
4. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. Clin. Infect. Dis. 2014;59 Suppl 7:S400-7.
5. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
6. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
7. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
8. EMA (European Medicines Agency). Guideline of the exposure to medicinal products during pregnancy: need for post-authorisation data. [Internet]. 2005 [cited 2016 Mar 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf
9. CIOMS & WHO. International ethical guidelines for biomedical research involving human subjects. [Internet]. 2002. [cited 2016 Mar 25]. Available from: http://www.cioms.ch/publications/layout_guide2002.pdf.
10. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
11. ORWH (United States. Department of Health and Human Services, Public Health Service, National Institutes of Health O of R on WH. Enrolling pregnant women: Issues in clinical research. 2011.
12. Danesh MJ, Murase JE. The new US Food and Drug Administration pregnancy and lactation labeling rules: Their impact on clinical practice. J. Am. Acad. Dermatol. American Academy of Dermatology, Inc.; 2015;73:310–1.
13. Addis a, Sharabi S, Bonati M. Risk classification systems for drug use during pregnancy: are they a reliable source of information? Drug Saf. 2000;23:245–53.
14. ACOG Statement on FDA Pregnancy Labeling Final Rule - ACOG [Internet]. [cited 2016 May 24]. Available from: http://www.acog.org/About-ACOG/News-Room/Statements/2014/ACOG-Statement-on-FDA-Pregnancy-Labeling-Final-Rule
15. Ramoz LL, Patel-Shori NM. Recent changes in pregnancy and lactation labeling: Retirement of risk categories. Pharmacotherapy. 2014. p. 389–95.
16. Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. Clin. Pharmacol. Ther. 2008;83:181–3.
17. Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, Van Den Anker JN. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. Am. J. Obstet. Gynecol. 2014. p. 690.e1-690.e11.
18. Tooher RL, Middleton PF, Crowther CA. A thematic analysis of factors influencing recruitment to maternal and perinatal trials. BMC Pregnancy Childbirth. 2008;8:36.
19. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. Elsevier Inc.; 2013;23:e39–45.
20. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton J a. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. 2013;23:e39-45.

21. Levine RJ. IRB perspective on inclusion of pregnant women in clinical research. ORWH Work. Enrolling pregnant women Issues Clin. Res. An ORWH 20th Anniv. Event. Bethesda, MD: National Institutes of Health; 2011. p. 37–43.
22. van der Zande ISE, van der Graaf R, Browne JL, van Delden JJM. Fair Inclusion of Pregnant Women in Clinical Research: A Systematic Review of Reported Reasons for Exclusion. In: F Baylis, A Ballantyne., editor. Clin. Trials Involv. Pregnant Women. 2016. p. 65–94.
23. Kenyon S. Participating in a trial in a critical situation: a qualitative study in pregnancy. Qual. Saf. …. 2006;15:98–101.
24. Oude Rengerink K, Logtenberg S, Hooft L, Bossuyt PM, Mol BW. Pregnant womens' concerns when invited to a randomized trial: a qualitative case control study. BMC Pregnancy Childbirth. 2015;15:207.
25. Rodger MA, Sc M, Makropoulos D, Sc B, Walker M, Keely E, et al. Participation of Pregnant Women in Clinical Trials : Will They Participate and Why ? 2003;20:69–76.
26. Charmaz K. Constructing Grounded Theory: A Practical Guide through Qualitative Analysis. Constr. Grounded Theory A Pract. Guid. Through Qual. Anal. 2006. p. SAGE Publications Ltd.
27. Braun V, Clarke V. Using thematic analysis in psychology. Qual. Res. Psychol. 2006;3:77–101.
28. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med. Res. Methodol. 2008;8:45.
29. QSR. NVivo 10 research software for analysis and insight [Internet]. www.qsr Int. 2014. Available from: http://www.qsrinternational.com/products_nvivo.aspx?utm_source=NVivo+10+for+Mac
30. Cain J, Lowell J, Thorndyke L, Localio a R. Contraceptive requirements for clinical research. Obstet. Gynecol. 2000. p. 861–6.
31. Westreich D, Rosenberg M, Schwartz S, Swamy G. Representation of women and pregnant women in HIV research: a limited systematic review. PLoS One. 2013;8:e73398.
32. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-Related Research Involving Humans. Geneva, Switzerland: Council for International Organizations of Medical Sciences. [Internet]. 2016. Available from: http://www.cioms.ch/ethical
33. van der Zande ISE, van der Graaf R, Oudijk MA, van Delden JJM. Vulnerability of pregnant women in clinical research. J. Med. Ethics. 2017;medethics-2016-103955.
34. Sharkey K, Savulescu J, Aranda S, Schofield P. Clinician gate-keeping in clinical research is not ethically defensible: an analysis. J. Med. Ethics. 2010;36:363–6.
35. van der Zande ISE, van der Graaf R, Oudijk MA, van Vliet-Lachotzki EH, van Delden JJM . A Qualitative Study on Stakeholders' views on the Participation of Pregnant Women in the APOSTEL VI study: a low-risk obstetrical RCT. submitted.
36. Madan A, Tracy S, Reid R, Henry A. Recruitment difficulties in obstetric trials: a case study and review. Aust. N. Z. J. Obstet. Gynaecol. 2014;54:546–52.
37. Nijman TAJ, van Vliet EOG, Naaktgeboren C a., Oude Rengerink K, de Lange TS, Bax CJ, et al. Nifedipine versus placebo in the treatment of preterm prelabor rupture of membranes: a randomized controlled trial. Eur. J. Obstet. Gynecol. Reprod. Biol. Elsevier Ireland Ltd; 2016;205:79–84.
38. Foulkes MA, Grady C, Spong CY, Bates A, Clayton JA. Clinical research enrolling pregnant women: a workshop summary. J. Womens. Health (Larchmt). 2011;20:1429–32.
39. Braunholtz D a., Edwards SJL, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." J. Clin. Epidemiol. 2001;54:217–24.
40. Terry SF, Terry PF, Rauen K a, Uitto J, Bercovitch LG. Advocacy groups as research organizations: the PXE International example. Nat. Rev. Genet. 2007;8:157–64.

# CHAPTER 4

## HOW SHOULD THE PRECAUTIONARY PRINCIPLE APPLY TO PREGNANT WOMEN IN CLINICAL RESEARCH?

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*Submitted*

## ABSTRACT

The precautionary principle is often invoked in relation to pregnant women and may be one of the underlying reasons for the continuous underrepresentation of pregnant women in clinical research. The precautionary principle has a specific appeal relative to clinical research in pregnant women, because potential foetal harm as a result of research participation is considered to be serious and irreversible, one of the prerequisites to invoke the precautionary principle. In our paper, we explore through conceptual analysis whether and if so how the precautionary principle should apply to pregnant women. We will argue that the precautionary principle is a decision-making strategy which can underlie risk-benefit decisions in clinical research. We establish that, as such, the precautionary principle can be applied to pregnant women in clinical research.

However, the current application of the precautionary principle to this subpopulation is a strong one, leading to the promotion of two extremes: absolute exclusion or, less often, absolute inclusion of pregnant women. The current interpretation is thus paralysing the situation, where the word 'pregnant' is automatically linked to halting any study in which pregnant women may face risks, even when there are also benefits. In order to change the current situation, a shift towards weak precautionary thinking is necessary. A weak interpretation leaves room for contextualisation of situations, it takes a broad scope of harms and alternatives into account, it requires a clear definition of a threat and it necessitates that the harms of the precautionary measure itself are taken into account. It is expected that shifting towards a weak interpretation of the precautionary principle will change the current paralysing situation by shifting the attention away from automatic extreme precaution to a focus on balancing harms and potential benefits of inclusion of pregnant women in clinical research.

## BACKGROUND

There has been a longstanding call for fair inclusion of pregnant women in clinical research, motivated by the need to develop effective treatments for women during pregnancy and prevent suboptimal care of pregnant women with acute or chronic obstetric or non-obstetric illnesses[1,2]. Not including pregnant women in clinical research leads to two problems. On the one hand, there is a problem of a high percentage of 84–99 % women who take, often off-label prescribed, medications for which there is no substantial data on safety, efficacy, and foetal risk evaluation, leaving pregnant women and clinicians in a difficult position[3–5]. For example, the drug ondansetron is currently prescribed off-label to treat extreme nausea and vomiting, while evidence is contradictory: some evidence is indicating no significant birth defects, while other evidence is pointing to birth defects[6]. On the other hand there is a problem of under-treatment of illnesses, which can also have negative effects. For example, poorly treated asthma and untreated depression is problematic for pregnant women and foetuses, associated with premature birth, low birth weight and foetal growth restriction and, in case of asthma, a higher risk of hypertension and preeclampsia[1,7]. However, despite the longstanding call for fair inclusion of pregnant women in research projects, they remain underrepresented[8,9].

The precautionary principle may be one of the underlying reasons for the continuous underrepresentation of pregnant women, as it is often invoked in relation to pregnant women[1,2,10]. To illustrate, the 2011 National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) workshop report noted: "Pregnancy may be the last remaining condition for the application of the precautionary principle even when a clinical practice or policy could be updated"[11]. And more recently, Angela Ballantyne stated: "Pregnancy continues to be dominated by the precautionary principle, advocating for the routine exclusion of pregnant women from medical research, particularly intervention studies, on the grounds of foetal vulnerability"[12]. The precautionary principle has a specific appeal relative to clinical research in pregnant women, because potential foetal harm as a result of research participation is considered to be serious and irreversible, one of the prerequisites to invoke the precautionary principle. Additionally, there may be secondary reasons for the particular appeal of the precautionary principle to pregnant women. An example is socio-cultural reasoning about risk in pregnancy in general, advocating a 'better safe than sorry' approach in relation to issues such as consumables or the use of technical devices that pregnant women are advised to avoid just to be sure, which might extrapolate to reasoning about risk in clinical research[1,2]. Moreover, there is a historical reason in the collective memory of tragedies such as thalidomide and diethylstilboestrol (DES), which may have resulted in a reluctance to include pregnant women in clinical research[7,10]. Furthermore, there may also be financial reasons that advocate precaution in the face of liability fears, especially present among manufacturers[13,14].

Concerns about foetal wellbeing are valid and it seems logical to start from a precautionary standpoint in light of the uncertainties and potential serious and irreversible harm surrounding clinical research in pregnant women. At the same time, assuming that risks are present and excluding pregnant women without looking at the costs and potential benefits of exclusion or inclusion may have the opposite effect, causing pregnant women to be both unsafe and sorry. The aim of our paper is to explore through conceptual analysis whether and if so how the precautionary principle should apply to pregnant women. First, we provide a brief overview of the literature on the origins and basic characteristics of the precautionary principle itself. Second, we analyse the current application of the precautionary principle to pregnant women. Third and finally, we discuss how a shift towards weak precautionary thinking is necessary. A weak interpretation applied to pregnant women in clinical research may shift the attention away from automatic extreme precaution to a focus on balancing harms and potential benefits of inclusion of pregnant women in clinical research.

## ANALYSIS OF THE PRECAUTIONARY PRINCIPLE

The precautionary principle was initially introduced in the early 1970's in light of environmental policy-making, by people favouring proof of safety to human health and environment before adapting new technologies[15]. The precautionary principle thus involves a reversal of the burden of proof, demanding a reasonable demonstration of the absence of risk and proof of safety by the proponents of a new technology[16,17]. In essence, the precautionary principle is a concept about plausibility and reasonableness, which applies to decisions under ignorance where there are threats that have not yet materialised into harm[18,19]. The precautionary principle involves a judgement and a normative choice relative to substantial values we attach to a certain state of affairs that is threatened[19,20]. The widespread endorsement of the precautionary principle was motivated by the idea that traditional risk-benefit analyses were flawed and not apt to deal with large scale uncertainty and global threats[21]. Ever since, many interpretations of the principle have developed and are currently applied in the broader field of public health.

In common language, the precautionary principle is best translated as "*in dubio abstine*", the Hippocratic adage, or "better safe than sorry". The former can only be interpreted as a requirement for inaction in the face of uncertainty, and is, in the context of healthcare, often based on the interest of the individual. The latter can theoretically result in a requirement for inaction, as well as action. An example of the requirement for action is the commonly quoted formulation of the precautionary principle of in Wingspread Declaration: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken, even if some cause-and-effect relationships are not established scientifically" (Wingspread Declaration, 1998). Here, the Wingspread Declaration is mandating decision-makers to take precautionary action

in the face of uncertainty, in light of a global threat. Consequently, the precautionary principle can result in precautionary inaction (e.g. bans on certain potentially harmful activities in order to be on the safe side) as well as precautionary action (e.g. promotion of certain precautionary measures) aiming to prevent a threat.

The basic characteristic of any interpretation of the precautionary principle is the dual trigger: i) if there is a potential for serious and irreversible harm (ia) and scientific uncertainty about the magnitude (ib), then some kind of ii) precautionary action or inaction *before* there is strong proof of the harm is required (Sandin's *if-clause*). Schematically portrayed, the precautionary principle necessitates[16,18,21,22]:

*i. a damage condition: some kind of adverse event, a threat of harm to an issue that is deemed to be valuable;*

*ii. a knowledge condition: an extent of scientific plausibility that this event will occur, but uncertainty about the impact and causality, and;*

*iii. a remedy: the precautionary response (action or inaction) that should be taken if the previous two conditions are present.*

It is with regard to the remedy that the interpretations of the precautionary principle differ. Roughly, a distinction between strong and weak interpretations can be made. Strong interpretations prioritise one goal over all others and require that precautionary action or inaction should be taken whenever there is any possibility, no matter how small, that harm may occur, without any consideration of potential benefits or economic costs. On the contrary, weak interpretations aim to strike a balance between different factors and allow but do not require precautionary action or inaction in the face of uncertainty. Additionally, there must be some evidence about the likelihood and severity of consequences. A common criticism is that strong interpretations are too extreme and narrow-mindedly paralyse progress, whereas weak interpretations are less controversial but too vague to be useful[23,24]. Notwithstanding the critiques, we propose that the precautionary principle, when viewed as a strategy for decision-making, can be useful.

We argue that, as a decision-making strategy, the precautionary principle underlies risk-benefit decisions in cases of scientific uncertainty and threats to something we deem valuable. The precautionary principle can never replace a traditional risk-benefit analysis. Instead, the precautionary principle may underlie traditional risk-benefit analyses that depend on a combination of for example statistical evidence and scientific understanding of causal relationships in order to make some sort of quantitative risk assessment with additional criteria. The precautionary principle assumes that probabilistic assessments of risk are inadequate (because there are also incalculable possible threats) and must be supplemented or replaced by other criteria[25]. Additionally, following the precautionary principle, we assume that risks do not have to be neutral but may be weighed differently based on moral importance[26].

While the precautionary principle is often related to environmental reasoning, the principle may also be used as a decision-making strategy underlying risk-benefit decisions in clinical research. To illustrate, Research Ethics Committees (RECs) may at times use the precautionary principle when they are confronted with large scale scientific uncertainty and conflicts between the risk for the individual and the potential benefits for the group. RECs may handle this uncertainty by adopting a version of the precautionary principle which implicates a willingness to take action (or inaction) in advance of full scientific proof of evidence or of the need of the proposed action[27]. RECs are advised to take all possible harms into account, including unquantifiable harms such as ethical risks to science and society, and then focus their discussion on what would constitute a reasonable response[28,29]. As such, the reasoning that underlies the protection of research subjects may be viewed as precautionary[30].

As an underlying strategy for decision-making, there are certain normative choices and commitments that have to be established before further specification of the principle[20]. One choice relates to the determination of the generally accepted level of risk which ultimately determines the threshold of the damage condition. In this case, where the precautionary principle is introduced to the regulatory context of the traditional risk-benefit analyses in clinical research, the generally acceptable level of risk for pregnant women will be minimal risk or a minor increase over minimal risk[31,32]. Following the absolute minimal risk standard, minimal risk implies that risks are not more than healthy pregnant women and foetuses ordinarily encounter in daily life or during the performance of routine clinical care; a minor increase over minimal risk constitutes a minor increase over that threshold. Another normative commitment is that serious and irreversible damage should be anticipated. As such, this commitment reflects a plea to narrow the scope of the lack of knowledge. A last commitment regards the norm to take pre-emptive actions in order to protect the thing we deem valuable. In the concrete, pre-emptive actions could include phase-outs or bans or a request for extra scientific information or extra pre-marketing testing[20].

Keeping the dual trigger and the notion of the precautionary principle as a strategy for decision-making in mind, we can analyse how the precautionary principle is currently applied to pregnant women in clinical research.

## Analysis of the Precautionary Principle applied to Pregnant Women

As mentioned earlier, the precautionary principle has an intuitive appeal in relation to clinical research in pregnant women and the accompanying safety concerns it poses. Erring on the side of caution seems logical for pregnant women, healthcare professionals, research ethics committee members and everyone else concerned with foetal and

maternal wellbeing[2,10]. Upon further reflection, it becomes apparent that the basic characteristics of the aforementioned dual trigger are met. First, ia) there is potential for serious and irreversible harm in the form of potential adverse effects (e.g. congenital malformations or long-term health consequences) which threaten something valuable, namely foetal well-being. Foetal wellbeing is considered to be a value of paramount importance, something we find worth protecting against the threat of possible harm of including pregnant women in clinical research. Even though we might disagree concerning the specific moral status of the foetus, we can reasonably agree that actions that would unjustifiably harm a future child should be avoided and protecting foetal wellbeing is therefore valuable[33]. Second, ib) there is scientific uncertainty about the magnitude and plausibility that this harm will occur. Paradoxically, because pregnant women are underrepresented in clinical research, scientific information on the actual harms that inclusion may cause is lacking. Following, ii) since the damage condition and the knowledge condition are present, a precautionary remedy is needed.

There broadly seem to be two different ways in which the precautionary principle is currently applied to clinical research in pregnant women. On the one hand, the precautionary principle seems to promote the *exclusion* of pregnant women from clinical research. This is the most common application of the precautionary principle. The primary motivation is concern about foetal well-being and potential irreversible adverse birth defects of the individual foetus in clinical research. The argument is that if there is a possibility that research participation can result in serious adverse effects for the foetus, the precautionary action should be to exclude pregnant women from clinical research. This stance seems to be taken in some regulations as well as in practice, where pregnant women are mostly excluded from participation in clinical research[8,34]. Advocates of this application of the precautionary principle seem to adhere to the *in dubio abstine* formulation of the principle. Schematically portrayed:

*i. Damage condition: serious and irreversible adverse effects for foetuses due to inclusion of pregnant women in clinical research;*

*ii. Knowledge condition: the inclusion of pregnant women in clinical research is currently a debated topic. There are concerns that research participation of pregnant women may result in adverse foetal effects due to uncertainties about drug use in pregnancy, but the evidence is not exclusive;*

*iii. Remedy: the proposed precautionary inaction is to exclude pregnant women from all clinical research in order to prevent possible adverse foetal effects from occurring.*

*The if-clause: if there is ia) a threat which is ib) uncertain, then some kind of (ii) remedy is required. The if-clause applied to pregnant women: adverse foetal effects may be caused by inclusion of pregnant women in clinical research, therefore a remedy is required: inaction, in the form of exclusion.*

On the other hand, the precautionary principle sometimes seems to promote the *inclusion* of pregnant women in clinical research. The primary motivation is the lack of evidence about how to safely and effectively treat pregnant women with a pre-existing condition or when they become ill during pregnancy. Advocates of this interpretation argue that exclusion of pregnant women simply shifts the risks to the community as a whole, resulting in more people at risk and in unsafe and less-controlled situations. "The danger to pregnant women and their foetuses arises primarily from the lack of evidence about medical treatment during pregnancy, not from research itself"[12]. The argument is that if there is a possibility that exclusion from research results in serious harm, the precautionary action should be to include pregnant women in clinical research. Including pregnant women may allow assessment of effectiveness and safety of treatments during pregnancy in a well-controlled fashion, with adequate long term follow-up of the offspring. Standard exclusion of pregnant women leaves the physicians with less or no information on effectiveness and safety of necessary treatments. Follow-up is less organised and it may take much more time to obtain clinical information on the effect on offspring. These scholars argue that the exact opposite lesson should have been learned from for example the thalidomide and DES tragedies. Therefore, they argue, inclusion should be the rule rather than the exception and pregnant women should not only be included in clinical trials specifically targeting pregnant women, they should also be included in clinical trials targeting the general population, as long as certain trial design matters and ethical issues are respected[6,12,35,36]. Advocates of this application of the precautionary principle seem to adhere to the "better safe than sorry" formulation of the principle that demands precautionary action. Schematically portrayed:

*i. Damage condition: serious and irreversible adverse effects for foetuses;*

*ii. Knowledge condition: presently, the lack of evidence-based medicine for pregnant women and foetuses is a debated topic. There is some evidence that the lack of evidence leads to a situation where the community of pregnant women who take medications is at risk, thereby putting foetuses at risk. Inclusion may decrease the risk for foetuses, but the evidence is not exclusive;*

*iii. Remedy: the proposed precautionary action is to include pregnant women whenever ethically and scientifically possible in order to test medications before they are marketed and thus prevent potential adverse foetal effects because of marketed medications that were not tested in pregnant women.*

*The if-clause: if there is ia) a threat which is ib) uncertain, then some kind of (ii) remedy is required. The if-clause applied to pregnant women: adverse foetal effects may be caused by inclusion of pregnant women in clinical research, therefore there is no reason to postpone precautionary measures to prevent the damage: remedy in the form of action, promote inclusion of pregnant women in clinical research.*

Both applications of the precautionary principle to pregnant women in clinical research are problematic for three reasons. First, both applications follow a strict interpretation of the precautionary principle, which results in inaction (promotion of exclusion of pregnant women) or action (promotion of inclusion of pregnant women), paralysing the situation. Especially the application which results in action demonstrates how precaution and inaction have become conflated relative to clinical research in pregnant women[10]. Second, the precautionary principle requires that potential threats are clearly defined. Threats should comprise plausible harms relating to specific cases: "for the precautionary principle to be coherent, the threat must be clearly identified, while the alleged causal relation between action and the exercise of the threat must be scientifically plausible"[17]. Contrarily, the precautionary principle is currently invoked about harms concerning the very broad scope of inclusion or exclusion in clinical research as a whole, not relative to specific instances. Third, the remedy offered by the precautionary principle should not be counter-productive[37].Avoidance of counter productivity requires that safety measures should not cause more harm than they prevent. The precautionary remedies that are provided can both be counter-productive. The inaction that favours exclusion of pregnant women from clinical research may be counterproductive because the consequence of exclusion is that research for pregnant women and foetuses is paralysed while there are no alternative ways to perform this research, and as such the risks are shifted to the population of pregnant women as a whole and actually put pregnant women at increased risk rather than preventing harm. And the action of routinely including pregnant women may be counter-productive because the remedy which aims to protect foetuses may have a counter-productive effect because it may include them in potentially hazardous research.

In summary, an analysis of the precautionary principle as currently applied to pregnant women demonstrates that both applications follow strong versions of the precautionary principle, which lead to both the promotion of exclusion and inclusion of pregnant women in clinical research.

## DISCUSSION

Our analysis shows that the precautionary principle as an underlying strategy for risk-benefit decision-making can be applied to pregnant women in clinical research. The current applications of the precautionary principle to pregnant women follow a strong version of the principle. In clinical research, the strong applications lead to either the promotion of precautionary measures that result in absolute inaction (routine exclusion of pregnant women from clinical research) or, less often, the promotion of precautionary measures that result in absolute action (including pregnant women whenever ethically and scientifically possible). The strong version that is applied in clinical research seems to be a reflection of the situation that pregnant women encounter in daily life. There appears to be a "*in dubio abstine*" paradigm of strong precaution that results in absolute inaction when it

comes to pregnant women. Many stakeholders such as RECs, funders, researchers and pregnant women themselves, seem to act in a manner where the word 'pregnant' is automatically linked to extreme precaution and a reluctance to face any risk. This attitude is in line with the earlier established tendency to notice the risks of taking any sort of action versus those of not doing anything and a distorted perception of risk when it comes to pregnant women[38,39]. As Lucy Langston has aptly phrased, it seems as if the stakeholders themselves have become affected by the norm of inaction as precaution when it concerns pregnant women[10].

However, the precautionary attitude in which risks are avoided at all costs is especially challenging in relation to clinical research, because while a reluctance to include pregnant women may prevent them from being exposed to some new risks, it also prevents them from reducing their exposure to existing risks[25]. As such, both strong applications of the precautionary principle that are currently applied to pregnant women in clinical research are morally problematic because they are unspecified and counter-productive and, moreover, they result in a paralysing situation. Changing the situation requires a shift towards weak precaution.

While a strong interpretation may not suffice, precautionary thinking in itself is still appropriate with regard to pregnant women in clinical research. Acting on weak evidence may be acceptable when so much is at stake. As the current applications function at two extremes, there is room for reasonable in-between, or weak, solutions. A weak interpretation sustains the ethical consideration that foetal wellbeing is an important value to protect, but it also takes alternatives into account. As such, a weak interpretation of the precautionary principle requires a balance between costs and benefits of inclusion and exclusion, taking a broad scope of harms and possible alternatives into account, and a clear definition of the threat. Moreover, a weak version also necessitates that the harms of the precautionary measure itself are taken into account, in order to prevent counter-productivity[37,40]. Finally, a weak interpretation allows, but does not require, precautionary action, which leaves room for contextualisation.

A case in which a weak precautionary approach is applied to decisions about clinical research may be illustrative. For example, a REC may be presented with a protocol in which researchers aim to establish the effects of using selective serotonin reuptake inhibitors (SSRIs) in pregnancy. SSRI use poses more than minimal risk of serious and irreversible adverse effects for foetuses due to the risk of congenital malformations, preterm birth and developmental issues (ia) damage condition)[41–43]. There are some studies that indicate that there is a plausibility of these risks, but the magnitude of the exposure is uncertain (ib) knowledge condition). Consequently, precautionary measures are called for (ii) remedy). In order to determine the precautionary measure required, the REC could look at the traditional risk-assessment of the risks that are quantifiable; the broader risks for society (the whole population of pregnant women versus a controlled group in a research

setting); the costs of exclusion (i.e. lack of knowledge), costs of inclusion (is it no more than a (minor increase over) minimal risk); societal risks and other potentially relevant considerations. Based on this information, the REC could decide upon a precautionary measure consisting of a rejection of the protocol. However, RECs also need to assess the harms of the precautionary measure itself. In this case, it may turn out that rejecting the protocol will cause more than minimal harm, for example because a larger group of pregnant women will be exposed. To illustrate, SSRI use during pregnancy is increasing and an estimated 4 – 10% of pregnant women currently use SSRIs, while no scientific evidence on the effects of SSRIs will be gathered[41,42,44,45]. Because the precautionary measure leads to more than minimal harm, a weak application of the precautionary principle may suggest a balanced approach. For example, careful inclusion of pregnant women who use SSRIs, with extra foetal monitoring and interim analyses as a safeguard. When new evidence about SSRI use becomes available, a new assessment is needed. In addition, long term follow-up of the offspring should be routinely performed in order to assess the effects of SSRIs on child development.

The case illustrates that a weak interpretation of the precautionary principle applied to pregnant women in clinical research may promote further inclusion of pregnant women. Instead of halting a study the moment there are any risks for the pregnant woman or her foetus, weak precaution requires that we take different elements into account, even when these elements may in itself be inconclusive. It is expected that shifting towards a weak interpretation of the precautionary principle will change the current paralysing situation by shifting the attention away from automatic extreme precaution to a focus on balancing harms and potential benefits of inclusion of pregnant women in clinical research.

## CONCLUSIONS

As a decision-making strategy underlying risk-benefit decisions, the precautionary principle can be applied to pregnant women in clinical research. However, the current application of the precautionary principle is a strong one, leading to the promotion of two extremes: absolute exclusion or, less often, absolute inclusion of pregnant women. As such, the two applications are paralysing the current situation, which is undesirable with regard to the already lacking evidence-base for pregnant women and foetuses. A shift towards a weak interpretation of the precautionary principle is necessary. A weak interpretation leaves room for contextualisation of a situation instead of automatically linking the word 'pregnant' to extreme precaution. Moreover, a weak interpretation means careful weighing of all harms, including harms resulting from the precautionary measure itself. By taking the harms of the precautionary measure into account, we expect that shifting towards a weak interpretation of the precautionary principle will in most instances lead to less overprotection or counter-productive inaction for pregnant women in clinical research.

## REFERENCES

1. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
2. F Baylis, A Ballantyne. Missed Trials, Future Opportunities. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
3. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
4. Lupattelli a, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby a C, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4:e004365.
5. Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. Clin. Pharmacol. Ther. 2008;83:181–3.
6. F Baylis, R MacQuarrie. Why Physicians and Women Should Want Pregnant Women Included in Clinical Trials. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
7. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
8. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
9. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
10. Langston L. Better Safe Than Sorry: Risk, Stigma and Research During Pregnancy. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
11. Foulkes MA, Grady C, Spong CY, Bates A, Clayton JA. Clinical research enrolling pregnant women: a workshop summary. J. Womens. Health (Larchmt). 2011;20:1429–32.
12. Ballantyne AJ. New Zealand needs guidelines for the safe and responsible inclusion of pregnant women in medical research. N. Z. Med. J. 2016;129:64–70.
13. ACOG. Research involving women. 2008.
14. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton J a. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. 2013;23:e39-45.
15. Kopelman LM. Minimal risk as an international ethical standard in research. J. Med. Philos. 2004;29:351–78.
16. Sandin P. Dimensions of the Precautionary Principle. Hum. Ecol. Risk Assess. An Int. J. 1999;5:889–907.
17. Petrenko A, McArthur D. Between Same-Sex Marriages and the Large Hadron Collider : Making Sense of the Precautionary Principle. Sci. Eng. Ethics. 2010;16:591–610.
18. Manson N. Formulating the precautionary principle. Environ. Ethics. 2008;24:263–74.
19. Cranor CF. Toward Understanding Aspects of the Precautionary Principle. J. Med. Philos. 2004;29:259–79.
20. Ahteensuu M. Rationale for Taking Precautions: Normative Choices and Commitments in the Implementation of the Precautionary Principle. Risk Ration. Conf. 2007;1–13.
21. Gardiner SM. A core precautionary principle. J. Polit. Philos. 2006. p. 33–60.
22. Steele KS. The precautionary principle: a new approach to public decision-making? Law, Probab. Risk. 2006;5:19–31.
23. Sunstein CR. Beyond the precautionary principle. Univ. PA. Law Rev. 2003;153:1003–58.
24. Holm S, Harris J. Precautionary principle stifles discovery. Nature. 1999;400:398–398.

25. Morris J. The relationship between risk analysis and the precautionary principle. Toxicology. 2002;181–182:127–30.

26. Munthe C. The price of precaution and the ethics of risk. New York: Springer.; 2011.

27. Barke R. Working Paper Series Balancing Uncertain Risks and Benefits in Human Subjects Research. Rev. Lit. Arts Am. 2007;

28. Resnik DB. The Precautionary Principle and Medical Decision Making. 2004;29:281–99.

29. CIOMS & WHO. CIOMS draft guidelines [Internet]. 2016. Available from: http://www.cioms.ch/index.php

30. McGuinness S. Research ethics committees: the role of ethics in a regulatory authority. J. Med. Ethics. 2008;34:695–700.

31. CIOMS & WHO. International ethical guidelines for biomedical research involving human subjects. [Internet]. 2002. [cited 2016 Mar 25]. Available from: http://www.cioms.ch/publications/layout_guide2002.pdf.

32. Secretariat on Responsible Conduct of Research. Tri-Council Policy Statement (TCPS-2): Ethical conduct for research involving humans. [Internet]. [cited 2016 Mar 25]. Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf

33. Strong C. Minimal risk in research involving pregnant women and fetuses. J. Law. Med. Ethics. 2011;39:529–38.

34. Scaffidi J, Mol B, Keelan J. The pregnant women as a drug orphan: A global survey of registered clinical trials of pharmacological interventions in pregnancy. BJOG An Int. J. Obstet. Gynaecol. 2016;

35. Baylis F, Halperin SA. Research involving pregnant women: Trials and tribulations. Clin. Investig. (Lond). 2012;2:139–46.

36. Kaposky, Chris . Presumptive Inclusion and Legitimate Exclusion Criteria. In: F Baylis, A Ballantyne, editor. Clin. Res. Involv. Pregnant Women.

37. Koen Kramer., Hans L. Zaaijer MFV. The Precautionary Principle and the Social Institution of Blood Donation. Am. J. Bioeth. 2017;17:52–4.

38. Lyerly AD, Mitchell LM, Armstrong EM, Harris LH, Kukla R, Kuppermann M, et al. Risks, values, and decision making surrounding pregnancy. Obstet. Gynecol. 2010;109:979–84.

39. van der Zande ISE, van der Graaf R, Oudijk MA, van Delden JJM. A qualitative study on acceptable levels of risk for pregnant women in clinical research. BMC Med. Ethics. 2017;18:35.

40. Wilson K, Atkinson K. Toward Neo-Precaution: A New Approach to Applying the Precautionary Principle to Public Health. Am. J. Bioeth. 2017;17:44–6.

41. Bérard A, Zhao J-P, Sheehy O, Cooper W, Willy M, Pont S, et al. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort. BMJ Open. 2017;7:544.e1-544.e5.

42. Brown AS, Gyllenberg D, Malm H, McKeague IW, Hinkka-Yli-Salomäki S, Artama M, et al. Association of Selective Serotonin Reuptake Inhibitor Exposure During Pregnancy With Speech, Scholastic, and Motor Disorders in Offspring. JAMA Psychiatry. 2016;73:1163–70.

43. G. S, A.C. E. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: A systematic review and metaanalysis. Am. J. Obstet. Gynecol. 2016. p. S443.

44. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. Am. J. Obstet. Gynecol. 2007;196.

45. Wichman CL, Fothergill A, Moore KM, Lang TR, Heise RHJ, Watson WJ. Recent trends in selective serotonin reuptake inhibitor use in pregnancy. J. Clin. Psychopharmacol. 2008. p. 714–6.

# CHAPTER 5

## VULNERABILITY OF PREGNANT WOMEN IN CLINICAL RESEARCH

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## ABSTRACT

**Background:** Notwithstanding the need to produce evidence-based knowledge on medications for pregnant women, they remain underrepresented in clinical research. Sometimes they are excluded because of their supposed vulnerability, but there are no universally accepted criteria for considering pregnant women as vulnerable. Our aim was to explore *whether* and if so *to what extent* pregnant women are vulnerable as research subjects.

**Method:** We performed a conceptual and empirical analysis of vulnerability applied to pregnant women.

**Analysis:** A conceptual analysis supports Hurst's definition of vulnerability. Consequently, we argue that pregnant women are vulnerable if they encounter an identifiably increased likelihood of incurring additional or greater wrong. According to the literature, this increased likelihood could exist of four alleged features for pregnant women's vulnerability: i) informed consent, ii) susceptibility to coercion, iii) higher exposure to risk due to lack of knowledge, iv) vulnerability of the foetus.

**Discussion:** Testing the features against Hurst's definition demonstrates that they all concern the same issue: pregnant women are only vulnerable because a higher exposure to risk due to lack of scientific knowledge comprises an increased wrong. Research Ethics Committees have a responsibility to protect the vulnerable, but a higher exposure to risk due to lack of scientific knowledge is a much broader issue and also needs to be addressed by other stakeholders.

**Conclusions:** The only reason why pregnant women are potentially vulnerable is to the extent that they are increasingly exposed to higher risks due to a lack of scientific knowledge. Accordingly, the discussion can advance to the development of practical strategies to promote fair inclusion of pregnant women in clinical research.

## BACKGROUND

Fair inclusion of pregnant women in clinical research has been widely promoted over the last decades, due to the pressing need to produce evidence-based knowledge concerning medications that are prescribed to women during pregnancy for both obstetric and non-obstetric illnesses [1–6]. A 2011 study on all medications approved by the FDA from 1980 to 2010 found that 91% of the medications approved for use by adults did not have sufficient data on safety, efficacy and foetal risk of medication taken during pregnancy[7]. At the same time, a 2004 study on drug use during pregnancy concluded that 64% of pregnant women took a prescription drug before delivery[8,9], and the total percentage of pregnant women who take medications including off-label medications may be as high as 84-99%[10–13]. Moreover, the number of pregnant women taking at least one prescription medication has increased over the past three decades, common ones including antibiotics, asthma medications and anti-nausea medications[14]. Inclusion of pregnant women in clinical research could provide information on prevention and treatment options and potentially promote maternal and foetal wellbeing.

Nevertheless, pregnant women remain underrepresented in clinical research. Sometimes they are excluded because of their supposed vulnerability, even though there is no universally accepted definition of vulnerability. Uncertainty about what constitutes vulnerability has resulted in a variety of different interpretations and heated debate about the practical applicability of the concept in relation to for instance pregnant women. The Code of Federal Regulations (CFR) classifies pregnant women as a vulnerable population[15] while the new guidelines of the Council for International Organisations of Medical Sciences (CIOMS) mention that pregnant women should not be considered vulnerable but that there are situations which can make them vulnerable[16]. At the same time, bioethicists have questioned the idea that pregnant women are a particularly vulnerable group all together[17–21]. Existing ambiguity poses a challenge for Research Ethics Committees (RECs), amplified by the lack of advice available through for example the letters of determination of the Office of Human Protection Research (OHRP) which address the requirement to protect vulnerable populations but do not provide substantive guidance on the matter [22]. Out of precaution, RECs sometimes choose to interpret guidelines in a conservative way thereby routinely excluding pregnant women[23,24]. The aim of our paper is to explore *whether* and if so *to what extent* pregnant women are vulnerable as research subjects, by way of an analysis of vulnerability applied to pregnant women.

## ANALYSIS OF VULNERABILITY

In the past decades, questions about what constitutes vulnerability have led to animated debate among bioethicists which has resulted in a complicated field with different interpretations of the concept. On one side of the spectrum, there are authors who argue for a broad approach to vulnerability. They state that every protocol needs to be assessed

on different features or layers which change depending on a specific situation[25,26]. In the middle of the debate there are authors who propose a more explicit approach to vulnerability, arguing that there are a number of set features that could possibly indicate a risk of increased or additional harm and which are therefore worth scrutiny at the minimum in each protocol[27–30]. Authors within this category have composed different lists of aspects that indicate when persons are vulnerable. On the other end of the spectrum, there are authors who state that the concept of vulnerability might not be useful at all and might as well be eliminated. They argue that vulnerability should rather be seen as a linguistic tool that functions as a warning signal but which does not require a further conceptual foundation[31], or that special scrutiny for all research participants instead of only the vulnerable should be employed[17].

But although a universally agreed definition of vulnerability is lacking in the bioethical literature on vulnerability of subjects in clinical research, a number of similarities can be noticed. First, there is a general consensus that all human beings are vulnerable due to their universal embodiment and fragility which might be at risk in clinical research. Because of this universal condition, all human subjects who are participating in clinical research are protected by some form of regulation, code or guideline. Second, there appears to be a sentiment that next to the universal vulnerability of all humans, there are particular persons who are at an *increased or additional risk* of being *harmed or wronged* in clinical research[28,32,33]. For example because they are less able to protect their own interests or because of specific circumstances which put them at a disadvantage[34,35].

Moreover, it is agreed that various stakeholders such as RECs, researchers and drug authorities, have *special obligations* to these vulnerable persons because the baseline protection as provided in the general guidelines or regulations does not suffice to protect them[26–30,32,35–38]. Previously, specific group characteristics were said to make a group vulnerable, for instance being a child, a prisoner, or a woman. However, the so-called labelling approach has been criticised as being too narrow, too broad, and stereotyping entire groups[17]. As a result, there is a last point of consensus in the literature, namely that mere characteristics of people alone are not sufficient to deem them vulnerable. Instead, the context of the person in the protocol as well as the research environment needs to be taken into account. As Florencia Luna explicates, it is not about "thinking that someone *is* vulnerable, but by considering a particular situation that *makes or renders* someone vulnerable"[25]. Vulnerability has become a matter of degree, depending on a specific situation.

To summarise, even though differences with respect to a conceptual analysis of vulnerability persevere, it is agreed that a) vulnerability is a universal human condition, b) some persons are vulnerable in the meaning of risking an increased harm or wrong in clinical research, c) vulnerable persons need special protection atop of the standard

guidelines, and d) establishing who qualifies as vulnerable requires a context-specific examination instead of a labelling approach. A definition of what constitutes vulnerability preferably incorporates these aspects.

## APPLICATION TO PREGNANT WOMEN

### Working definition

Adding yet another definition to the already large body of literature on vulnerability is not our objective. Instead, we aim to move the discussion forward by electing a working definition from the existing literature that best encompasses the common aspects that are agreed upon. As such, we find that Samia Hurst has undertaken one of the most extended analyses of vulnerability. Her formulation of vulnerability expresses the common ground mentioned above. The formulation also resembles formulations in a number of guidelines[35,37]. According to Hurst's definition, vulnerability as a claim to special protection should be understood as "an identifiably increased likelihood of incurring additional or greater wrong"[28]. We use her formulation as our working definition. However, her definition does not clarify what constitutes vulnerability in pregnant research participants. In order to determine when research participants are vulnerable, Hurst starts by assessing the set of research ethics principles as described by Emanuel and colleagues (among others social value, scientific validity and informed consent) and argues that if any of these principles is fragile or threatened, research participants may be vulnerable [39,40]. However, if all acts that render a certain study unethical would also render a research participant as vulnerable, it would be too demanding and little specific in what constitutes an identifiably increased likelihood compared to ordinary research participants. Therefore, we will have to further reflect on what constitutes this increased likelihood.

We have chosen to employ a bottom-up approach in the form of a literature review in addition to our conceptual analysis, to determine the increased or additional wrongs. Using empirical methods to obtain insight into issues of ethical interest is nowadays a respected method. The literature may provide us with morally relevant facts and considered judgements about vulnerability applied to pregnant women participating in clinical research[41]. We will identify these issues and accordingly test them to our working definition of vulnerability, which means that we assess whether they comprise an increased risk for pregnant women in comparison with ordinary, non-vulnerable research populations in clinical research.

### Literature search

Our study design for the literature search was based on the review of reasons as developed by Sofaer and Strech and the thematic synthesis method for the categorisation of

the reasons, since it is well-suited to identify arguments to address conceptual questions enhance ethically relevant discussion[42,43]. For the literature search on indications of vulnerability of pregnant women in clinical research we used a broad search strategy in PubMed/MEDLINE (February 2016). Table1 contains the database and search string. We included articles in which reasons for the presumed vulnerability of pregnant women in clinical research were specifically mentioned. We screened 65 unique references on title and abstract; 49 were assessed in full text; 28 met the inclusion criteria. After further assessment for eligibility, 13 articles were finally included (Figure 1. PRISMA flow diagram). We were able to gather all the features indicating vulnerability of pregnant women in clinical research from the articles (Table 2). Since there was considerable consistency among the reported reasons, we were able to categorise them around four themes (Table 3): informed consent (n=9), susceptibility to coercion (n=7), higher exposure to risk due to lack of knowledge (n=7) and vulnerability of the foetus (n=6). The results are discussed below.

## DISCUSSION OF THE RESULTS

The results of the literature search seem to indicate that the alleged vulnerability of pregnant women in clinical research is particularly related to autonomy issues, such as informed consent and coercion. Since there is no immediately obvious reason to assume that pregnant women are incapacitated during pregnancy, the results are unexpected. We need to adequately assess the features and discuss the meaning in order to establish if the results mentioned in the literature are indeed increased features of vulnerability. In accordance with Hurst, pregnant women would be vulnerable and in need of protection if their research participation would mean risking an identifiably increased likelihood of incurring additional or greater wrong. We briefly describe and then assess the four features that were found in the literature, before determining in which case protection because of vulnerability is rightly warranted.

### Informed consent

Informed consent was most frequently cited as a reason for vulnerability (n=9). Six authors argue that there are two specific circumstances, namely during labour and when a serious foetal condition is diagnosed, when informed consent of pregnant women would be hindered due to the severe pain and highly stressed emotional state women are in[44,45]. Another reason that the authors mention as problematic for informed consent is the complex risk-benefit consideration that pregnant women have to make (n=3). The decision about research participation would be more complex due to the lack of scientific knowledge on research in pregnant women. As such, the decision often has to be made without much knowledge on possible risks of participation[46].

Assessing informed consent as a reason for vulnerability, it becomes evident that having to deal with acute circumstances such as being in labour or having to decide on research participation shortly after having received emotionally stressful news, is not specific for pregnant women. Although pregnant women have to make a decision about themselves and their foetus at the same time, there is no reason to assume that in competent adult pregnant women their decision-making capacity is at fault. Instead, their decision-making capacity can be compared to for example the capability of acute patients in the emergency room or parents caring for a child with cancer, or other persons who are highly dependent on medical care[33,34,47]. Similarly, although they are confronted with stressful situations possibly affecting themselves as well as their family, and often in light of a lack of knowledge on risks, these persons are competent to make this decision. Moreover, in relation to the case of labour, the acute situation and following problems with informed consent could often be prevented. From the start of a pregnancy it is known that a woman will at some point be in that acute situation, and by informing and obtaining consent about existing studies for which they might be asked at an earlier stage in the pregnancy, recruitment during labour could be prevented[20,48].Such innovate strategies are already successfully implemented in practice [49]. Most importantly, the narrow focus on labour undesirably diverts the discussion from the broader discussion about vulnerability of pregnant women in clinical research, which is what should be focused upon.

In relation to the perceived informed consent issues due to greater risk-benefit difficulties, it could be argued that due to a lack of knowledge on risks, deciding upon research participation might indeed be a challenge. Nevertheless, patients in similar situations in which there is no evidence-base, such as patients with orphan diseases or elderly patients, are confronted with a similar choice. In short, although consent may be complicated due to a lack of scientific knowledge on possible risks and benefits, *pregnant women do not risk an identifiably increased likelihood of incurring additional or greater wrong with regard to the feature of informed consent.*

## Susceptibility to coercion

Susceptibility to coercion was noted as another feature indicating pregnant women's vulnerability (n=7). Authors state that pregnant women might have an increased likelihood to be susceptible to coercion due to both their own desire as well as society's expectation to prioritise the needs of the foetus regardless of their own[21,45,50]. This expected protectionism towards the foetus could mask their (un)willingness to participate in clinical research.

We speak of coercion when an agent is confronted by another agent with a deliberative threatening proposal whereby not accepting the proposal will leave the agent worse

off[51]. Neither a woman's own desire nor society's expectation to prioritise the foetus' health encompasses a threatening proposal. Therefore, there is no immediately obvious indication that pregnant women are vulnerable because of coercion in comparison with ordinary research subjects. On further exploration of the topic, it becomes evident that while the term coercion, which was coined in the literature, can be disregarded, a type of moral pressure may be observable. To illustrate, the expectation of potential direct individual benefit for the mother, the foetus or both, could influence pregnant women's consent to participate in potentially beneficial clinical research. Pregnant women may be more prone to misconceptions or over- or underestimation of risks and benefits for the foetus[52].

Another example is pressure from society or from the father to conform to standards of good motherhood may influence pregnant women's decisions[18,53]. As such, the "pregnant woman's wish to prioritise the needs of the foetus" could be compared to the situation of parents of children (whether or not enrolled in clinical research). Here, the assumption is also that parents are best suited to make decisions about their children, in which they will often prioritise the need of their children above the need of themselves and have a desire to do what is best for them. One could argue that the decision for pregnant women is different in that it affects the foetus as well as herself. However, pregnant women generally want to stay well on behalf of themselves and their foetus, and we believe that they will therefore not (completely) disregard their own health[47]. Although in these scenario's we should be aware that moral pressure might indeed influence one's reasoning, thinking that pregnant women are being wronged because of *coercion* seems rather paternalistic and unfair. It is interesting that guidelines keep referring to coercion relative to pregnant women[15,35], since *there is no indication that pregnant women are susceptible to coercion in clinical research.*

## Higher exposure to risk due to lack of scientific knowledge

A higher exposure to risk due to a lack of knowledge was cited as another reason for vulnerability (n=7). Authors explicate that both historically as well as juridically (referring to guidelines and regulations), pregnant women have been routinely excluded from clinical research which, as a result, has led to a lack of knowledge on medications and treatment options for their population. Consequently, information is based on incomplete sources which are often flawed and less dependable than randomised controlled trials. As such, authors argue, pregnant women are now a medically disadvantaged group risking an increased likelihood of incurring a higher exposure to risk when participating in clinical research[21,50].

Examining this feature, it appears that recent efforts to promote inclusion have started to be effective, for instance illustrated by guidelines which are currently changing their direction towards inclusion of pregnant women[35,38]. In addition, pregnant women are

not always disadvantaged as subjects in clinical research, since not all medications lack knowledge on safety and efficacy. Some medications *are* extensively studied in pregnant women, such as anti-epileptic drugs (AEDs) or labour inhibitors, and in those cases pregnant women in clinical research are not necessarily exposed to higher risks.

However, in the majority of cases, pregnant women in clinical research are indeed exposed to a higher risk in comparison to ordinary research populations due to the lack of knowledge on safety and efficacy of medications or interventions which are not always tested in their population. As a result, the majority of medications are currently characterised by the FDA as pregnancy category B[1] or category C[2] [14]. Pregnant women are rarely included in clinical trials and even in phase IV trials they are usually excluded[5]. Hence, dosing and safety information is typically extrapolated from studies in non-pregnant patients. When (market approved) medications for humans are finally tested in pregnant women, phase I and sometimes phase II trials involving pregnant women are no longer undertaken due to various issues such as time and cost issues, liability fears or a fear of harming the foetus[20,54]. Instead, phase III trials are initiated based on information obtained from safety data in non-pregnant humans; based on preclinical information with pregnant animals; based on voluntary case-reports; or based on information from inadvertent pregnancy exposures in which women became pregnant during a clinical trial. Such information is often incomplete and difficult to interpret, for example because coincidence and causation are hard to distinguish and because the information cannot be used to assess teratogenic risk[9,55]. Moreover, in case of inadvertent pregnancy exposures during clinical trials of new products, available data are usually insufficient to permit an adequately powered statistical analysis that could then later be used for clinical research in pregnant women[55]. We therefore assume that due to the lack of scientific knowledge on medications and interventions in the population of pregnant women, *pregnant women may face an increased likelihood of incurring a higher exposure to risk in clinical research.*

## Vulnerability of the foetus

A last feature from the literature that seems to indicate vulnerability of pregnant women, is the vulnerability of the foetus (n=6). Authors mention that the mere existence of the foetus which could potentially be harmed sometimes seems to deem pregnant women vulnerable. Moreover, it is argued that the lack of deliberative capacity of the foetus indicates that pregnant women are vulnerable[56].

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[1] Category B: "Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women"

[2] Category C: "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"

Assessing this feature, it appears that the cognitive vulnerability of the foetus is not equivalent to the cognitive vulnerability of the pregnant woman. The fact that the foetus is incapacitated only means that there should be a surrogate decision-maker, which can be found in the pregnant woman herself. Relative to the risk of harming the foetus, it can be noted that this risk, which is often disproportionally weighed and sometimes not at all present, is in fact related to the complexities of the risk-benefit analysis, which is more difficult in the case of pregnant women due to lack of scientific knowledge. Nevertheless, there is no reason to assume that the vulnerability of the foetus renders pregnant women increasingly vulnerable in comparison with ordinary research subjects. *Neither the existence of the foetus nor the cognitive vulnerability of the foetus increases pregnant women's likelihood of incurring additional or greater wrong.*

The literature search indicated four different features of pregnant women's alleged vulnerability in clinical research. However, after assessment of these features, it seems that all aspects of vulnerability which are factually present can be attributed to the same feature: a higher exposure to risk due to lack of scientific knowledge.

## DISCUSSION

Neither informed consent, susceptibility to coercion, or vulnerability of the foetus leads to an identifiably increased likelihood of incurring additional or greater wrong for pregnant women in comparison with ordinary research participants. Instead, all features concern the same issue: a higher exposure to risk due to a lack of scientific knowledge. This last feature does comprise an increased wrong and, depending on the context of a research protocol, may render pregnant women particularly vulnerable and in need of special protection. As such, we are confronted with a dilemma: pregnant women are potentially vulnerable in clinical research because of a lack of scientific knowledge (because they have not been included in clinical research), but in order to overcome this state of vulnerability, pregnant women should be more frequently included. Decreasing vulnerability is essential in order to overcome the dilemma.

By charging RECs with the task to approve or disapprove clinical research protocols, guidelines and regulations indirectly designate RECs as the institutions responsible for the protection of vulnerable persons in clinical research[37]. However, since the vulnerability of pregnant women primarily comprises the lack of scientific knowledge, relying on RECs alone for protection is not sufficient for a number of reasons. First, RECs are concerned with assessment of research protocols (usually not including pregnant women) and when researchers do not put protocols up for assessment there is only so much RECs can do. Second, RECs are only involved at a later stage in the research process and by that time it might be too late to compel researchers to include pregnant women in order to reduce the knowledge gap.

Third and most importantly, RECs are simply not the only bodies responsible for increasing the evidence-base for pregnant women. Research Ethics Committees unquestionably have a role to fulfil in safeguarding pregnant women's interests in clinical research, for example by interpreting guidelines more progressively and requesting justifications for the exclusion of pregnant women[4,18,57]. But the issue, addressing the knowledge gap, comprises a much broader domain than that of RECs and the development of special protections alone. One could for example imagine a role for funding agencies and research sponsors. These organisations can prioritise clinical research in pregnant women by including at least one grant for research in this population per each application round. Or, as Greer Donley suggests, by creating financial incentives to generate data on pregnant women by granting a three-month period of market exclusivity for drug companies that invest in research in this population (similar to the paediatric setting[58]).

In addition, the involvement of manufacturers will also be essential in addressing the lack of scientific knowledge, which is challenging due to their liability fears in relation to clinical research in pregnant women. However, as we have argued elsewhere, shifting liability or demonstrating the predicted low occurrence of liability claims could be viable solutions[54]. Evidently, different stakeholders at different times in the research process have their own obligations with regard to reducing the lack of scientific knowledge. As several authors have previously indicated, reducing pregnant women's vulnerability requires a collaborative partnership among stakeholders such as funding agencies, drug authorities, researchers, methodologists, pharmacologists, guideline committees and RECs. Raising awareness on the efficiency and potential benefits of partnerships could motivate stakeholders to collaborate, particularly when supportive research structures are facilitated. At present, different strategies to increase the evidence-base for pregnant women are explored, such as the development of new ways to systematically collect data or implement innovative research designs[2,4]. Further collaboration might lead to new insights which could advance the process with the final goal to improve maternal and foetal wellbeing.

## CONCLUSIONS

Our study once and for all demonstrates that there is no indication that pregnant women are vulnerable because of informed consent, susceptibility to coercion, or vulnerability of the foetus. The only reason why pregnant women are potentially vulnerable in clinical research is to the extent that they are increasingly exposed to higher risks due to a lack of scientific knowledge which might render them vulnerable as research subjects. Depending on the context of a research protocol, pregnant women may therefore have a claim to special protection. RECs have a responsibility to protect vulnerable persons and as such they have certain obligations with regard to pregnant women. However, discussing the lack of scientific knowledge in committee review meetings is insufficient, for the issue

comprises a much broader domain. Only a joint effort to promote fair inclusion by funding agencies, drug authorities, researchers, methodologists, pharmacologists, guideline committees and RECs, can successfully reduce pregnant women's vulnerability. Now that we have established that there really is only one vulnerability that needs to be addressed, the discussion can advance to the development of practical strategies to promote fair inclusion of pregnant women in clinical research.

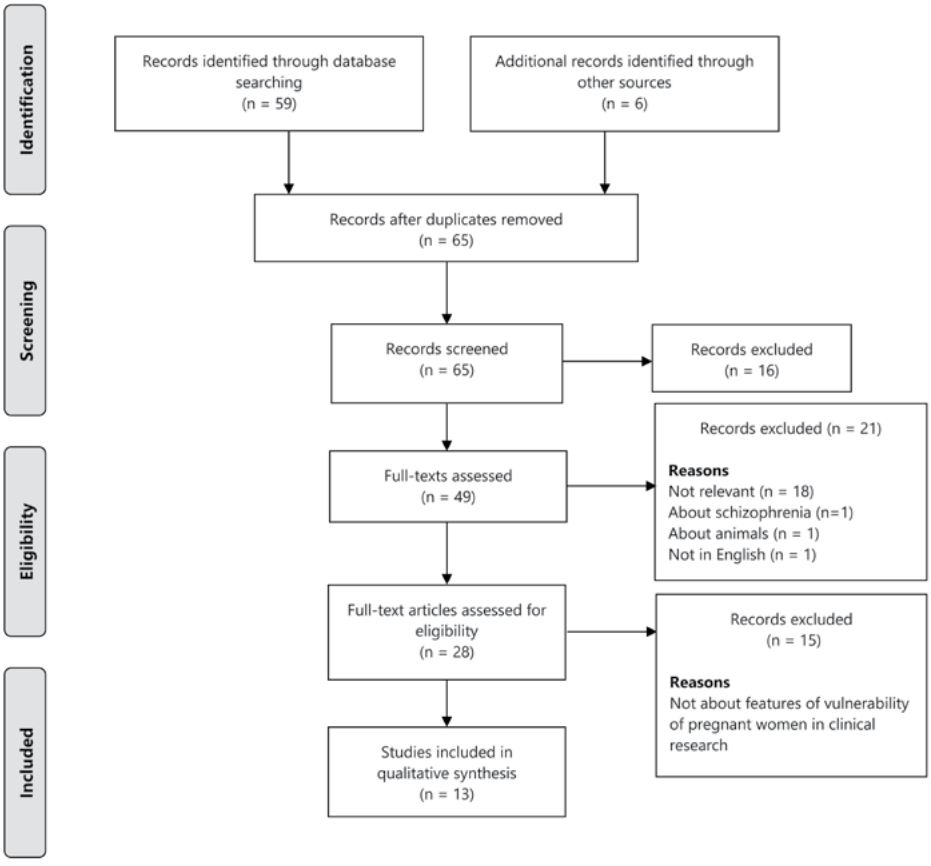
## FIGURES AND TABLES

**Table 1.** PUBMED literature search

| Search | Terms | Hits |
|---|---|---|
| 1 | ((vulnerab*[Title/Abstract]) AND pregnan*[Title/Abstract]) AND ethic*[Title/Abstract] | 86 |
| 2 | research*[Title/Abstract] OR stud*[Title/Abstract] OR trial*[Title/Abstract] | 9020431 |
| 3 | #1 AND # 2 | 59 |

Date of search: February 15th, 2016

**Figure 1.** PRSIMA Flow Diagram




From: Moher D., A. Liberati, J. Tetzlaff, D.G. Altman, and The PRISMA= Group. 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prismastatement.org

**Table 2.** Summary of selected articles

| | Reference | Paper type | Scope of paper | Mentioned feature(s) of vulnerability* |
|---|---|---|---|---|
| 1 | Chwang 2014[59] | Reasoned opinion | Shared vulnerabilities in research (CFR) | Pregnant women are a vulnerable population because they are mentioned as such in the CFR and often excluded. |
| 2 | Deprest et al. 2011[60] | Reasoned opinion | Ethical aspects of foetal therapy | The pregnant patient is a vulnerable subject whose vulnerability is increased when a serious foetal condition is diagnosed. |
| 3 | Donley 2014[61] | Reasoned opinion | Regulations governing medications in pregnant women | There are three reasons why pregnant women are (incorrectly) seen as vulnerable: 1. susceptibility to coercion, 2. inherent vulnerability and 3. harm to the foetus |
| 4 | Helmreich et al. 2007[48] | Reasoned opinion | Informed consent in research in pregnant women | Although pregnant women have the capacity to make autonomous decisions, they are considered to be vulnerable due to the potential harm to the foetus (vulnerable duo). A pregnant woman also has a greater risk of coercion due to the desire to make best decisions for the baby. |
| 5 | Kilama 2005[62] | Reasoned opinion | Malaria research in Africa | (Young) women in their first and second pregnancies are extremely vulnerable because (specifically in rural malarious areas and poor urban settings in Africa) they are often denied autonomy and their participation in research is therefore highly liable to exploitation. |
| 6 | Levine et al. 2004[17] | Reasoned opinion | Limitations of vulnerability | Pregnant women might become vulnerable in labour. |
| 7 | Lott 2005[46] | Module in journal | Vulnerable/special populations | Informed consent becomes hindered because of a lack of scientific knowledge on research with pregnant women. |
| 8 | Lupton and Williams 2004[56] | Reasoned opinion | Ethics of research in pregnant women | What distinguishes pregnant women is the prospect of causing harm to the vulnerable 'future people'. It is the incapacity of the vulnerable future person, developing within them, that makes the maternal-foetal unit a vulnerable unit. |
| 9 | Naqvi 2014[63] | Reasoned opinion | Cardiology research in pregnancy | Research in pregnancy concerns a special vulnerable group due to the involvement of the mother and the foetus which can potentially be harmed. In addition, the ethical considerations, informed consent requirements and risk-benefit issues are often more complex than in nonpregnant populations. |

**Table 2.** (continued)

| | Reference | Paper type | Scope of paper | Mentioned feature(s) of vulnerability* |
|---|---|---|---|---|
| 10 | Reid et al. 2011[44] | Literature search and survey | Consent during labour | Pregnant women during labour might be even more vulnerable and it is unclear if they are capable of giving fully informed consent (in severe pain, using opioids). They are also a disadvantaged group in research and because of the unwillingness (of the research community) to seek informed consent for inclusion because it would be complex. |
| 11 | Schonfeld 2013[21] | Reasoned opinion | Vulnerability of pregnant women in clinical research | There is an (incorrect) idea that the mere existence of the foetus suffices to classify pregnant women vulnerable demonstrated by assessing Kipnis' vulnerability requirements: 1) cognitive: possibly during labour; foetus lacks deliberative capacity. 2) juridic: foetus makes pregnant women vulnerable; they create additional vulnerability. 3) deferential: pregnant women refrain from participating because of what others expect. 4) medical: because of *lack* of inclusion (or about *foetal medical vulnerability).* 5) allocational and 6) infrastructural: not present. 7) social: protectionism towards foetus and other expectations. |
| 12 | Sheppard 2015[45] | Reasoned opinion | Informed consent in foetus-regarding clinical trials | In the situation where the pregnant woman is newly diagnosed with a foetal condition for which the only option, other than watchful waiting, is enrolment in a clinical trial, she should be considered a cognitively and medically vulnerable research participant due to respectively stress and lack of inclusion. In addition there is a moral pressure to do what is best for unborn child. |
| 13 | Welch et al. 2015[50] | Reasoned opinion | Vulnerable populations in Pragmatic Clinical Trials | Pregnant women are deferential, -social and -situationally vulnerable. |

* N.B.: authors often only report on features of vulnerability without actually advocating them.

**Table 3.** Categorisation of features of vulnerability

| General feature | Article* |
|---|---|
| Informed consent (n=9) | 2, 6, 7, 9, 10, 10, 11, 12, 13 |
| Susceptibility to coercion (n=7) | 3, 4, 5, 11, 11, 12, 13 |
| Higher exposure to risk due to a lack of scientific knowledge (n=7) | 1, 3, 10, 11, 11, 12, 13 |
| Vulnerability of the foetus (n=6) | 3, 4, 8, 9, 11, 11 |

*Several articles mentioned multiple reasons; in that case the number of the article is repeated

## REFERENCES

1. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
2. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
3. Zajicek A, Giacoia GP. Obstetric clinical pharmacology: coming of age. Clin. Pharmacol. Ther. 2007;81:481–2.
4. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
5. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
6. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. Clin. Infect. Dis. 2014;59 Suppl 7:S400-7.
7. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am. J. Med. Genet. Part C Semin. Med. Genet. 2011;157:175–82.
8. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, et al. Prescription drug use in pregnancy. Am. J. Obstet. Gynecol. 2004;191:398–407.
9. Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. Clin. Pharmacol. Ther. 2008;83:181–3.
10. EMA (European Medicines Agency). Guideline of the exposure to medicinal products during pregnancy: need for post-authorisation data. [Internet]. 2005 [cited 2016 Mar 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf
11. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
12. Noah BA. The inclusion of pregnant women in clinical research barbara a. noah* a. 2014;353–89.
13. Lupattelli a, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby a C, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4:e004365.
14. Parisi MA, Spong CY, Zajicek A, Guttmacher AE. We don't know what we don't study: The case for research on medication effects in pregnancy. Am. J. Med. Genet. Part C Semin. Med. Genet. 2011. p. 247–50.
15. DHHS (US Department of Health and Human Services. Code of Federal Regulations Part 46: Protection of human subjects. [Internet]. 2009 [cited 2016 Mar 25]. Available from: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.
16. CIOMS & WHO. CIOMS draft guidelines [Internet]. 2016. Available from: http://www.cioms.ch/index.php
17. Levine C, Faden R, Grady C, Hammerschmidt D, Eckenwiler L, Sugarman J. The limitations of "vulnerability" as a protection for human research participants. Am. J. Bioeth. 2004;4:44–9.
18. Lyerly AD, Mitchell LM, Armstrong EM, Harris LH, Kukla R, Kuppermann M, et al. Risks, values, and decision making surrounding pregnancy. Obstet. Gynecol. 2010;109:979–84.
19. Macklin R. Enrolling pregnant women in biomedical research. Lancet. 2010. p. 632–3.
20. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton J a. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. 2013;23:e39-45.

21. Schonfeld T. The perils of protection: Vulnerability and women in clinical research. Theor. Med. Bioeth. 2013;34:189–206.
22. Iltis AS, Wall A, Lesandrini J, Rangel EK, Chibnall JT. Federal interpretation and enforcement of protections for vulnerable participants in human research. J. Empir. Res. Hum. Res. Ethics. 2009;4:37–41.
23. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. Elsevier Inc.; 2013;23:e39–45.
24. Levine RJ. IRB perspective on inclusion of pregnant women in clinical research. ORWH Work. Enrolling pregnant women Issues Clin. Res. An ORWH 20th Anniv. Event. Bethesda, MD: National Institutes of Health; 2011. p. 37–43.
25. Luna F. Elucidating the concept of vulnerability: Layers not labels. Int. J. Fem. Approaches Bioeth. 2009;2:121–39.
26. Lange MM, Rogers W, Dodds S. Vulnerability in research ethics: A way forward. Bioethics. 2013;27:333–40.
27. Kipnis K. Vulnerability in research subjects: a bioethical taxonomy. Ethical Policy Issues Res. Involv. Hum. Particip. Vol. 2 Comm. Pap. Staff Anal. 2001. p. G1–13.
28. Hurst S a. Vulnerability in research and health care; Describing the elephant in the room? Bioethics. 2008. p. 191–202.
29. Schroeder D, Gefenas E. Vulnerability: too vague and too broad? Camb. Q. Healthc. Ethics. 2009;18:113–21.
30. Tavaglione N, Martin AK, Mezger N, Durieux-Paillard S, Fran??ois A, Jackson Y, et al. Fleshing out vulnerability. Bioethics. 2015;29:98–107.
31. Wrigley A. An Eliminativist Approach to Vulnerability. Bioethics. 2014;9702:478–87.
32. Kottow MH. The vulnerable and the susceptible. Bioethics. 2003;17:460–71.
33. Rogers W, Mackenzie C, Dodds S. Why bioethics needs a concept of vulnerability. Int. J. Fem. Approaches Bioeth. 2012;5:11–38.
34. Rogers W, Ballantyne A. Special populations: vulnerability and protection. Reciis. 2008;2:30–40.
35. CIOMS & WHO. International ethical guidelines for biomedical research involving human subjects. [Internet]. 2002. [cited 2016 Mar 25]. Available from: http://www.cioms.ch/publications/layout_guide2002.pdf.
36. Nickel PJ. Vulnerable populations in research: The case of the seriously Ill. Theor. Med. Bioeth. 2006;27:245–64.
37. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. [Internet]. 2013 [cited 2016 Mar 25]. Available from: http://www.wma.net/en/30publications/10policies/b3/
38. Secretariat on Responsible Conduct of Research. Tri-Council Policy Statement (TCPS-2): Ethical conduct for research involving humans. [Internet]. [cited 2016 Mar 25]. Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf
39. Hurst S. Clarifying Vulnerability : The Case of Children Clarifying Vulnerability : The Case of Children. 2015;7:126–38.
40. Emanuel EJ, Wendler D, Killen J, Grady C. What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research. J. Infect. Dis. 2004;189:930–7.
41. Van Thiel GJMW, Van Delden JJM. Reflective Equilibrium as a Normative Empirical Model. Ethical Perspect. 2010;17:183–202.

42. Strech D, Sofaer N. How to write a systematic review of reasons. J. Med. Ethics. 2012;38:121–6.
43. Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: a critical review. BMC Med. Res. Methodol. 2009;9:59.
44. Reid R, Susic D, Pathirana S, Tracy S, Welsh AW. The ethics of obtaining consent in labour for research. 2011;485–92.
45. Sheppard MK. Vulnerability , therapeutic misconception and informed consent: is there a need for special treatment of pregnant women in fetus-regarding clinical trials ? 2016;127–31.
46. Lott JP. Module three: Vulnerable/special participant populations. Dev. World Bioeth. 2005. p. 30–54.
47. van der Zande ISE, van der Graaf R, Oudijk MA, van Vliet-Lachotzki EH, van Delden JJM . A Qualitative Study on Stakeholders' views on the Participation of Pregnant Women in the APOSTEL VI study: a low-risk obstetrical RCT. submitted.
48. Helmreich RJ, Hundley V, Norman A, Ighedosa J, Chow E. Research in pregnant women: the challenges of informed consent. Nurs. Womens. Health. 2007;11:576–85.
49. Kaandorp JJ, Benders MJNL, Rademaker CM a, Torrance HL, Oudijk M a, de Haan TR, et al. Antenatal allopurinol for reduction of birth asphyxia induced brain damage (ALLO-Trial); a randomized double blind placebo controlled multicenter study. BMC Pregnancy Childbirth. 2010;10:8.
50. Welch MJ, Lally R, Miller JE, Pittman S, Brodsky L, Caplan AL, et al. The ethics and regulatory landscape of including vulnerable populations in pragmatic clinical trials. Clin. Trials. 2015;12:503–10.
51. Wertheimer A. Coercion. Princeton, New Jersey: Princetion University Press; 1987.
52. van der Zande ISE, van der Graaf R, Oudijk MA, van Delden JJM. A qualitative study on acceptable levels of risk for pregnant women in clinical research. BMC Med. Ethics. 2017;18:35.
53. Lupton D. Risk and the ontology of pregnant embodiment. Risk Sociocult. theory new Dir. Perspect. 2016.
54. van der Zande ISE, van der Graaf R, Browne JL, van Delden JJM. Fair Inclusion of Pregnant Women in Clinical Research: A Systematic Review of Reported Reasons for Exclusion. In: F Baylis, A Ballantyne. editor. Clin. Trials Involv. Pregnant Women. 2016. p. 65–94.
55. Services H. Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies Reviewer Guidance Evaluating the Risks of Drug Exposure in Human Pregnancies. Epidemiology. 2005.
56. Lupton MGF, Williams DJ. The ethics of research on pregnant women: Is maternal consent sufficient? BJOG An Int. J. Obstet. Gynaecol. 2004. p. 1307–12.
57. Baylis F, Kaposky C. Wanted: inclusive guidelines for research involving pregnant women. Obstet. Gynaecol. Canada JOGC. 2010;473–6.
58. Donley G. Encouraging Maternal Sacrifice: How Regulations Governing the Consumption of Pharmaceuticals During Pregnancy Prioritize Fetal Safety over Maternal Health and Autonomy. Rev. Law Soc. Change. 39:45–88.
59. Chwang E. Shared Vulnerabilities in Research. 2014;14:3–11.
60. Deprest J, Toelen J. The fetal patient-ethical aspects of fetal therapy. Facts, Views. 2011;3:221–7.
61. Donley G. Encouraging Maternal Sacrifice: How Regulations Governing the Consumption of Pharmaceuticals During Pregnancy Prioritize Fetal Safety over Maternal Health and Autonomy. Rev. Law Soc. Change. 39:45–88.
62. Kilama WL. Ethical perspective on malaria research for Africa. 2005;95:276–84.
63. Naqvi TZ. Challenges in cardiology research in pregnancy. Future Cardiol. 2014;10:759–68.

# CHAPTER 6

## FAIR INCLUSION OF PREGNANT WOMEN IN CLINICAL TRIALS: AN INTEGRATED SCIENTIFIC AND ETHICAL APPROACH

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## ABSTRACT

**Background:** Since pregnant women are severely underrepresented in clinical research, many take the position that we need to shift to a default of inclusion, where exclusion of pregnant women from research must be justified unless there is compelling justification for exclusion. However, it is unclear what this suitable justification entails and whether this approach does render research with pregnant women fair. This paper analyzes and evaluates when research with pregnant women can be considered as fair and what constitutes scientific reasons for exclusion.

**Methods:** Conceptual ethical and methodological analysis and evaluation of fair inclusion.

**Results:** Fair inclusion of pregnant women means 1) that pregnant women who are eligible are not excluded solely for being pregnant and 2) that the research interests of pregnant women are prioritized, meaning that they ought to receive substantially more attention. Fairness does not imply that pregnant women should be included in virtually every research project, as including only a few pregnant women in a population consisting of women will not help to determine the effectiveness and safety of a treatment in pregnant women. Separate trials in pregnant women may be preferable once we assume, or know, that effects of interventions in pregnant women differ from the effects in other subpopulations, or when we assume, or know, that there are no differences. In the latter case, it may be preferable to conduct post-marketing studies or establish registries. If there is no conclusive evidence indicating either differences or equivalence of effects between pregnant and non-pregnant women, yet is seems unlikely that major differences or exact equivalence exists, inclusion of pregnant women should be sufficient. Depending on the research question, this boils down to representativeness in terms of the proportion of pregnant and non-pregnant women, or to oversampling pregnant women.

**Conclusions:** Fair inclusion of pregnant women in research implies that separate trials in pregnant women should be promoted. Inclusion of pregnant women has to be realized at the earliest phases of the research process. In addition to researchers and research ethics committees, scientific advisory councils, funders, drug regulatory agencies, pharmaceutical companies, journal editors and others have a joint responsibility to further develop the evidence base for drug use in pregnant women.

## BACKGROUND

The development of drugs for obstetric and non-obstetric illnesses for pregnant women is a slowly evolving process. Even though more than half of pregnant women take (prescription) medications during pregnancy for both obstetric and non-obstetric indications[1,2], there has always been a widespread reluctance to include pregnant women in clinical research due to amongst others potential harm to the fetus. Although sound data is unfortunately lacking, there are estimates that the total percentage of women who take medications during pregnancy, either prescribed or over-the-counter, may currently be as high as 64-90%[2–5]. Common medications include painkillers, antibiotics, asthma, sleep and anti-nausea medications[6].

If drugs are tested in pregnant women, studies usually concern investigator initiated studies of long-existing and used medications (that were previously approved for non-pregnant conditions) that are now tested for effectiveness during pregnancy and labor, such as a low dose aspirin to prevent spontaneous preterm labor. The results of these studies seldom lead to registrations for new indications during pregnancy, but at best to evidence for off-label use. Innovative drugs for pregnant women are hardly developed. As refraining from taking medication during pregnancy could also harm the mother and the fetus, in the past decades regulators, bioethicists and researchers seemed to have reached consensus that inclusion of pregnant women in research should be promoted[7–12]. Extrapolation of data from studies conducted in men and non-pregnant women is often uncertain, as pregnancy alters the way drugs are metabolized by the body and act on the body in a fashion difficult to predict from the pharmacokinetics and pharmacodynamics of non-pregnant groups[1,11,13,14]. Risk-benefit profiles are likely to differ as well[8]. Gathering conclusive data in order to develop effective treatments for pregnant women with acute or chronic non-obstetric illnesses as well as innovative medications for obstetric illnesses therefore requires research in pregnant women.

The poor evidence base for drug use in pregnancy is widely regarded as unfair[9]. In 1994, the Office of Research on Women's Health (ORWH) of the Department of Health and Human Services (DHHS) in the United States endorsed the view that pregnant women are to be presumed eligible for participation in clinical research and stated that pregnant women ought to be "fairly enrolled" in clinical research. This view was later supported by the Council for International Organizations of Medical Sciences (CIOMS) that claimed that exclusion of pregnant women as a class is unjust and that pregnant women should be presumed eligible for research participation[12]. And also by regulatory agencies such as the FDA and the EMA[15–17], and by many individual bioethicists. Despite this longstanding consensus on the need to include pregnant women in clinical research, the situation has not significantly changed since 1994. Exclusion of pregnant women from research is still common practice[18,19]. A recent review demonstrated that between 1960 and 2013 only about 1% of pharmacokinetic clinical trials were conducted for pregnant women, and

the ones that were undertaken had a strong focus on acute labor and delivery issues[20]. Not surprisingly, a 2011 study on all medications approved by the FDA from 1980 to 2010 found that 91% of the medications approved for use by adults did not have sufficient data on safety, efficacy and fetal risk of medication taken during pregnancy[21]. At the same time, the number of pregnant women who take medications, as well as the number of medications that these pregnant women take, has increased[6,20].

Evidently, even after the awareness of "fair enrolment", pregnant women remain poorly represented. Among the different reasons for the continuous underrepresentation is the problem that guidelines are ambiguous with respect to if and when pregnant women should be included in clinical research and what renders their inclusion fair[22–25]. Many scholars and guidelines currently argue for a shift to a default of inclusion and take the position that fairness comes down to the demand to justify exclusion of pregnant women from research unless there are compelling justifications for exclusion[9,26–30]. Based on the literature, we presume that a compelling justification refers to sound scientific reasons for exclusion. Yet it is questionable whether this approach to fairness does render research with women fair, since it would transform from the one extreme (no inclusion) to having to justify exclusion except when scientific reasons exist. Furthermore, apart from clear-cut cases such as shown teratogenicity in preclinical studies or unfavorable high risks for the pregnant woman or the fetus, it is unclear what constitutes a scientifically compelling reason to exclude pregnant women. The National Institutes of Health's *Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research* (2001 amendment) is currently the most elaborated guidance document to clarify this "scientific reason" in relation to clinical research in women[31]. Nevertheless, we will argue below that this document has methodological and ethical shortcomings when applied to *pregnant women*. Therefore, the aim of this paper is to analyze and evaluate when research with pregnant women can be considered as fair and what constitutes scientific reasons for exclusion. We will first perform a conceptual ethical analysis of fair inclusion and then look at fair inclusion from an integrated ethical and methodological perspective by applying the NIH Policy document to pregnant women.

It is important to note that we assume that scientific and justice-based reasons are highly integrated and in principle not easy to distinguish. If research is not designed in a scientific rigorous manner, participants may unnecessarily be exposed to research risks[32]. We will focus primarily on Phase III drug research and we assume that a phase III is always preceded by sufficient Phase I and Phase II trials in pregnant women, in order to obtain safety and dosing data to be able to expect that the drug is and will remain safe enough in pregnant women, and that therefore the risk of serious adverse effects is low[33]. We will not touch upon the level of evidence needed to be able to conduct trials in pregnant women, nor on timing of trials in pregnant women. Elsewhere we have written more extensively on these topics[33].

## CONCEPTUAL ETHICAL ANALYSIS OF FAIR INCLUSION

Fair inclusion of study participants in research is one of the core principles of human subjects research[32]. Scandals and tragedies in the past have highly determined the interpretation of fair subject selection. High-risk research with populations that were "readily available", such as illiterate, marginalized and powerless groups, has taught us that the scientific objectives of a study and not the "compromised" position nor the "ease of manipulation" should determine the choice of the study population[32,34]. At the same time, sometimes as a result of an attempt to protect those groups that are easy to recruit, they are categorically excluded which has led to substantial gaps in knowledge about the treatment for conditions that affect these frequently excluded or underrepresented groups, such as children and incompetent persons[34]. Pregnant women take an interesting position among these underrepresented groups since they have not been excluded because of their ease of manipulation but because tragedies with medications that have *not b*een studied in pregnant women, particularly thalidomide and diethylstilbestrol (DES), have caused widespread resistance to test medications in this population[35]. But the response is the same, the scandals have caused underrepresentation and therefore exacerbation of knowledge gaps. Therefore, many currently propose to justify exclusion as a way to promote inclusion unless there is a sound scientific reason not to include them.

The demand to justify exclusion of subpopulations is typically grounded in two principles of justice[36,37]. Sometimes having to justify exclusion is seen as *justice as equity*, meaning that eligible people should be included without regard to age, gender, race, economic status, or ethnicity. Justice as equity applies to the level of individual research projects, meaning that in every research project, pregnant women should be treated as equal to other potentially eligible research participants. As a result, some argue that pregnant women should be *routinely included*, unless there are scientific and ethical reasons not to do so[38,39]. Fair inclusion may also be regarded as a form of *corrective justice*, meaning that we should prioritize the inclusion of minorities as long as they have been and continue to be, underrepresented in research. Mastroianni and colleagues argue that "justice may require a policy of preferential treatment toward these specific areas in order to remedy a past injustice and to avoid perpetuating that injustice"[36]. For pregnant women specifically it has been claimed that "justice supports the dedicated use of public funds to redress the lack of data about treatments during pregnancy"[40]. This second approach to justice may apply to researchers of specific projects and companies applying for marketing authorization of a drug, but may also be directed at an (inter) national level, applying to funding agencies and governments to promote programs that stimulate research that responds to the health needs of pregnant women[36,37].

Mastroianni and colleagues discern a third approach to fair inclusion, which aims to fairly benefit all people regardless of their sex or gender and class. According to their

third approach, a national research agenda must actively promote research in all areas. As we see it, this third approach is a mixture of the two forms of justice that we have just discerned since it implies that there is no a priori reason not to benefit pregnant women who participate in research (equity) and that specific agencies in a society may be designated to ensure that the interests of women are sufficiently promoted (corrective justice). In addition, the third approach focuses on a just distribution of benefits. This aspect has been disregarded in our paper since we primarily discuss in- and exclusion.

It is important to note here that factual inclusion of pregnant women will, as is the case for any research group, also be determined by other ethical considerations such as the potential of pregnant women to give voluntary informed consent and whether the risk-benefit ratio of a study is favorable[36]. For example, due to unknown risks, planning a trial in pregnant women and exposing larger numbers of pregnant women would only be warranted if drug dose and drug safety is sufficiently established in the non-pregnant population[33]. However, for the purposes of this paper we have only considered the implications of the fair inclusion requirement as such, assuming that all other relevant ethical principles apply equally[32].

## FAIR INCLUSION OF PREGNANT WOMEN FROM AN INTEGRATED ETHICAL AND METHODOLOGICAL PERSPECTIVE

As we argued above, the NIH Policy document seems to be the most elaborated document that discusses scientific reasons for exclusion of subgroups. At the same time, although the document focuses on women and minorities, we may over-interpret the document when applying it to pregnant women since the NIH has some specific guidance on inclusion of pregnant women[41]. Yet this specific guidance on inclusion of pregnant women lacks the criteria mentioned in the NIH Policy document on women and minorities[31]. Therefore, we use the insights in the policy document on women and minorities and consider to what extent these insights can identify legitimate scientific reasons for excluding pregnant women from research. Moreover, before we apply the policy document it is important to note that the NIH Revitalization Act that led to the NIH Policy document has been extensively evaluated from an ethical and legal perspective, but less so from a methodological perspective[36]. Thus our paper is one of the first attempts to evaluate insights that exist since a long time and to consider to what extent they are applicable to our discussion on scientific reasons *to exclude pregnant women*. The NIH Policy document presents three scenarios in which (non-pregnant) women and minorities should (not) be included in clinical research (Box 1). In an earlier article we have described our position towards inclusion of these subgroups in research[37]. Below we will summarize this position, and elaborate on it by applying the position to the inclusion of pregnant women in phase III drug research in these three

scenarios. In particular, we will evaluate what constitutes a "scientific reason" to justify exclusion of pregnant women.

## Relevant differences exist (NIH scenario 1)

In this scenario we 'know' (meaning that we are very confident) that the (un)intended effects of the intervention differ between non-pregnant humans and pregnant women, yet safety (whether it has unwanted side-effects) and efficacy are unknown in magnitude. If we are confident that the effects will differ between women who are pregnant and women who are not, one overall effect estimate based on a study population that is a mixture of these two groups will be little informative and applies neither to pregnant nor to non-pregnant women. The estimated overall effect will apply only to a population with a similar distribution of pregnant and non-pregnant women. In such a situation, indeed, the NIH Policy document advises to set up different trials or to conduct one trial with two objectives (i.e. investigate the effect in pregnant and non-pregnant women separately, but within the same trial). Thus, if, prior to conducting a trial, it is evident that the effects of an intervention will differ between pregnant and non-pregnant women, running a trial in a group of women, part of whom is pregnant, seems futile. Either a trial is conducted in one of these subgroups, or a larger trial is designed, with pre-specified subgroup analyses looking at the effects of the intervention in the two groups of women separately. Estimating a single overall intervention effect, in our case not taking into account the pregnancy status of a woman, will in such a case be a senseless thing to do.

We think that scenario 1 should be the default for clinical research with pregnant women. Because of the limited evidence about safety and efficacy of drugs in pregnant women we typically rather assume than know that differences exist. If we assume rather

**Box 1: Sections of the NIH Policy document of relevance to inclusion of pregnant women**

*The NIH is mandated by law (Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2 ) to ensure the inclusion of women and minority groups in clinical research*

Inclusion of women and minorities in NIH sponsored research is mandated by law. "The director of NIH shall, subject to subsection (b) of this section, ensure that…women are included as subjects in each project of such research"…, unless the research "(1) is inappropriate with respect to the health of the subjects;(2) is inappropriate with respect to the purpose of the research; or (3) is inappropriate under such other circumstances as the Director of NIH may designate"

Section c: Design of clinical trials
In the case of any clinical trial in which women or members of minority groups will under subsection (a) of this section be included as subjects, the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial.

**Box 1:** (continued)

**NIH Policy**

**A. Inclusion of Women and Minorities as Subjects in Clinical Research**

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy applies to research subjects of all ages in all NIH-supported clinical research studies.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract proposal appropriate to the scientific objectives of the study/contract. The research plan/proposal should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

**B. NIH-defined Phase III Clinical Trials: Planning, Conducting, and Reporting of Analyses for Sex/Gender and Race/Ethnicity Differences**

When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

Investigators must consider the following when planning, conducting, analyzing, and reporting an NIH-Defined Phase III clinical trial. Based on prior studies, one of the three situations below will apply:

*1. Prior Studies Support the Existence of Significant Differences*

If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, the primary question(s) to be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this. For example, if men and women are thought to respond differently to an intervention, then the Phase III clinical trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.

*2. Prior Studies Support No Significant Differences*

If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and/or relevant subpopulation comparisons, then sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

*3. Prior Studies Neither Support nor Negate Significant Differences*

If the data from prior studies neither strongly support nor strongly negate the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, then the NIH-defined Phase III clinical trial will be required to include sufficient and appropriate entry of sex/gender and racial/ethnic participants, so that valid analysis of the intervention effects can be performed. However, the trial will not be required to provide high statistical power for these comparisons.

than know that there are differences, scenario 1 is preferred in order to avoid taking unnecessary risks and instead be on the safe side. At the same time, it does not follow from our default position that separate trials should always automatically be set up in pregnant women, where this is the case for non-pregnant women to whom the NIH policy document applies. Pregnant women differ from the general population of women in this scenario since risks of research may be different and may affect both the pregnant woman as well as the fetus. As such, research in pregnant women may at times be unwarranted due to risk considerations. Moreover, a disadvantageous result of assuming that scenario 1 should be the default position for which separate trials are preferred, is that we will never establish whether our assumed differences are factual.

Including pregnant women in a trial in a scenario 1 situation may be easier said than done. Practically, there may be reasons not to start a separate or larger trial that also includes pregnant women. To illustrate, if researchers primarily have experience in studying interventions in non-pregnant women or if the budget is limited such that a single trial answering two questions is beyond their ability, there may be no incentive to test a drug in pregnant women. Practical reasons for excluding subgroups may seem valid from a political perspective, but considerations of corrective justice should outweigh those reasons. Attention of designated third parties, such as regulators, governmentally funded research bodies and grant organizations will most likely be essential to stimulate the setup separate or larger trials. Corrective justice obligations may be relatively easily fulfilled in the NIH situation, which requires the set-up of different trials for women and minorities and, in our case, pregnant women, but other ethical guidelines for human subject research currently lack this requirement.

## No relevant differences exist (NIH scenario 2)

In scenario 2 we know (meaning that we are very confident) that the effect is equal in pregnant and non-pregnant women. In the case of equal effects between subpopulations, the NIH "encourages" the inclusion of women and minorities. In the case of non-pregnant women encouragement is conceivable, albeit with hesitations. It is not so clear what is meant with encouragement. If we already know that there are no differences then adding more subgroups seems useless and therefore harmful since these subgroups are then unnecessarily exposed to research risks. As in scenario 1, it may also be the case that there is no conclusive evidence, but that we *assume* that there are no differences. For instance, if a drug only works locally, is not systemic and does not cross the placenta, such as local anesthetics for suturing wounds or local corticosteroids for skin lesions, we may assume that the effect in pregnant women is similar to that observed in non-pregnant women. If we only assume that no relevant differences exist we could theoretically encourage subgroups to participate for instance because, as the report of Mastroianni and colleagues claims, "greater heterogeneity among research subjects may permit

the investigator to spot trends that might otherwise be missed, even if the numbers are too small for statistically reliable subgroup analysis"[36]. However, this exploratory approach will imply a trial with minimum social value for the subgroups included. Simply encouraging inclusion without further specifying the hypothesis and the number needed to include may result in exploratory research only. In most cases, another trial will be needed to demonstrate efficacy which implies that more participants will have to be enrolled in research.

At the same time, if results can be extrapolated, one could argue against inclusion of pregnant women specifically, because if the trial effects of an intervention are already known, including pregnant women would mean unnecessarily exposing fetuses to potential risks. If the effects of a drug have already been well-studied in non-pregnant women and are known to be applicable to pregnant women, we merely expose pregnant women and their fetuses to research risks. Alternatively, we may *assume* that there are no differences. Accordingly, the precautionary action would be to err on the side of caution which may result in an automatic referral to scenario 1[42]. Or, if the data to be gathered are primarily safety related and if it is not necessary to conduct a trial in pregnant women to demonstrate efficacy, it may be preferable to conduct post-marketing studies, use registries, and establish small registry studies to pick up safety signals[43].

## It is unclear whether differences exist (NIH scenario 3)

In this scenario it is unclear whether differences exist, which is, due to the vast lack of clinical research in pregnant women, currently the most common situation in practice. Data on drug safety and drug dose range is usually lacking and while phase III trials should not be initiated based on incomplete information, they currently are in practice. As we set out in the introduction, earlier phase trials will be necessary to minimize the risks and optimize the benefits when pregnant women can be included in phase III trials[33]. Given the objections, precaution requires referral back to scenario 1, and hence to assume that there are differences and thus to apply scenario 1[42]. In other words, scenario 3 is the factual default, whereas scenario 1 should be the normative default for research with pregnant women. But erring on the side of caution does not mean automatically halting any study in which pregnant women may face risks and thereby paralyzing the situation. One should weigh the risks of participating in the trial versus the risks of not treating pregnant women, or treating them based on insufficient information. Instead, assuming differences may actually imply the setup of separate drug trials for pregnant women.

Another option in scenario 3 can be oversampling, in case prior studies have been conducted but the differences between pregnant and non-pregnant groups are unclear. To understand what oversampling of pregnant women implies, we first have to scrutinize

the sufficiency criterion. In scenario 3, the NIH Policy document recommends inclusion of a "sufficient" number of participants from a specific subpopulation in order to be able to perform a "valid analysis" of the intervention. However, this sufficiency criterion as such does not guide researchers on how many participants of a certain subpopulation should be included. Evidently, adding only one or two pregnant women to a population consisting of women is no substantial inclusion and cannot be sufficient. What is sufficient very much depends on the research setting. If intervention effects may differ between subgroups of pregnant and non-pregnant women, an estimated overall effect could still be informative for the whole population, be it that it is only informative for a population with similar proportions of pregnant and non-pregnant women. In that case, sufficiency comes down to representativeness in terms of the proportion of pregnant and non-pregnant women. So, if one aims at estimating an effect for a future population of women of whom, say, 5% is pregnant, including 5% pregnant women in a trial would be sufficient. However, if one is actually interested in estimating to what extent effects differ between pregnant and non-pregnant women, a larger sample size is required. Effectively oversampling pregnant women, leading to, for example, 50% pregnant and 50% non-pregnant women would probably be much more efficient for a study with such an objective. Hence, whether sufficiency comes down to (representative) proportionality or oversampling depends on the research question.

And yet, oversampling pregnant women for phase III research in scenario 3 may be challenging for several reasons. First, recruitment and retention of pregnant women in trials is difficult due to a variety of reasons. One of the reasons concerns the individual risk perception of researchers, research ethics committees, sponsors and pregnant women themselves, which plays an important role in the inclusion of pregnant women. Even if the research intervention poses low risks and may potentially benefit the participating pregnant women, when researchers perceive a trial to pose more than low risks to their patients, they may be reluctant to recruit eligible participants (gatekeeping) and pregnant women may be reluctant to participate[44]. Second, for many drugs in pregnant women the purpose will often not be to determine differences in efficacy between pregnant women and non-pregnant women but rather to determine aspects such as effectiveness and safety, including birth defects and teratogenicity. For the latter purpose, it is preferable to follow pregnant women over time because some defects may only manifest over the long term. Moreover, irrespective of the sampling approach, trials may be too small to detect important safety signals. Third, even if pregnant women are oversampled in order to make up 50% of the trial participants, trials that aim at estimating *differences* in intervention effects between subgroups usually require much larger sample size than studies of main effects[45]. Therefore, also in scenario 3, corrective justice is essential and (inter)national and regulatory agencies which stimulate the conduct of these projects in pregnant women and the establishment of registries have to be found.

## DISCUSSION

Fair inclusion of pregnant women means 1) that pregnant women who are eligible are not excluded solely for being pregnant, and 2) that the research interests of pregnant women are prioritized, meaning that they ought to receive substantially more attention. The first component of fair inclusion should not be mistaken for routine inclusion in virtually every trial. Fair inclusion has methodological limitations and exclusion can be justified for scientific reasons. We have described 3 scenarios that outline where scientific considerations should be taken into account. In scenario 1, it is known that intervention effects for pregnant women differ from those for non-pregnant women. We recommend that pregnant women in this scenario should not be included in phase III drug research that consists of non-pregnant women, but to initiate separate trials for pregnant women during phase III or to conduct phase IV and post-marketing studies.

Alternatively, we know that no differences exist (scenario 2), or we are uncertain whether differences exist (scenario 3). In scenario 2, when we know that there are no differences, it may be best to conduct post-marketing studies or to establish registries, such as the pREGnant registry that has been developed by the Netherlands Pharmacovigilance Centre Lareb[46]. And when we assume rather than know that there are no differences, we should refer back to the default of scenario 1. In scenario 3, when there is no sufficient prior information, which will in most instances be the case, it may be preferable to return to scenario 1 and conduct separate trials in pregnant women, based on scientific and precautionary considerations. If there is prior information but the information does not indicate either differences or no differences, inclusion of pregnant women should be sufficient, which explicitly should not mean just enrolling only a few pregnant women in a trial. In this scenario, sufficiency boils down to representativeness in terms of the proportion pregnant and non-pregnant women or to the actual oversampling of pregnant women, depending on the research question.

Regarding the second component of fair inclusion, our paper has shown that fair inclusion cannot and should not be realized at the moment of ethical review of already designed research projects, but rather that fair inclusion requires a joint effort. Due to the current vagueness of the demand to justify exclusion unless scientific reasons exist and the ambiguity as to the level at which and the actors at whom fair inclusion is directed, no group or institution seems to make fair inclusion its sincere priority.

At present, it seems that fair inclusion only comes into play at the moment of ethical review of already designed individual research projects. However, our paper has demonstrated that the establishment of separate trials has to be realized at the earliest phases of research with pregnant women and that the demand to justify exclusion of pregnant women cannot be bestowed upon individual researchers and research ethics committees, since protocols are not easily adjusted once researchers have planned their study methods

and budgets may be restricted. Additionally, researchers that may be willing to include more pregnant women or to develop separate trials will need extra budget to do so. And thus funders and scientific advisory councils must see it as their priority to promote research with pregnant women and to facilitate the research infrastructure[36]. In this respect, it will also be important to pay more attention to *in vitro* studies, which currently hardly distinguish between sexes in cell lines and hence contribute to the poor pre-clinical evidence base for drugs in (pregnant) women.

Moreover, in order to develop truly innovative medications for pregnant women, we cannot rely on investigator initiated research only and we have to look at pharmaceutical companies. Pharmaceutical companies may be asked to substantially invest in sex-specific dosage or medications, yet, with the costs involved in research and development on this topic, together with additional packaging, marketing and liability fears, they may, understandably, be reluctant. Their additional risk is that an alternate company will claim equal effectiveness for both men and women for their compound, which may be preferred by doctors and society. The marketing campaign for sex-specific medications could turn out to be detrimental. Nevertheless, this year Ferring Pharmaceuticals launched NOCDURNA with gender-specific doses tailored to men and women. The success of this compound and the success of the gender-specific strategy are to be determined in the coming years.

In addition, the integrated analysis of fair inclusion has demonstrated that in most cases it will be essential to establish separate trials or registries and this is typically an activity that necessitates the involvement of authorities, such as national pharmacovigilance centers or regulatory authorities such as the FDA and EMA. However, although the role of the FDA and EMA is regulatory and they may guide the directions, they cannot require of pharmaceutical companies to conduct separate trials in (pregnant) women, unless it is laid down in a regulation or directive such as the EU regulation, comparable to research with children[47]. Similar to the Paediatric Regulation in Europe with a Paediatric Committee and the requirements for Paediatric Investigation Plans (PIPs) for marketing approval, the EMA could establish a pregnancy committee and require pregnancy investigation plans if the drug can potentially be used by pregnant women.

Additional stakeholder groups are journal editors and pregnant women themselves. Journal editors could for instance require subgroup analyses from researchers that submit papers to their journal. Currently, this requirement is still a rarity and does not apply to the conduct of separate trials. Pregnant women could associate in patient groups which in other medical fields, such as the field of orphan diseases or pediatric research, has had success in stimulating drug development. Without patient groups, radical breakthroughs can only be initiated by others than those whose interests are at stake.

In sum, although it is beyond the scope of this paper to conclusively state whose responsibility it is to ensure corrective justice and to prioritize the health interests of

pregnant women in research, our paper shows that fair inclusion of pregnant women in research must primarily be seen as a joint responsibility to further the evidence base for drug use in pregnant women.

## CONCLUSIONS

The demand to justify exclusion of pregnant women from research is not only essential for reasons of equity but also for reasons of corrective justice. Since scientific knowledge on the effects of treatments for the health needs of pregnant women is relatively underrepresented, fair inclusion implies that intensive stimulation of research in this population is justified. Fairness does not imply that pregnant women should be included in virtually every research project. Inclusion of only a few pregnant women in a population of women will not help to determine the effectiveness and safety of a treatment in pregnant women. If pregnant women are included it should be done representatively or they should be oversampled in order to be able to determine a difference in intervention effects between groups of pregnant and non-pregnant women. In the few cases where we may be certain that there are no differences between pregnant and non-pregnant women, we should conduct post-marketing studies or arrange the establishment of registries. But since evidence is typically limited for the treatment of health conditions that affect pregnant women, we either know, or otherwise have to assume, that pregnant women differ from other subpopulations. Separate trials may then be preferable. The current vagueness of the demand to justify exclusion unless scientific reasons exist seems to indicate that fair inclusion only comes into play at the moment of ethical review of already designed individual research projects. However, fair inclusion is not only an obligation for individual researchers and research ethics committees. The development of separate trials has to be realized at the earliest phases of research with pregnant women. In addition to researchers and research ethics committees, scientific advisory councils, funders, drug regulatory agencies, pharmaceutical companies, journal editors and others all have a joint responsibility to further the evidence base for drug use in pregnant women.

## REFERENCES

1. Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. Clin. Pharmacol. Ther. 2008;83:181–3.
2. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, et al. Prescription drug use in pregnancy. Am. J. Obstet. Gynecol. 2004;191:398–407.
3. Mitchell A a., Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am. J. Obstet. Gynecol. Elsevier Inc.; 2011;205:51.e1-51.e8.
4. Lupattelli a, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby a C, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4:e004365.
5. Noah BA. The Inclusion of Pregnant Women in Clinical Research. 2014;
6. Parisi MA, Spong CY, Zajicek A, Guttmacher AE. We don't know what we don't study: The case for research on medication effects in pregnancy. Am. J. Med. Genet. Part C Semin. Med. Genet. 2011. p. 247–50.
7. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
8. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton J a. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. 2013;23:e39-45.
9. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
10. Kennedy Institute of Ethics. Institute News: The Second Wave Workshop: Toward the Responsible Inclusion of Pregnant Women in Medical Research 2009.
11. Little BB. Pharmacokinetics during pregnancy: Evidence-based maternal dose formulation. Obstet. Gynecol. 1999. p. 858–68.
12. CIOMS. International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva, 1993 & 2002; and International ethical guidelines for health-related research involving humans, Geneva, 2016.
13. Sheffield JS, Siegel D, Mirochnick M, Heine RP, Nguyen C, Bergman KL, et al. Designing Drug Trials: Considerations for Pregnant Women. Clin. Infect. Dis. 2014;59:S437–44.
14. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
15. Food and Drug Administration (FDA). Pregnancy and Lactation Labeling (Drugs) Final Rule [Internet]. 2015 [cited 2017 Jul 22]. Available from: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm
16. EMA (European Medicines Agency). Guideline of the exposure to medicinal products during pregnancy: need for post-authorisation data. [Internet]. 2005 [cited 2016 Mar 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf
17. Saint-Raymond A, de Vries C. Medicine safety in pregnancy and ambitions for the EU medicine regulatory framework. Clin. Pharmacol. Ther. 2016;100:21–3.
18. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
19. Scaffidi J, Mol B, Keelan J. The pregnant women as a drug orphan: A global survey of registered clinical trials of pharmacological interventions in pregnancy. BJOG An Int. J. Obstet. Gynaecol. 2016;

20. McCormack S a, Best BM. Obstetric Pharmacokinetic Dosing Studies are Urgently Needed. Front. Pediatr. 2014;2:9.
21. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am. J. Med. Genet. C. Semin. Med. Genet. 2011;157C:175–82.
22. van der Zande ISE, van der Graaf R, Browne JL, van Delden JJM. Fair Inclusion of Pregnant Women in Clinical Research: A Systematic Review of Reported Reasons for Exclusion. In: F Baylis, A Ballantyne. ., editor. Clin. Trials Involv. Pregnant Women. 2016. p. 65–94.
23. Levine RJ. IRB perspective on inclusion of pregnant women in clinical research. ORWH Work. Enrolling pregnant women Issues Clin. Res. An ORWH 20th Anniv. Event. Bethesda, MD: National Institutes of Health; 2011. p. 37–43.
24. Macklin R. Enrolling pregnant women in biomedical research. Lancet. 2010. p. 632–3.
25. Foulkes MA, Grady C, Spong CY, Bates A, Clayton JA. Clinical research enrolling pregnant women: a workshop summary. J. Womens. Health (Larchmt). 2011;20:1429–32.
26. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. Elsevier Inc.; 2013;23:e39–45.
27. Baylis F, Kaposky C. Wanted: inclusive guidelines for research involving pregnant women. J. Obstet. Gynaecol. Canada. 2010;32:473–6.
28. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
29. Baylis F, Halperin SA. Research involving pregnant women: Trials and tribulations. Clin. Investig. (Lond). 2012;2:139–46.
30. Secretariat on Responsible Conduct of Research. Tri-Council Policy Statement (TCPS-2): Ethical conduct for research involving humans. [Internet]. [cited 2016 Mar 25]. Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf
31. National Institutes of Health (NIH). NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001 [Internet]. [cited 2017 Jul 22]. Available from: https://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm
32. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA. 2000;283:2701–11.
33. Roes KCB, van der Zande ISE, van Smeden MC, van der Graaf R . Towards an appropriate framework to facilitate responsible inclusion of pregnant women in drug development programs. submitted.
34. CIOMS & WHO. CIOMS draft guidelines [Internet]. 2016. Available from: http://www.cioms.ch/index.php
35. Langston L. Better Safe Than Sorry: Risk, Stigma and Research During Pregnancy. In: Baylis F, Ballantyne A, editors. Clin. Res. Involv. Pregnant Women. Cham: Springer International Publishing; 2016. p. 1–8.
36. Anna C. Mastroianni, Ruth Faden and DF, editor. Women and Health Research. Washington, D.C.: National Academies Press; 1994.
37. van der Graaf, Rieke; Groenwold, Rolf H. H.; Kalkman, Shona; Grobbee, Diederick E.; Van Delden JJM. From Justifying Inclusion to Justifying Exclusion of Study Populations: Strengths and Limitations. World Med. J. 2013;59:192.
38. Kaposky, Chris . Presumptive Inclusion and Legitimate Exclusion Criteria. In: F Baylis, A Ballantyne, editor. Clin. Res. Involv. Pregnant Women.
39. Halperin SA. Research involving pregnant women : trials and tribulations. 2012;2:139–46.

40. Ballantyne A, Rogers W . Pregnancy, Vulnerability, and the Risk of Exploitation in Clinical Research. In: Clinical Research Involving Pregnant Women. In: F Baylis, A Ballantyne ., editor. Clin. Res. Involv. Pregnant Women. Springer. Switzerland; 2016.

41. Office of Research in Women's Health, NIH . An NIH Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research [Internet]. [cited 2017 Jul 22]. Available from: https://orwh.od.nih.gov/toolkit/nih-policies-inclusion/guidelines.html

42. Van der Zande ISE, van der Graaf R, Oudijk MA, van Delden JJM . How should the precautionary principle apply to pregnant women in clinical research? submitted.

43. EMA (European Medicines Agency). Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling [Internet]. 2008 [cited 2017 Jul 22]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003307.pdf

44. van der Zande ISE, van der Graaf R, Oudijk MA, van Delden JJM. A qualitative study on acceptable levels of risk for pregnant women in clinical research. BMC Med. Ethics. 2017;18:35.

45. Schmidt AF, Groenwold RHH, van Delden JJM, van der Does Y, Klungel OH, Roes KCB, et al. Justification of exclusion criteria was underreported in a review of cardiovascular trials. J. Clin. Epidemiol. Elsevier Inc; 2014;67:635–44.

46. pREGnant [Internet]. [cited 2017 Jul 22]. Available from: https://www.pregnant.nl/

47. EMA (European Medicines Agency). Paediatric Regulation [Internet]. 2007 [cited 2017 Jul 22]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp

# CHAPTER 7

## FACILITATORS AND BARRIERS TO PARTICIPATION: A SYSTEMATIC REVIEW ON THE WILLINGNESS OF PREGNANT WOMEN TO PARTICIPATE IN CLINICAL RESEARCH

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*Submitted after revisions*

## ABSTRACT

**Background:** Although there is consensus among many that exclusion of pregnant women from clinical research should be justified, there is uncertainty as to whether and why pregnant women themselves would be willing to participate even if they were found to be eligible. The objective was to identify the reasons why pregnant women participate in clinical research and thereby to distinguish between facilitators and barriers.

**Methods:** We conducted a systematic review of articles regarding pregnant women's reasons for participation in clinical research. We used the PubMed/MEDLINE, EMBASE, PsycINFO and CINAHL databases and retrieved additional articles through manually searching the reference lists. We included all articles that reported on pregnant women's reasons for participation in clinical research. We accumulated all reasons that were mentioned in the total of articles and collated them to themes, classifying these themes as a facilitator or a barrier.

**Results:** The search identified thirty articles that met the inclusion criteria. Themes classified as facilitators: aspirational benefits, collateral benefits, direct benefits, third party influence and lack of inconvenience. Themes classified as barriers: inconveniences, risks, randomisation, lack of trust in research enterprise, medical reasons and third party influence.

**Conclusions:** Pregnant women report mostly altruistic and personal reasons for their willingness to participate in clinical research, while barriers primarily relate to inconveniences. It appears that pregnant women's described reasoning is similar to the described reasoning of non-pregnant research subjects. Enhancing the facilitators and overcoming the barriers is the next step increase the evidence-base underlying maternal and foetal health.

## BACKGROUND

Over the past decades pregnant women have been underrepresented in clinical research which has led to a problematic situation where treatments and medications for pregnant women are often not evidence-based. At the same time, women do need treatment and medication during their pregnancy because of obstetric illnesses and chronic conditions such as hypertension, depression, or asthma[1,2]. The percentage of pregnant women taking medications for which there is no substantial data on safety, efficacy and foetal risk evaluation may currently be as high as 84-99%[3–5]. To illustrate, in the Unites States almost one half of all pregnant women receive prescription drugs from categories C, D, or X of the U.S. Food and Drug Administration (FDA) risk classification system, used to determine the potential to cause birth defects if used during pregnancy[6][1]. The lack of evidence is most prevalent in pharmacological research. Yet, non-pharmacological research in pregnant women is also scarce, as demonstrated by systematic reviews that often have to rely on very small numbers of studies which hamper evidence-based recommendations[7,8]. It is argued that there is a vast need for more research aimed at pregnant women in need of treatment and the only way such research can be performed is by including pregnant women in clinical research, which has been promoted for years by bioethicists, pharmacologists and regulators[2–4,9]. But despite various efforts to challenge underrepresentation of pregnant women in research, exclusion remains common practice[10].

There are different regulatory and clinical barriers sustaining the underrepresentation of pregnant women, such as concerns about harming the foetus, liability fears, research design issues and collective memory of historical tragedies such as diethylstilboestrol and thalidomide, even though neither of these tragedies comprised clinical research[11]. But even if all these barriers would be solved, an open question that remains is whether and why pregnant women themselves would be willing to participate even if they were found to be eligible[1,10,11]. Inclusion depends on the willingness of a target group to enrol in research and before we can speak of (routine) inclusion we need to know if pregnant women are interested in participation at all and what reasons they report as a barriers to participation. Identifying the facilitators and barriers that influence pregnant women's willingness to participate can inform development of clinical research aimed at pregnant women. For example, if it transpires that pregnant women are not willing to

[1] Category B: "Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women"
Category C: "Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"
Category X: "Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits"

participate in certain types of clinical research, developing such research, with all the costs it entails, might not be warranted. The objective of our paper was therefore to identify and systematically review all articles regarding pregnant women's reasons to participate in clinical research.

# METHODS

## Design

We conducted a systematic review of pregnant women's reasons for participation in clinical research for which we used the review of reasons as the starting point and combined it with the thematic synthesis method for the categorisation of the reasons[12,13]. The review of reasons incorporates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[14], which allows for analysis of argument-based literature that is typical for qualitative research, while the thematic synthesis method helps to identify central themes across different article types.

## Search strategy

A PubMed/MEDLINE, EMBASE, PsycINFO (February 2016) and CINAHL (October 2016) search was conducted to identify relevant studies. Additional articles were retrieved through cross-referencing by way of manually searching the reference lists. We used a broad search strategy including the following range of keywords: (challeng* OR reason* OR motivation* OR view* OR decision*OR attitude* OR willing* OR consideration* OR concern* OR barrier* OR issue*) AND (participat* OR enrol* OR include AND (stud*OR trial* OR research) AND (pregnan* OR expecting wom*). No date limits were applied. Table 1 contains the databases and detailed search strings.

## Study selection and inclusion criteria

One researcher (IvdZ) independently reviewed all titles and abstracts and in case of any uncertainty about exclusion, the article was included for full text assessment. A second reviewer (RvG) independently checked a random sample (> 10%) of the initially selected abstracts from the PubMed/MEDLINE results for consistency. Full text selection was performed by 2 reviewers (IvdZ and RvdG) independently of each other. Any remaining inconsistencies were resolved in a consensus meeting with a third reviewer (HvD). We included articles regarding both pregnant and previously pregnant women's views on participation in actual and hypothetical clinical research; this was determined on the basis of references to the topic in the title or the abstract. Clinical research was understood as any research that studies health or illness in human participants. When it was apparent from the title that the content was outside of the research scope, we excluded the articles. When we could not determine whether pregnant women's views would be explicitly

mentioned based on the title, we consulted the abstract or if necessary the full text. We excluded articles that were not in English, only reported on primary research reports of trials, or were outside the scope of clinical research during pregnancy, for example about abstaining or delaying pregnancy or about strategy or care.

### Data extraction and analysis

Our first strategy was to collect all contextual data of included articles, such as the country of origin, the type of intervention, the study population, the aim and methods of the article and the study intervention the article reported on. We categorised each article as comprising a retrospective, prospective or hypothetical study design. We extracted all reasons identified in the articles. In the first stage of analysis, we developed categories that included clusters of reasons. At this point, we did not apply a hierarchical structure and where possible used text descriptors from the included articles. In the second stage of analysis, we generated higher order analytical themes, thereby classifying the themes either as a facilitator or barrier[15]. Where possible, we chose themes that closely related to the reasons that were provided in the articles. Ultimately, the content of the themes was determined by consensus within the study team. First, the themes were discussed by two researchers (IvdZ and RvG). When there were any further disagreements they were resolved in consultation with a third researcher (HvD).Through this discussion, more abstract and analytical themes sometimes emerged.

## RESULTS

### Search and selection

After removing duplicate references, we screened 2278 unique references on title and then 141 on abstracts of which 52 met the inclusion criteria and were screened full text. After further full text assessment for eligibility, 22 articles were excluded because they did not provide pregnant women's views regarding participation in clinical research. In case of the excluded articles, the topics involved inclusion or exclusion of pregnant women, or aspects relating to their informed consent, but without specifically mentioning pregnant women's own motivations. Consequently, 30 articles were included in the final review (see Figure 1. PRISMA Flow diagram).

### Study characteristics

In Table 2 we summarise our findings on the reasons identified in all selected articles, as well as the characteristics of the articles themselves. Eleven articles reported on reasons for participation, eight articles reported on reasons for refusal, and eleven articles reported on both. Most articles were retrospective (n=13), where the researchers asked previous research participants about their experiences in that study. Some articles

were hypothetical (n=10), in which case (pregnant) women were asked to envision their motivations with regard to a hypothetical scenario. And other articles were prospective (n=7), regarding the views of participants whom were currently enrolled in a study. Moreover, most articles reported on obstetric conditions (n=19) while only a few articles reported on non-obstetric conditions (n=8). In some articles the condition was unreported or both obstetric and non-obstetric conditions were researched (n=3). In addition, most articles reported on non-pharmacological interventions (n=17). Apart from three articles, all articles originated from western countries, especially the UK (n=10), the USA (n=7) and Canada (n=5). Since all articles reported on other studies or interventions ("original study design"), we provided the information on those other studies as well in order to shed light on the context in which the reasons were given. All data that we retrieved originated from the secondary add-on studies, i.e. the studies that reported on pregnant women's reasons for participating, which were performed after or in addition to the primary study.

## Synthesis of the reasons

Table 3 provides an overview of the total number of reasons that were identified in the articles in the review. The aim of the review of reasons is to collect and summarise all the reasons that are mentioned in the total of empirical literature. Therefore, Table 3 presents all reasons without any hierarchical order (to clarify: we do not aim to give weight to the reasons or the articles, and the most frequently mentioned reasons are not presented as the most important reasons). In some instances, the reasons were mentioned in a specific phrasing in the article by the authors themselves, whereas in other instances we categorised the given motivations as such ourselves. For example, sometimes authors mentioned 'altruism', whereas other times they mentioned 'wanting to help others', we classified both of these reasons under the theme 'altruism'. Since there was considerable consistency among the reported reasons we were able to apply a thematic evaluation which led to a categorisation of most reasons around different themes (Table 4).

Five themes incorporated reasons that we classified as facilitators (n=reasons): aspirational benefits (n=23), collateral benefits (n=22), direct benefits (n=15), third party influence (n=5) and lack of inconvenience (n=4). Here, we grouped the first three themes according to the so-called benefit typology[16]. Hence, direct benefits refer to benefits for the participant directly arising from receiving the intervention that is being studied; collateral benefits are indirect benefits stemming from being in the study; and aspirational benefits refer to benefits for others which could arise from the results of the study. Six themes regard reasons that we classified as barriers (n=reasons): inconveniences (n=24), risks (n=9), randomisation (n=7), lack of trust in the research enterprise (n=6), medical reasons (n=5) and third party influence (n=5). The themes are described below.

## Facilitators

Aspirational benefits were cited in all studies describing reasons for participation (n=23), with the exception of three studies, two of the studies originating from non-western countries[17,18]. A distinction could be found between altruistic motives to help others in similar situations such as future women and babies, and motives to advance science in general.

Collateral or indirect benefits emerged as another theme motivating women to take part in research (n=22). These indirect benefits entail both materialistic benefits, for example receiving a free ultrasound or a vaccination (n=8), as well as the perceived benefit stemming from being monitored more closely or receiving better treatment while in a research setting (n=7). The latter was most frequently mentioned when studies involved randomised controlled trials (RCTs) involving more invasive interventions, such as magnesium sulphate versus placebo treatment in women with preeclampsia[19], expected management versus amniocentesis-based management in women with premature rupture of membranes (PROM)[20] or the comparison of two dosages of H1N1 vaccines[21]. Another indirect benefit recurrently cited was learning about pregnancy health (n=7), primarily in studies among less privileged population groups. Five out of seven studies in which learning was mentioned comprised either research in a Low-and Middle-Income Country or involved study populations encompassing minority groups or persons with lower education levels.

Potential direct benefits (n=15) were also reported as reasons for participation. Women indicated that their research participation could result in better treatment and more favourable outcomes for the foetus, the baby or the mother. One case illustrated that women perceived the intervention as being favourable and participated because the intervention was not available outside of the trial[22]. Finally, the least cited reasons related to the themes of third party influence (n=5) and a lack of inconveniences (n=4). The former refers to suggestions for participation by either a partner or a healthcare professional, while the latter concerns pregnant women's interest in research participation as long as inconveniences such as having to travel or spending excessive time on the study are absent.

## Barriers

The most frequently mentioned reasons for refusing to participate related to the theme of inconveniences (n=24), encompassing both practical inconveniences and physical inconveniences. The former includes practicalities such as time investments and distance to the study site. The latter includes physical distress, such as fearing the pain of an intervention or the need to take additional tests , as particularly observed in case of longitudinal studies[23–25]. Other reported reasons related to respectively the theme of risks (n=9) and randomisation (n=7). With regard to the former, potential risks for either the mother or the foetus were primarily mentioned in studies involving slightly

more invasive study designs and thus higher levels of risk[20,26–28]. Additionally, an apprehension to take medications during pregnancy was cited, referring to the fear that taking medications could potentially be hazardous for the foetus[26,27]. With regard to the latter, a reluctance to take placebos as part of an RCT and a disbelief in equipoise were cited as reasons. In these instances, it was reported that women wanted the assurance of receiving the actual intervention and being deprived of that choice was a reason to refuse participation. However, three of the studies in which the process of randomisation was cited as a reason to decline participation, involved very specific hypothetical trials on vaginal delivery versus an elective caesarean section[28–30]. These studies indicated that pregnant women preferred vaginal delivery in the first place and henceforth did not want to be randomly assigned to an arm of the trial.

Another theme was a lack of trust in the research enterprise (n=6), which related to both distrust in the researchers or pharmaceutical companies, or to previous negative experiences with research. A lack of trust in the research enterprise was reported by pregnant women from a minority population as well as pregnant women that were not from a minority population[31–33]. Finally, the less cited reasons concerned the themes medical reasons (n=5), indicating women's refusal based on either acute health problems which took prominence over research participation or an overall poor pregnancy health situation, and the theme of third party influence (n=5),either referring to the need for discussion with the family or to a lack of a social support system.

# DISCUSSION

## Facilitators

This review demonstrates that aspirational benefits, meaning motivations to contribute to science or a willingness to help future pregnant women in general, was the most frequently cited theme. Aspirational benefits could be addressed at the time of study recruitment by highlighting the lack of available research and value of involvement for participants and other pregnant women. Nevertheless, our review demonstrates that aspirational benefit is not the only facilitator to participation. Although sometimes cited as the primary motive for participation[23,34], aspirational benefits are often mentioned as one of many equally important reasons influencing the willingness to participate, for instance conditional upon the potential risk or benefit for the mother or foetus[19,20,27,35]. Other review studies incorporating patients or healthy volunteers have also identified 'conditional altruism', noting that altruistic motives are often conditional upon financial reward[36,37], or personal benefits[38,39].

The frequent citing of collateral benefits, referring to additional services or learning about pregnancy health or enhanced care, seems to be another illustration of the complexity of motivations for participation. Often, collateral benefits cannot be assigned to one

single reason, but depend on a broader context in which decisions are taken. Notably, the perceived idea of receiving enhanced care, mentioned seven times, could suggest that participants might sometimes suffer from therapeutic misestimation, where research participants misunderstand the probability of direct benefit or harm and could in this case overestimate the benefits[40]. Although some have argued that pregnant women are more prone to be subject to therapeutic misestimation than non-pregnant research subjects[41], this claim has not yet been validated.

## Barriers

With regard to themes that could be classified under barriers to participation one might have expected more reasons regarding a fear of harm to the foetus. However, few of the included studies involved more than minimal risk[20,26,27]. It appears that only in clinical research that encompasses more than slightly invasive interventions, the reasons for refusal particularly involve the foetus. With regard to other types of study designs, pregnant women report similar reasons as non-pregnant participants and it thus seems remarkable that pregnant women have been excluded from for example observational research or research about physiological processes involving FDA approved drugs that are already used by pregnant women[42,43]. Here, risks are negligible or absent and *a priori* exclusion of pregnant women seems unjustified.

Relative to clinical research where risks are negligible, reasons of inconveniences constitute the most frequently mentioned theme, in line with the lack of inconvenience that was cited as a facilitator for participation and similar to reported barriers in studies among other non-pregnant research groups[44–47]. Finally, reasons referring to a lack of trust in the research enterprise were also reported and classified under a barrier to participation. Mistrust in the research enterprise is not an uncommon theme in relation to participation in clinical research, mostly noted in cases of clinical research with minority populations[48]. Nevertheless, a lack of trust may also be particularly relevant to research in pregnant women, possibly due to the collective memory of several historical tragedies such as DES (Diethylstilboestrol) and thalidomide[11,42]. In this review, a lack of trust in the research enterprise was reported by pregnant women from both minority and non-minority populations[31–33].

Our review reveals that there are a variety of reasons why pregnant women participate in clinical research, seemingly similar to those described by non-pregnant research subjects. Particularly the reasons that were most often reported, aspirational benefits or conditional altruism, or inconveniences or a lack thereof, are reasons that are reported by pregnant and non-pregnant research subjects alike. One way in which aspirational benefits could be addressed in a useful manner is by referring to these benefits in the recruitment phase of a study. For example, by informing pregnant women about the current lack of scientific

data in their population, thus raising awareness about the value of participation for both current and future pregnant women. Additionally, it may feasible to (partly) take away the barrier of inconveniences, for example by keeping demands to a minimum by reducing the number of hospital visits or limiting the amount of questionnaires[24,49]. Assessing all possibilities which might contribute to lowering the threshold of participation due to inconveniences is beyond the scope of this paper, but could be interesting for future debate.

Finally, education of pregnant women and sensitive communication by researchers may contribute to decreasing the lack of trust in the research enterprise. Ultimately, the likelihood that pregnant women will participate shows that it is at least feasible to develop research in which pregnant women are included. Moreover, recognising and understanding the facilitators and barriers enables researchers to develop recruitment strategies that promote altruism and that offer collateral benefits, while taking away practical and physical inconveniences where possible. Evidently, there are other barriers that may hinder inclusion of pregnant women in clinical research, for example gatekeeping by healthcare professionals and RECs[50–52], or ambiguity on the acceptable level of risk[52,53]. Yet this review at least answers the question on the willingness to participate of pregnant women themselves. If pregnant women are indeed willing to participate for altruistic and personal reasons they might decide to enrol in research which does not entail many inconveniences, which could be beneficial in increasing the overall evidence-base underlying maternal and foetal health.

## Limitations

This systematic review has some limitations. First, the articles that were included varied regarding study design and study sample, therefore challenging the generalizability of the findings. To illustrate, the majority of included articles were from the US, the UK and Canada, possibly reflecting a different research culture than other countries. Furthermore, since only eight articles discussed both reasons why women did and why women did not choose to participate in a study, the reasons we gathered could be one-sided and therefore misleading. Second, since we specifically looked for articles in which the views of pregnant women on participating in clinical research were a major subject, we choose to exclude a large number of articles based on title and abstract and as such we might have excluded relevant articles. Third, since there is no tool available to perform a quality assessment of different reasons, we were unable to determine whether the most mentioned reasons also correspond to the strongest reasons.

Fourth, it was striking that the majority of the studies in our review either employed retrospective or hypothetical methods. Within these studies, it is difficult to adjust for the fact that women were not confronted with an actual situation which perhaps

affected their reasoning, or a time gap or pregnancy outcomes which might have altered the answers or resulted in recall bias. For example, in two studies in which women were retrospectively interviewed about trial participation which involved the administration of antibiotics in pre-term labour, they did not recall that there was any risk involved in the study even though the provided information leaflets explicated the possibility of increased risks[54,55]. Further prospective research on pregnant women's motivations for participation could provide more accurate insights into pregnant women's decision making process at the time of recruitment, which understanding could help to make clinical research in pregnant women more conducive. Finally, the majority of articles included in our review reported on, unsurprisingly, obstetric and non-pharmacological studies. As such, further research about pregnant women's reasons for participation in pharmacological studies is necessary.

## CONCLUSIONS

The systematic review of reasons demonstrates that pregnant women are willing to participate for a variety of reasons. Classifying these reasons into themes, it becomes evident that altruistic and personal reasons are most frequently cited on the facilitator side, while the barriers primarily relate to the theme of inconveniences. Even though more prospective research is needed, these results reveal that pregnant women's described reasoning with regard to participation seems similar to the described reasoning of non-pregnant research subjects. Having identified facilitators and barriers to involvement of pregnant women in clinical research, it is important to consider how future research can overcome barriers to participation. If pregnant women are indeed willing to participate for altruistic and personal motives, they might decide to enrol in research which does not entail many inconveniences, thereby possibly increasing the overall evidence-base underlying maternal and foetal health.

# FIGURES AND TABLES

**Table 1.** Databases and search strings

| Search | Terms | Hits |
|---|---|---|
| **PubMed/MEDLINE** | | |
| **Date of search: February 2016** | | |
| 1 | ((((((((((((((challeng*[Title]) OR reason*[Title]) OR motivation*[Title]) OR view*[Title]) OR decision*[Title]) OR attitude*[Title]) OR willing*[Title]) OR consideration*[Title]) OR concern*[Title]) OR barrier*[Title]) OR issue*[Title])) | 437924 |
| 2 | (((participat*[Title/Abstract]) OR enrol*[Title/Abstract]) OR include[Title/Abstract]) | 994898 |
| 3 | #1 AND # 2 | 33040 |
| 4 | (((stud*[Title/Abstract]) OR trial*[Title/Abstract]) OR research[Title/Abstract]) | 8930839 |
| 5 | (pregnan*[Title/Abstract]) OR expecting wom*[Title/Abstract] | 423399 |
| 6 | #4 AND #5 | 202761 |
| 7 | #3 AND #6 | 850 |
| **EMBASE** | | |
| **Date of search: February 2016** | | |
| 1 | (challenge*:ab,ti OR reason*:ab,ti OR motivation*:ab,ti OR view*:ab,ti OR decision*:ab,ti OR willing*:ab,ti OR attitude*:ab,ti OR consideration*:ab,ti OR concern*:ab,ti OR barrier*:ab,ti OR issue*:ti,ab) | 2972129 |
| 2 | (participat*:ti OR enrol*:ti OR include*:ti) AND (stud*:ab,ti OR trial*:ab,ti OR research*:ab,ti) | 23963 |
| 3 | (pregnan*:ti,ab OR expecting wom*:ti,ab) | 214940 |
| 4 | #1 AND #2 AND #3 | 179 |
| **PsycINFO** | | |
| **Date of search: February 2016** | | |
| 1 | (reason* or challeng* or motivation* or view* or decision* or consideration* or willing* or attitude* or concern* or barrier*).ab,ti. | 1108600 |
| 2 | (participat* or enrol* or include*).ab,ti. | 609130 |
| 3 | #1 AND #2 | 210950 |
| 4 | (pregnan* or expecting wom*).ti,ab. | 36359 |
| 5 | (stud* or trial* or research*).ab,ti. | 2245439 |
| 6 | #4 AND #5 | 22609 |
| 7 | #3 AND #6 | 2341 |
| 8 | limit 7 to (peer reviewed journal and human and English language and "0100 journal") | 1568 |
| **CINAHL** | | |
| **Date of search: October 2016** | | |
| 1 | TX reason* or challeng* or motivation* or view* or decision* or consideration* or willing* or attitude* or concern* or barrier* or issue* | 650,655 |
| 2 | TI participat* or enrol* or includ* or join | 25034 |

**Table 1.** (continued)

| Search | Terms | Hits |
|---|---|---|
| 3 | AB participat* or enrol* or includ* or join | 382233 |
| 4 | #2 AND #3 | 8598 |
| 5 | #1 AND #4 | 4485 |
| 6 | TX pregnan* or expecting wom* | 117669 |
| 7 | AB stud* or trial* or research* | 770623 |
| 8 | #5 AND #6 AND #7 | 139 |

**Figure 1.** PRISMA Flow Diagram

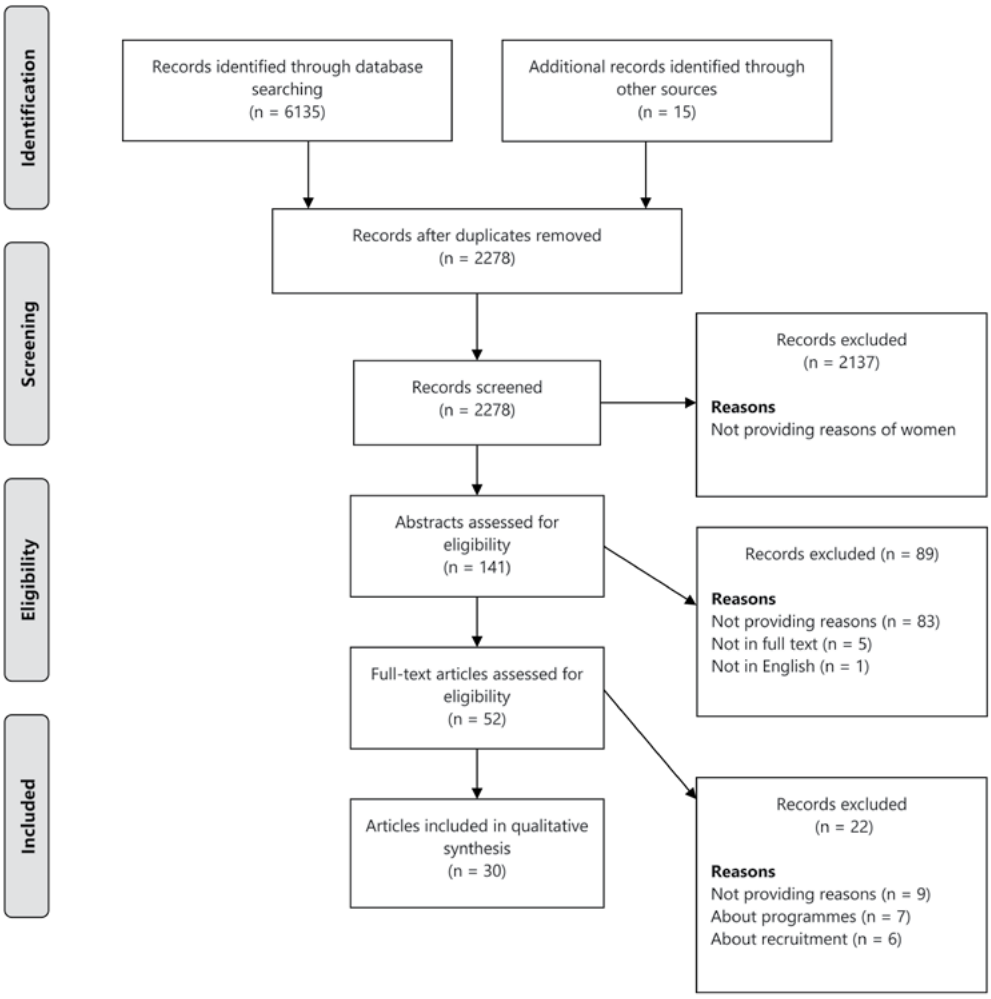

**Table 2.** Summary of articles included in the review

| | REF | Classification original study design | Type of intervention original study | Researched condition + research type original study* | Reasons identified for participating | Reasons identified for not participating |
|---|---|---|---|---|---|---|
| 1 | Baker et al. 2005[31] | Multiple studies | Both invasive and non-invasive studies | Unreported (multiple) | Altruism, enhanced/ inferior care, professional guidance, methodology | Feeling disempowered by the process, inability to believe in equipoise, practical inconvenience |
| 2 | Brogly et al. 2007[55] | Observational | Clinically indicated laboratory tests | Non-obstetric condition + research with no potential individual benefit | | Mistrust, time requirements, distance to clinic, spontaneous abortion |
| 3 | Brumatti et al. 2013[23] | Observational | Collection of among other blood and chord samples | Non-obstetric condition + research with no potential individual benefit | Contribute to research, benefit future babies' and mothers' health, proposed by trusted institution | Study too demanding (time), need to collect biological samples and conduct neurocognitive test |
| 4 | Daniels et al. 2006[56] | Observational | Biological specimen collection | Obstetric condition + research with no potential individual benefit | Interest in science, learning about pregnancy, free ultrasound | |
| 5 | van Delft et al. 2013[24] | Observational | Endovaginal and transperineal ultrasonography | Obstetric condition + unreported | | Being too busy, other pregnancy problems, no additional (internal) examination, moving (abroad), husband |
| 6 | Founds 2007[57] | Hypothetical (RCT) | Maternal knee-chest postural management of breech presentation | Obstetric condition + research with potential individual benefit | Encouraged by provider, gathering health information, altruism, reciprocity | |
| 7 | Garg et al. 2016[58] | Hypothetical (observational) | Collection of information and biological samples | Non-obstetric condition + research with no potential individual benefit | Altruistic motivation, gaining knowledge about infection, material incentives, health benefits from participation, study should be locally, engagement of children | Concerns about data protection, use of needles and blood tests, conflict consenting child for research, consenting healthy children, time pressure, intrusiveness, language barriers |

| Study design secondary article | Country | Aim secondary article | Methods secondary article | Study population secondary article |
|---|---|---|---|---|
| Retrospective | UK | Investigate views of women who participated/ declined in a study during pregnancy | Semi-structured interviews and focus group | A purposive sample of postnatal women who were asked for research at a study hospital (n=17) |
| Retrospective | USA | Report on the rates of and reasons for non-enrolment in a prospective cohort study | Analysis of group data (individual data was abstracted) | HIV-infected pregnant women (n=739) who refused enrolment when presented at clinical sites for prenatal care |
| Prospective | Italy | Verify the reasons that lead pregnant women to give consent/refuse participation into a new-born cohort study with a long follow up time | Question-naires | Mothers of healthy new-borns who participated (n=430) followed up at 18 months, and women who refused (n=304) at the time of refusal |
| Retrospective | USA | Investigate what initially motivated pregnant women to participate in a pregnancy cohort study | Attitude surveys | Previously pregnant women (n=183) who recently participated in the most recent phase of the primary study |
| Prospective | UK | Identify factors that could influence recruitment in a prospective longitudinal study | Telephone interviews | Nulliparous women (n=1043) who declined participation in the longitudinal study |
| Hypothetical | USA | Report on what would influence women's participation in research on breech presentation | Interviews | Pregnant women with breech presentation (n= 7) recruited from two urban obstetric practices |
| Hypothetical | UK | Explore the attitudes of women around regarding themselves and their children to taking part in a large proposed birth cohort study | Focus groups | (Pregnant) women (n=40) recruited from waiting rooms of different general practices |

**Table 2.** (continued)

| | REF | Classification original study design | Type of intervention original study | Researched condition + research type original study* | Reasons identified for participating | Reasons identified for not participating |
|---|---|---|---|---|---|---|
| 8 | Gatny and Axinn 2011[59] | Hypothetical | Biological specimens during pregnancy and at delivery | Unreported (multiple) | Contributing to science, learning about pregnancy health, helping future patients | |
| 9 | Infanti et al. 2012[60] | Interventional (RCT) | Lifestyle intervention compared with standard care in a diabetes prevention trial | Obstetric condition + research with potential individual benefit | | Travel distance /transport, childcare commitments, lack of time/too busy, R&I deterrents, not concerned about diabetes risk, lack of social support, already taking action, health too poor, other |
| 10 | Kenyon et al. 2006[35] | Interventional (RCT) | Antibiotics in pre-term labour | Obstetric condition (emergency situation (labour) + research with potential individual benefit | Possibility of an improved outcome for baby, opportunity to help others (conditional on no-risk situation) | |
| 11 | Lacerte et al. 2008[61] | Hypothetical (RCT) | Amniocentesis management in PROM | Obstetric condition + research with potential individual benefit | Health foetus, advancement own knowledge, receiving active management, finding out best management, feeling of doing more for baby (selection high importance reasons) | Painful, risks foetus, stimulate contractions (selection of reasons classified as high importance) |
| 12 | Lamvu et al. 2005[62] | Observational | Ultrasounds | Obstetric condition + unreported | Free ultrasound, contribution medical knowledge, learning about pregnancy health, concerned with current pregnancy, cash interviews, suggestion provider | |
| 13 | Lavender and Kingdon 2009[63] | Hypothetical (RCT) | Planned vaginal versus planned caesarean birth | Obstetric condition + research with no potential individual benefit | Do what doctor requested, assist with research | Process of randomisation (no control), undesirable trial (not natural), inconvenience of intervention |

| Study design secondary article | Country | Aim secondary article | Methods secondary article | Study population secondary article |
|---|---|---|---|---|
| Hypothetical | USA | Examine the willingness of pregnant women to participate in health research | Survey interviews | A sample of pregnant women (n=90) in a matched control-comparison study of patients with prenatal care |
| Retrospective | Ireland | Examine the characteristics of the participants versus the decliners | Analysis of recorded reasons | Summary of stated barriers to participation available from 156 decliners of the primary study |
| Retrospective | UK | Explore women's experience of being recruited to a RCT in a critical situation | Interviews | Previously pregnant women (n=22) from a specific region who participated in the trial |
| Hypothetical | CAN | Determine the acceptability of a RCT comparing different managements in women with PROM | Question-naires | Pregnant women (n=40) admitted to a tertiary care centre |
| Prospective | USA | Examine women's reasons for participation in an ongoing prospective cohort study | Telephone interviews | Pregnant women (n=1106) during/ at conclusion of their participation in the study |
| Retrospective | UK | Explore women's views of participating in a RCT comparing different birth methods without clinical indication | In-depth interviews | Postnatal women (n=64) who enrolled in a longitudinal study in a teaching maternity hospital |

**Table 2.** (continued)

| | REF | Classification original study design | Type of intervention original study | Researched condition + research type original study* | Reasons identified for participating | Reasons identified for not participating |
|---|---|---|---|---|---|---|
| 14 | Lyerly et al. 2012[21] | Interventional (RCT) | Phase II H1N1 vaccine trial | Non-obstetric condition + research with potential individual benefit | Early access to vaccination, safety advantages of research setting, altruism in relation to science | |
| 15 | Magee et al. 2007[64] | Interventional (RCT) | Tight vs non-tight control of blood pressure management | Obstetric condition + research with no potential individual benefit | Helping others, answering an important research question | |
| 16 | McLeod et al. 2004[30] | Hypothetical (RCT) | Multicentre RCT comparing planned vaginal birth to planned Caesarean for twins | Obstetric condition + research with no potential individual benefit | Altruistic reasons (90%). | Preferred mode of delivery instead of randomisation. |
| 17 | Meshaka et al. 2016[65] | Observational | Observational trial investigating the role of micro-nutrients in gestational diabetes | Obstetric condition + research with no potential individual benefit | An interest in helping medical research advancement, a personal connection to the disease and the lack of inconvenience | |
| 18 | Mihrshahi et al. 2002[66] | Interventional (RCT) | Dietary modification and house mite allergen reduction | Non-obstetric condition + research with potential individual benefit | | Not interested, too busy, did not want tests, too long, medical issues, family problems, no benefit from participation |
| 19 | Mohanna and Tunna 1999[67] | Interventional (RCT) | Nifedepine vs placebo in high risk group | Obstetric condition + benefit unreported | | Presence of placebo arm, communication concerning the language of risk, apprehension about taking medicine (risk for foetus) |
| 20 | Oude Rengerink et al. 2015[22] | Interventional (RCTs) | Clinical trials during pregnancy or shortly after giving birth | Obstetric conditions: benefit unreported (multiple studies) | Contribution to scientific research (also conditional), intervention seemed favourable and not available outside of trial, no harm trying. | Dislike of intervention (either because of harm or because of practical reasons), already in exceptional situation. |

| Study design secondary article | Country | Aim secondary article | Methods secondary article | Study population secondary article |
|---|---|---|---|---|
| Prospective | USA | Assess factors relevant to participating in drug or vaccine trials from the perspective of pregnant women | Interviews | Women (n=22) who were enrolled in a vaccine trial while pregnant |
| Retrospective | CAN | Compare women's views on their likes and dislikes during trial participation | Questionnaires | Postpartum women (n=126) who participated in the trial while pregnant |
| Hypothetical | CAN | Determine women's views regarding participation in a proposed RCT of twin delivery comparing two modes of delivery | Questionnaires | A sample pregnant women (n=64) with known live twin gestations in the second or third trimester (less than 38 weeks) |
| Prospective | UK | Elucidate the opinions of women involved in an observational trial in those at risk of diabetes in pregnancy | Q-Methodology | Women (n=30) involved in a clinical trial investigating the role of micronutrients in the development of gestational diabetes. |
| Prospective | AUS | Report methods for recruitment and reasons why eligible subjects choose to refuse | Telephone interviews | Pregnant women (n=1303) who were eligible for study but decided not to participate |
| Retrospective | UK | Identify why so many women refused to take part in the trial and find out what influences decision-making | Interviews | Women (n=18) who declined participation in the trial |
| Prospective | The Nether-lands | Identify barriers and motivators for participation in a range of clinical trials, regardless of recruitment performance | Interviews | Women (n=21) who were asked to participate in one of eight clinical trials within three months after recruitment for original study. |

**Table 2.** (continued)

| | REF | Classification original study design | Type of intervention original study | Researched condition + research type original study* | Reasons identified for participating | Reasons identified for not participating |
|---|---|---|---|---|---|---|
| 21 | Palmer et al. 2016[32] | Hypothetical (presumably interventional) | Medication and vaccines | Obstetric and non-obstetric conditions + research with and research with no potential individual benefit | Incentive, no extra time, extra healthcare mother + baby, reduced risk sickness during pregnancy, reduced risk sickness baby after birth, birth defects due to infection, improve pre-existing health condition, improve pregnancy outcome | Risk mother during pregnancy, risk mother after pregnancy, risk baby during pregnancy, risk baby after birth, extra time, lack trust researchers, lack trust pharmaceutical companies |
| 22 | Qiu et al. 2013[18] | Hypothetical (observational) | Both invasive and non-invasive studies | Non-obstetric conditions (multiple) + research with no potential individual benefit | Non-monetary incentives | Too much time, need for more information, need to discuss with family members |
| 23 | Rodger et al. 2003[68] | Hypothetical (RCT) | Injections of low molecular weight heparin prophylaxis against thrombophilia | Non-obstetric condition + potential individual benefit | Benefit health foetus, benefit health mother, altruism | Apprehension to take medication during pregnancy, risks for mother, reluctance to take a placebo |
| 24 | Rohra et al. 2009[69] | Observational | Collection of amongst others blood samples | Obstetric condition + research with no potential individual benefit | | Inability to get permission from family members (husband), afraid of prick, not interested, miscellaneous (delivery other hospital/medical) |
| 25 | Smith et al. 2010[70] | Interventional (RCT) | Comparing malaria treatment versus screening methods | Non-obstetric condition + research with potential individual benefit | Health baby, health mother, learning about pregnancy, services (malaria nets etc.) | |
| 26 | Smyth et al. 2009[33] | Interventional (RCT) | Randomisation for magnesium sulphate or placebo in women with preeclampsia | Obstetric condition + research with potential individual benefit | (Reasons def participate again:) benefit self, research important, benefit others, no inconvenience, better care | (Reasons for definitely not participate again:) negative experience |

| Study design secondary article | Country | Aim secondary article | Methods secondary article | Study population secondary article |
|---|---|---|---|---|
| Hypothetical | CAN | Obtain information on women's attitudes and opinions about participation in vaccine and medication trials during pregnancy | Cross-sectional survey | Pregnant women (n=110) who had an appointment at an ambulatory obstetrics and gynaecology clinic |
| Hypothetical | China | Determine the willingness of pregnant women to participate in a large-scale birth cohort study | Cross-sectional survey | Pregnant women (n=526) attending a prenatal clinic |
| Hypothetical | CAN | Investigate the willingness of pregnant women to participate in a RCT and to explore the determinants of decision making | Cross-sectional survey and interviews | Pregnant women (n=50) who were asked to participate in the hypothetical event of thrombophilia |
| Retrospective | Pakistan | Determine the reasons underlying the refusals to participate in a nested case-control study | Analysis of recorded reasons | Pregnant women (n=244) who refused participation in the study |
| Retrospective | Ghana | Investigate the acceptability of different strategies among women enrolled in RCT | Focus group discussions (n=12) | A combination of a purposive and random sample of women (n=unknown) who participated in the trial |
| Retrospective | UK | Provide insight into pregnant women's experiences of participating in a large multi-centre RCT | Questionnaires | A sample of women (n=619) who participated in the trial during their pregnancy |

**Table 2.** (continued)

| | REF | Classification original study design | Type of intervention original study | Researched condition + research type original study* | Reasons identified for participating | Reasons identified for not participating |
|---|---|---|---|---|---|---|
| 27 | Smyth et al. 2012[19] | Interventional (RCT) | Randomisation for magnesium sulphate or placebo in women with preeclampsia | Obstetric condition + potential individual benefit | Self-benefit (idea of receiving better treatment), benefit child, altruism (future women/good for medical science) (major factors) | |
| 28 | Tarrant et al. 2015[54] | Interventional (RCT) | Antibiotics in pregnancy | Obstetric condition _ potential individual benefit | Hope for personal benefit (help the baby) , altruistic motives and a reliance on assumptions of safety | |
| 29 | Turner et al. 2008[28] | Hypothetical (RCT) | Planned vaginal versus planned caesarean | Obstetric condition + potential individual benefit | | Loss of choice (randomisation), accepted level of risk, lack of equipoise |
| 30 | Zielinski 2010[49] | Hypothetical (observational) | Pelvic exams | Obstetric condition + benefit unreported | | Too far, did not want the bother, moved out of state |

* The research condition and the type of original study design (i.e. obstetric/non-obstetric and research with potential individual benefit/research with no potential individual benefit) was often unreported in the primary articles and was instead based on the authors' interpretation.

| Study design secondary article | Country | Aim secondary article | Methods secondary article | Study population secondary article |
|---|---|---|---|---|
| Retrospective | UK | Provide in-depth insight into pregnant women's experiences of participating in a large multi-centre RCT | Semi-structured interviews | A sample of women (n=40) who participated in the trial during their pregnancy and who had already filled out a follow up questionnaire |
| Retrospective | UK | Explore how women revisited their decision to enrol in the original trial while receiving findings | Semi-structured interviews | Sample of women (n=380 who had participated in the original study and the follow-up study and received the results in the form of a feedback leaflet. |
| Hypothetical | AUS | Ascertain the feasibility of a RCT concerning delivery modes | Interviews | Pregnant women (n=102) presenting at a tertiary referral centre |
| Hypothetical | USA | Determine whether women would agree to pre-pregnancy, follow up and postpartum data collection | Reported by study co-ordinator | Women (n=9) who achieved pregnancy and remained eligible for the follow up study |

**Table 3a.** Overview of reasons for participating*

| General theme | Article number (number in Table 1) |
|---|---|
| **ASPIRATIONAL BENEFITS (n=23)** | |
| **Altruism in relation to others (n=12)** | |
| Altruism | 1 |
| Benefit future babies' and mothers' health | 3 |
| Altruism | 6 |
| Altruistic motivation | 7 |
| Helping future patients | 8 |
| Opportunity to help others | 10 |
| Helping others | 15 |
| Altruistic reasons | 16 |
| Altruism | 23 |
| Benefit to others | 26 |
| Altruism (future women/medical science) | 27 |
| Altruistic motives | 28 |
| **Altruism in relation to advancing science (n=11)** | |
| Contribute to research | 3 |
| Interest in science | 4 |
| Contributing to science | 8 |
| Finding out what the best management is | 11 |
| Contribution to medical knowledge | 12 |
| Assist with research | 13 |
| Altruism in relation to science | 14 |
| Answering an important research question | 15 |
| interest in helping medical research advancement | 17 |
| Contribution to scientific research | 20 |
| Research important | 26 |
| **COLLATERAL BENEFITS (n=22)** | |
| **Extra (medical) benefits (n=15)** | |
| Enhanced care of being in the study | 1 |
| Free ultrasound | 4 |
| Material incentives | 7 |
| Cash for doing interviews | 12 |
| Receiving active management | 11 |
| Free pregnancy ultrasound | 12 |
| Early access to vaccination | 14 |

**Table 3a.** (continued)

| General theme | Article number (number in Table 1) |
|---|---|
| Safety advantage of research setting | 14 |
| Extra healthcare for the baby | 21 |
| Extra healthcare for the mother | 21 |
| Provided with an incentive | 21 |
| Non-monetary incentives | 22 |
| Services (malaria nets) | 25 |
| Better care | 26 |
| Receiving better treatment | 27 |
| Learning about pregnancy (n=7) | |
| **Learning about pregnancy** | 4 |
| Gathering health information | 6 |
| Gaining knowledge about infection | 7 |
| Learning about pregnancy health | 8 |
| Improve knowledge of obstetrical care | 11 |
| Learn about pregnancy health | 12 |
| Learning about pregnancy | 25 |
| **DIRECT BENEFITS (n=15)** | |
| **Potential benefit for the mother (n=7)** | |
| Participation potentially beneficial for the health of the mother | 7 |
| Intervention seemed favourable and not available outside of trial (mother/child) | 20 |
| Reduced risk of becoming sick during pregnancy | 21 |
| Improved pre-existing health condition | 21 |
| Participation potentially beneficial for the health of the mother | 23 |
| Participation potentially beneficial for the health of the mother | 25 |
| Benefit to self | 26 |
| Potential benefit for the foetus (n=8) | |
| Improved outcome for baby | 10 |
| **Benefit health foetus** | 11 |
| Improved pregnancy outcome | 21 |
| Reduced risk of baby becoming sick/birth defects after birth | 21 |
| Benefit health foetus | 23 |
| Health baby | 25 |
| Benefit for child | 27 |
| Hope for personal benefit (help the baby) | 28 |

**Table 3a.** (continued)

| General theme | Article number (number in Table 1) |
|---|---|
| **THIRD PARTY INFLUENCE (n=5)** | |
| Guidance by others (professionals/partner) | 1 |
| Proposed by trusted institution | 3 |
| Encouraged by provider | 6 |
| Would do what doctor requested | 13 |
| Suggestion prenatal care provider | 12 |
| **LACK OF INCONVENIENCE (n=4)** | |
| Study should be locally | 7 |
| Lack of inconvenience | 17 |
| No extra time | 21 |
| No inconvenience | 26 |
| **MISCELLANEOUS** | |
| Methodology (e.g. number of times asked to participate/study design) | 1 |
| Reciprocity | 6 |
| Engagement of children | 7 |
| Feeling of doing more for baby | 11 |
| Concerned with current pregnancy | 12 |
| Personal connection to the disease | 17 |
| No harm trying | 20 |
| Reliance on assumptions of safety | 28 |

**Table 3b.** Overview of reasons for not participating

| General theme | Article number (number in Table 1) |
|---|---|
| **INCONVENIENCES (n=24)** | |
| **Practical inconveniences (n=15)** | |
| Practical things | 1 |
| Time requirements | 2 |
| Distance to clinic | 2 |
| Too demanding (time-wise) | 3 |
| Time pressure | 7 |
| Too busy | 5 |
| Travel distance/transport | 9 |

**Table 3b.** (continued)

| General theme | Article number (number in Table 1) |
|---|---|
| Lack of time/too busy | 9 |
| Childcare commitments | 9 |
| Too busy | 18 |
| Too long | 18 |
| Extra time | 21 |
| Too much time | 22 |
| Too far | 30 |
| Did not want the bother of clinic visits | 30 |
| **Physical inconveniences (n=9)** | |
| Need to collect biological samples and tests | 3 |
| Additional (internal) examination | 5 |
| Use of needles and blood tests | 7 |
| Intrusiveness | 7 |
| Painful | 11 |
| Inconvenience of intervention | 13 |
| Did not want the tests | 18 |
| Dislike of intervention | 20 |
| Afraid of (blood)prick | 24 |
| **RANDOMISATION (n=7)** | |
| Did not believe in equipoise | 1 |
| Process of randomisation (no control) | 13 |
| Undesirable trial (not natural) | 13 |
| Preferred mode of delivery instead of randomisation | 16 |
| Presence of placebo arm | 19 |
| Reluctance to take a placebo | 23 |
| Loss of choice through randomisation (in relation to a disbelief in equipoise) | 29 |
| **RISKS (n=9)** | |
| **Risk limitation (n=7)** | |
| Risk foetus (afraid needle will touch baby) | 11 |
| Afraid treatment stimulate contractions | 11 |
| Communication about risk | 19 |
| Risk mother during pregnancy and after pregnancy | 21 |
| Risk baby during pregnancy and after birth | 21 |
| Risks to mother | 23 |
| Levels of risk | 29 |

**Table 3b.** (continued)

| General theme | Article number (number in Table 1) |
|---|---|
| **Apprehension to take medication and increase risk for foetus (n=2)** | |
| Apprehension to take medicine (risk foetus) | 19 |
| Apprehension to take medication during pregnancy | 23 |
| **MEDICAL REASONS (n=5)** | |
| Spontaneous abortion | 2 |
| Other pregnancy problems | 5 |
| Health too poor to participate | 9 |
| Medical issues | 18 |
| Already in exceptional situation (health-wise) | 20 |
| **THIRD PARTY INFLUENCE (n=5)** | |
| Opinion husband | 5 |
| Lack of social support | 9 |
| Family problems | 18 |
| Need to discuss with family members | 22 |
| Permission family members | 24 |
| **LACK OF TRUST IN THE RESEARCH ENTERPRISE (n=6)** | |
| Disempowered by the process | 1 |
| Mistrust | 2 |
| Concerns about data protection | 7 |
| Lack of trust in the researchers | 21 |
| Lack of trust in pharmaceutical companies | 21 |
| Negative experience with research participation | 26 |
| **MISCELLANEOUS** | |
| Conflict consenting child/children for research | 7 |
| Language barriers | 7 |
| Research and intervention deterrents (research fatigue, discomfort tests) | 9 |
| Not concerned about (diabetes) risks | 9 |
| Already taking action on own | 9 |
| Other reasons | 9 |
| Move (abroad) | 5 |
| No benefit from the study | 18 |
| Miscellaneous (delivery other hospital/medical) | 24 |
| No interest in study | 18 |

**Table 3b.** (continued)

| General theme | Article number (number in Table 1) |
|---|---|
| Need for more information | 22 |
| Not interested in research | 24 |
| Moved out of state | 30 |

**Table 4.** Facilitators and Barriers

| Reasons for participating | Article number* ** |
|---|---|
| **4a. Facilitators** | |
| **Aspirational benefits (n=23)** | |
| Altruistic reason of helping others | 1,3,6,7,8,10,15,16,23,26,27,28 |
| Contribute to science | 3,4,8,11,12,13,14,15,17,20,26 |
| **Collateral benefits (n=22)** | |
| Services (free ultrasound, vaccination, malaria nets) | 4,7,12,12,14,21,22,25 |
| Learning about pregnancy | 4,6,7,8,11,12,25 |
| Enhanced care of being in the study | 1,11,14,21,21,26,27 |
| **Direct benefits (n=15)** | |
| Potential benefit for the foetus | 10,11,21,21,23,25,27,28 |
| Potential benefit for the mother | 7,20,21,21,23,25,26 |
| **Third party influence (n=5)** | |
| Suggested by healthcare providers | 3,6,13,12 |
| Suggested by healthcare provider or family member | 1 |
| **Lack of inconvenience (n=4)** | |
| Location and time requirements of study | 7,21 |
| No extra inconveniences | 17,26 |
| **4b. Barriers** | |
| **Inconveniences (n=24)** | |
| Time requirements | 2,3,7,9,9,18,21,22 |
| Physical inconveniences (blood pricks, samples) | 3,5,7,7,11,13,18,20,24 |
| General inconvenience | 1,9,18,30 |
| Distance | 2,9,30 |

**Table 4.** (continued)

| Reasons for participating | Article number* ** |
|---|---|
| **Risks (n=9)** | |
| Risks for mother or foetus | 11,11,21,21,23,29 |
| Apprehension to take medication during pregnancy | 19,23 |
| Communication about risk | 19 |
| **Randomisation (n=7)** | |
| Process of randomisation in relation to a lack of believe in equipoise | 1,13,16,29 |
| Presence of placebo arm, no control | 13,19,23 |
| **Lack of trust in the research enterprise (n=6)** | |
| Lack of trust in research enterprise | 2,7,21,21 |
| Negative experiences | 1,26 |
| **Medical reasons (n=5)** | |
| Other health issues | 2, 5, 9,18,20 |
| **Third party influence (n=5)** | |
| Discussion with family members | 5, 22,24 |
| Family problems | 9,18 |

*Several articles mentioned multiple reasons; in that case the number of the article is repeated
** Article number corresponds to the article number in Table 1.

## REFERENCES

1. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. Elsevier Inc.; 2013;23:e39–45.
2. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
3. EMA (European Medicines Agency). Guideline of the exposure to medicinal products during pregnancy: need for post-authorisation data. [Internet]. 2005 [cited 2016 Mar 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf
4. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
5. Chambers CD, Polifka JE, Friedman JM. Drug safety in pregnant women and their babies: ignorance not bliss. Clin. Pharmacol. Ther. 2008;83:181–3.
6. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, et al. Prescription drug use in pregnancy. Am. J. Obstet. Gynecol. 2004;191:398–407.
7. Hollenbach D, Broker R, Herlehy S, Stuber K. Non-pharmacological interventions for sleep quality and insomnia during pregnancy: A systematic review. J. Can. Chiropr. Assoc. 2013;57:260–70.
8. Zairina E, Stewart K, Abramson MJ, George J. The effectiveness of non-pharmacological healthcare interventions for asthma management during pregnancy: a systematic review. BMC Pulm. Med. 2014;14:46.
9. CIOMS & WHO. CIOMS draft guidelines [Internet]. 2016. Available from: http://www.cioms.ch/index.php
10. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
11. van der Zande ISE, van der Graaf R, Browne JL, van Delden JJM. Fair Inclusion of Pregnant Women in Clinical Research: A Systematic Review of Reported Reasons for Exclusion. In: F Baylis, A Ballantyne. ., editor. Clin. Trials Involv. Pregnant Women. 2016. p. 65–94.
12. Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: a critical review. BMC Med. Res. Methodol. 2009;9:59.
13. Strech D, Sofaer N. How to write a systematic review of reasons. J. Med. Ethics. 2012;38:121–6.
14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst. Rev. 2015;4:1.
15. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med. Res. Methodol. 2008;8:45.
16. King NMP. Defining and describing benefit appropriately in clinical trials. J. Law. Med. Ethics. 2000;28:332–43.
17. Smith LA, Jones C, Adjei RO, Antwi GD, Afrah NA, Greenwood B, et al. Intermittent screening and treatment versus intermittent preventive treatment of malaria in pregnancy : user acceptability. 2010;1–10.
18. Qiu X, He J, Qiu L, Larson CP, Xia H, Lam KBH. Willingness of pregnant women to participate in a birth cohort study in China. Int. J. Gynecol. Obstet. 2013;122:216–8.
19. Smyth RMD, Jacoby A, Elbourne D. Deciding to join a perinatal randomised controlled trial: experiences and views of pregnant women enroled in the Magpie Trial. Midwifery. 2012;28:E478-85.

20. Lacerte M, Bujold E, Audibert F, Mayrand M-H. Amniocentesis for PPROM management: a feasibility study. J. Obstet. Gynaecol. Can. 2008;30:659–64.
21. Lyerly AD, Namey EE, Gray B, Swamy G, Faden RR. Women's views about participating in research while pregnant. IRB Ethics Hum. Res. 2012;34:1–8.
22. Oude Rengerink K, Logtenberg S, Hooft L, Bossuyt PM, Mol BW. Pregnant womens' concerns when invited to a randomized trial: a qualitative case control study. BMC Pregnancy Childbirth. 2015;15:207.
23. Vecchi Brumatti L, Montico M, Russian S, Tognin V, Bin M, Barbone F, et al. Analysis of motivations that lead women to participate (or not) in a newborn cohort study. BMC Pediatr. 2013;13:53.
24. van Delft K, Schwertner-Tiepelmann N, Thakar R, Sultan a H. Recruitment of pregnant women in research. J. Obstet. Gynaecol. 2013;33:442–6.
25. Mihrshahi S, Vukasin N, Forbes S, Wainwright C, Krause W, Ampon R, et al. Are you busy for the next 5 years? Recruitment in the Childhood Asthma Prevention Study (CAPS). Respirology. 2002;7:147–51.
26. Mohanna K, Tunna K. Withholding consent to participate in clinical trials: decisions of pregnant women. Br. J. Obstet. Gynaecol. 1999;106:892–7.
27. Rodger M a, Makropoulos D, Walker M, Keely E, Karovitch A, Wells PS. Participation of pregnant women in clinical trials: will they participate and why? Am. J. Perinatol. 2003;20:69–76.
28. Turner CE, Young JM, Solomon MJ, Ludlow J, Benness C, Phipps H. Willingness of pregnant women and clinicians to participate in a hypothetical randomised controlled trial comparing vaginal delivery and elective caesarean section. Aust. New Zeal. J. Obstet. Gynaecol. 2008;48:542–6.
29. Lavender T, Kingdon C. Primigravid women's views of being approached to participate in a hypothetical term cephalic trial of planned vaginal birth versus planned cesarean birth. Birth. 2009;36:213–9.
30. McLeod L, Barrett J, Hewson S, Hannah ME. Women's Views Regarding Participation in a Proposed Randomized Controlled Trial of Twin Delivery. J. Obstet. Gynaecol. Canada. 2004;26:575–9.
31. Baker L, Lavender T, Tincello D. Factors that influence women's decisions about whether to participate in research: An exploratory study. Birth. 2005;32:60–6.
32. Palmer S, Pudwell J, Smith GN, Reid RL. Optimizing Participation of Pregnant Women in Clinical Trials: Factors Influencing Decisions About Participation in Medication and Vaccine Trials. J. Obstet. Gynaecol. Canada. 2016;
33. Smyth RMD, Duley L, Jacoby A, Elbourne D. Women's experiences of participating in the magpie trial: A postal survey in the United Kingdom. Birth. 2009;36:220–9.
34. Daniels JL, Savitz DA, Bradley C, Dole N, Evenson KR, Eucker B, et al. Attitudes toward participation in a pregnancy and child cohort study. Paediatr. Perinat. Epidemiol. 2006;20:260–6.
35. Kenyon S. Participating in a trial in a critical situation: a qualitative study in pregnancy. Qual. Saf. 2006;15:98–101.
36. Tishler CL, Bartholomae S. The recruitment of normal healthy volunteers: a review of the literature on the use of financial incentives. J Clin Pharmacol. 2002;42:365–75.
37. Stunkel L, Grady C. More than the money: A review of the literature examining healthy volunteer motivations. Contemp. Clin. Trials. 2011. p. 342–52.
38. Edwards SJL, Lilford RJ. The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals. BMJ. 1998;
39. Dainesi SM, Goldbaum M. Reasons behind the participation in biomedical research: A brief review. Rev. Bras. Epidemiol. 2014;17:842–51.
40. Horng S, Grady C. Misunderstanding in clinical research: Distinguishing therapeutic misconception, therapeutic misestimation, & therapeutic optimism. IRB Ethics Hum. Res. 2003. p. 11–6.

41. Sheppard MK. Vulnerability , therapeutic misconception and informed consent : is there a need for special treatment of pregnant women in fetus-regarding clinical trials ? 2016;127–31.
42. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
43. Westreich D, Rosenberg M, Schwartz S, Swamy G. Representation of women and pregnant women in HIV research: a limited systematic review. PLoS One. 2013;8:e73398.
44. Tooher RL, Middleton PF, Crowther CA. A thematic analysis of factors influencing recruitment to maternal and perinatal trials. BMC Pregnancy Childbirth. 2008;8:36.
45. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: A systematic review. J. Clin. Epidemiol. 1999. p. 1143–56.
46. Ellis PM, Butow PN, Tattersall MHN, Dunn SM, Houssami N. Randomized Clinical Trials in Oncology: Understanding and Attitudes Predict Willingness to Participate. J. Clin. Oncol. 2001;19:3554–61.
47. Knechel N a. The challenges of enrolling older adults into intervention studies. Yale J. Biol. Med. 2013;86:41–7.
48. Corbie-Smith G, Thomas S, St George D. Distrust, race, and research. Arch. Intern. Med. 2002;162:2458–63.
49. Zielinski R, Ackerson K, Misiunas RB, Miller JM. Feasibility of a longitudinal study of women anticipating first pregnancy and assessed by multiple pelvic exams: recruitment and retention challenges. Contemp. Clin. Trials. Elsevier Inc.; 2010;31:544–8.
50. van der Zande ISE, van der Graaf R, Oudijk MA, van Vliet-Lachotzki EH, van Delden JJM . A Qualitative Study on Stakeholders' views on the Participation of Pregnant Women in the APOSTEL VI study: a low-risk obstetrical RCT. submitted.
51. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. Clin. Infect. Dis. 2014;59 Suppl 7:S400-7.
52. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton J a. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. 2013;23:e39-45.
53. van der Zande ISE, van der Graaf R, Oudijk MA, van Delden JJM. A qualitative study on acceptable levels of risk for pregnant women in clinical research. BMC Med. Ethics. 2017;18:35.
54. Kenyon S, Dixon-Woods M, Jackson CJ, Windridge K, Pitchforth E. Participating in a trial in a critical situation: a qualitative study in pregnancy. Qual. Saf. Health Care. 2006;15:98–101.
55. Tarrant C, Jackson C, Dixon-Woods M, McNicol S, Kenyon S, Armstrong N. Consent revisited: the impact of return of results on participants' views and expectations about trial participation. Health Expect. 2015;18:2042–53.

# CHAPTER 8

## A QUALITATIVE STUDY ON STAKEHOLDERS' VIEWS ON THE PARTICIPATION OF PREGNANT WOMEN IN THE APOSTEL VI STUDY: A LOW-RISK OBSTETRICAL RCT

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## ABSTRACT

**Background:** Bioethicists argue that inclusion of pregnant women in clinical research should be more routine to increase the evidence-base for pregnant women and foetuses. Yet, it is unknown whether pregnant women and others directly involved are willing to be routinely included. Therefore, we first need to establish what these stakeholders think about research participation in regular pregnancy-related research. However, studies on their views are scarce. In our study, we piggy-backed on a relatively conventional randomised controlled trial (RCT), the APOSTEL VI study, to identify the views of stakeholders on inclusion of pregnant women in this study.

**Methods:** We conducted a prospective qualitative study using 35 in-depth semi-structured interviews and one focus group. We interviewed pregnant women (n=14) recruited for the APOSTEL VI study, in addition to healthcare professionals (n=14), Research Ethics Committee members (RECs) (n=5) and regulators (n=7) involved in clinical research in pregnant women.

**Results:** Three themes characterise stakeholders' views on inclusion of pregnant women in the APOSTEL VI study. Additionally, one theme characterises stakeholders' interest in inclusion of pregnant women in clinical research in general. First, pregnant women participate in the APOSTEL VI study for potential individual benefit and secondarily for altruistic motives, contrary to hypothetical studies. Second, a gatekeeping tendency hampers recruitment of pregnant women who might be eligible and willing, and questions about pregnant women's decisional capacities surface. Third, healthcare professionals sometimes use the counselling conversation to steer pregnant women in a direction. Fourth, all stakeholders are hesitant about inclusion of pregnant women in clinical research in general due to a protective sentiment.

**Conclusions:** Pregnant women are willing to participate in the APOSTEL VI study for potential individual benefit and altruistic motives. However, an underlying protective sentiment, resulting in gatekeeping and directive counselling, sometimes hampers recruitment in the APOSTEL VI study as well as in clinical research in general. While bioethicists claim that inclusion of pregnant women should be customary, our study indicates that healthcare professionals, regulators, RECs and pregnant women themselves are not necessarily interested in inclusion. Advancing the situation and increasing the evidence-base for pregnant women and foetuses may require additional measures such as investing in the recruitment and feasibility of RCTs and stimulating pregnant women's decisional capacities.

## BACKGROUND

For decades, bioethicists, pharmacologists, researchers, clinicians and regulators have argued that research participation of pregnant women is essential in order to increase the evidence-base for drugs and treatments for their population, which is needed to achieve fair healthcare opportunities and overcome current suboptimal care and under-treatment[1–10]. Various efforts to challenge pregnant women's underrepresentation in clinical research have been undertaken by the research community. The Unites States Office of Research on Women's Health (ORWH) of the Department of Health and Human Services (DHHS) has endorsed the view that pregnant women are to be presumed eligible for participation in clinical research[11]. Another example is the Second Wave Initiative which was launched in 2009, a collaborative academic initiative to find ethically and scientifically responsible means to increase the knowledge base for the treatment of pregnant women with medical illness[1]. Some ethical guidelines have also made an attempt to promote fair inclusion of pregnant women, for example by stating that research in pregnant women should be encouraged[6] or that women should not be inappropriately excluded from research solely because they are pregnant[12].Others have even argued for the routine inclusion of pregnant women, referring to the regular inclusion of pregnant women in both obstetric and non-obstetric potentially beneficial clinical research (potentially beneficial for the group and/or the individual), except when there are compelling scientific or ethical reasons to exclude them[13,14]. The term 'routine inclusion' is not hitherto defined, but one proposal is to instigate stand-alone Phase I trials that begin at the same time as Phase III trials in the general population, or to instigate Phase I trials embedded into late Phase II or Phase III trials in the general population[13].

Nevertheless, research participation of pregnant women remains a complex issue, since inclusion of the woman also means inclusion of the foetus, with possibly far-reaching consequences for the future child. So while some bioethicists and guidelines claim that exclusion of pregnant women should be justified or that these women should be routinely included, for ethical reflection on practice it is essential to also identify the considered moral judgements of stakeholders who are directly involved in clinical research in pregnant women. However, literature on stakeholders' views is presently scarce and there is uncertainty as to whether pregnant women themselves would be interested in participation in clinical research, even if they were found to be eligible. In the current literature on pregnant women's willingness to participate in research, it appeared that they report similar motivations as non-pregnant research subjects in their reasoning about participation. For instance, reported reasons for participation were altruistic and personal motives whereas reported reasons for refusal primarily focused around inconveniences[15–20]. However, the majority of these studies employed either retrospective or hypothetical methods, which are problematic due to their recall bias and the gap between reported and actual behaviour.

In addition to continuing ambiguity regarding pregnant women's willingness to participate, there are also concerns whether other stakeholders such as research ethics committee members (RECs) and physician-researchers are willing to include them. Currently, the literature indicates that even though RECs and researchers recognise the value of clinical research in pregnant women, they might be hesitant to conduct or promote research in pregnant women[20–25]. One underlying reason may be that recruitment and retention of pregnant women poses specific challenges, with choices around childbirth potentially being highly emotionally charged for both women and clinicians[24]. Apart from recruitment issues, there may also be additional reasons for stakeholders' reluctance. The aim of our paper was to explore what stakeholders think about inclusion of pregnant women in the APOSTEL VI study: a low-risk obstetrical randomised controlled trial (RCT). In an effort to understand pregnant women's reasoning while being confronted with an actual recruitment scenario, we conducted our in-depth interviews with pregnant women shortly after they had decided upon enrolment, thereby avoiding the drawbacks common to retrospective and hypothetical studies. Moreover, we explicitly piggy-backed on a relatively conventional obstetrical study, where risks were low and where potential individual benefit was not by itself a reason why every pregnant woman would automatically participate. As such, the decision to participate was not an obvious one and the respondents had to critically consider their choice with regard to participation.

# METHODS

## Study design

We employed a qualitative study design using semi-structured in-depth interviews and one focus group to explore stakeholders' views on the topic of inclusion of pregnant women in the APOSTEL VI study. Because our aim was to explore the context and the attitude and beliefs of stakeholders beyond the medical outcomes of the APOSTEL VI study, we chose in-depth interviews as the primary method of investigation. We conducted an exploratory focus group before instigating the interviews, in order to explore the topic among professionals and restructured the interview questions where necessary.

## Sample and Setting

We sought to reach maximum variation in context and conducted the study among a variety of stakeholders whom were contacted by the researcher. We explored the topics through interviews with four groups: pregnant women, healthcare professionals, REC members and regulators. We recruited pregnant women (n=14) from the University Medical Center Utrecht (UMC Utrecht) and the Academic Medical Center (AMC) in Amsterdam, the Netherlands. Pregnant women were eligible when they were recruited for the APOSTEL VI study and had made their decision about enrolment in that study (see Box 1). As such, we included women who decided to participate in the study as well as women who declined

participation in the study. At the time, the APOSTEL VI study was the only obstetrical study in the Netherlands that provided us access to the purposive sample of pregnant women recruited for a clinical study and the possibility to prospectively interview them. Accordingly, shortly after the women had decided about enrolment in the primary study, they were approached by research midwifes at the study sites. When they indicated an interest in our qualitative study they were later contacted by the researcher of the qualitative study and asked to participate in an interview. We interviewed the respondents after they were randomised to either perceive the pessary or no intervention.

Healthcare professionals and REC members were recruited from the two previously mentioned academic hospitals in the Netherlands. We interviewed gynaecologists (n=3), gynaecologists-in-training (n=6), (research)midwifes (n=5), and REC members (n=5). Of the five REC members, two were also gynaecologists. Additionally, we organised one focus group of 1:15h with regulators (n=5) from LAREB, a Dutch pharmacovigilance centre, where we spoke with employees from the Teratogenic Information Service (TIS) department. Finally, we interviewed two regulators from the Dutch Medicine Evaluation Board (MEB). The ethical framework that guides professionals in the Netherlands primarily consists of national legislation (the Medical Research Involving Human Subject Act (WMO)) and additionally of international guidance documents such as the Declaration of Helsinki. The WMO offers no specific guidance on research involving pregnant women. See Table 1 with characteristics of participants and Figure 1 with the flowchart of inclusion. The REC of the UMC Utrecht assessed the qualitative research proposal and issued a waiver for the project.

**Box 1. APOSTEL VI**

The APOSTEL studies are a series of studies in the field of treatment of preterm labour within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (NVOG Consortium 2.0). The APOSTEL VI study in particular assesses whether a cervical pessary prolongs pregnancy in women who have been admitted for threatened preterm birth but remained undelivered after 48 hours (http://www.studies-obsgyn.nl/apostel6). Women are randomly allocated to receive either a cervical pessary or no intervention. Women participating in the study were not perceived to be at an increased risk since previous studies using the pessary had shown no foetal adverse effects and the cervical pessary was not associated with increased neonatal or maternal morbidity and mortality (APOSTEL VI Research Protocol). The REC of the UMC Utrecht classified the APOSTEL VI study as a low-risk study.

The APOSTEL VI study took place from November 2013 until September 2016, when the study was prematurely stopped following the advice of the Data and Safety Monitoring Board (DSMB). The premature cancellation was due to the fact that after interim analysis the intervention was unlikely to improve outcome, and maternal side effects were often present in the intervention arm.

Our qualitative study took place from March 2015 till September 2016. We interviewed pregnant women shortly after they were randomised to receive either the pessary or no intervention. We reached saturation before the APOSTEL VI itself was cancelled and in all our interviews it was therefore assumed that the APOSTEL VI would be completed. Following the premature cancellation of the APOSTEL VI study, we re-contacted the interviewed women and we asked them to reflect on their experiences in order to develop a comprehensive view of the research process.

## Data collection

All participants were interviewed by one researcher (IvdZ). The focus group was conducted by two researchers (IvdZ and RvdG). Verbal informed consent and written informed consent in case of the pregnant women was obtained from all participants. Initial interview topics and questions were formulated after examination of the relevant literature and discussion with members of the team (see Table 2 for the general topic list and the Appendix for examples of extended topic lists). The semi-structured in-depth interviews were conducted according to a predefined topic list, however, according to the technique of constant comparative analysis, the interview topics evolved as the interviews progressed through an iterative process where the desired result is reached by repeating rounds of analysis[26]. Interviews took place at the workplace or the home of the respondents. Thematic saturation was reached after 20 interviews. Data collection took place from March 2015 to September 2016.

## Data analysis

The analysis was carried out according to the thematic analysis method[27,28]. The focus group and the interviews were transcribed verbatim and the data was imported in the software programme Nvivo 10[29]. IvdZ independently coded the transcripts and through comparison across transcripts higher order themes were found. RvdG checked codes for consistency and the found themes were discussed at team meetings until a consensus was reached. To enhance the validity of our findings, we organised an expert meeting in the last phase of data collection in which we discussed whether our results were an accurate representation of the practice of clinical research in pregnant women.

# RESULTS

Based on the responses of the interviewees, we were able to identify three themes characterising stakeholder's views on the inclusion of pregnant women in the APOSTEL VI study. Additionally, we identified one theme that characterised stakeholders' views on the inclusion of pregnant women in clinical research in general. These themes emerged consistently in one way or another in all interviews. Per theme, the views of pregnant women, healthcare professionals, REC members and regulators are presented. The starting point of the interviews was the APOSTEL VI study, but respondents sometimes extended their observations to include research participation in general, in which cases we included that in the theme as well. Moreover, the fourth theme as a whole relates to participation of pregnant women in clinical research in general. Representative quotations were chosen in order to illustrate the identified themes (Table 3).

## Theme 1. Motivations for participation

The interviews with pregnant women demonstrated that they experienced the decision process about enrolment in the APOSTEL VI study as difficult, also in light of their particular situation: a healthy pregnancy up till the moment they were suddenly admitted to the hospital for threatened preterm birth and having to decide upon study enrolment. Six women were pregnant for the first time, while of the other eight women, seven had had one or more miscarriages in the past. The medical history did not seem to have an effect on participation. Pregnant women who chose to participate reasoned that participation could potentially be beneficial for the foetus (preventing a preterm birth) while they perceived there to be no risk since the pessary would not reach the foetus in any way. Another mentioned reason for participation was an altruistic motive to help future women and children and to advance science in general, although this reason was secondary and most women mentioned that they would not have participated if there was no potential benefit.

Reported reasons for refusal were the required extra internal exam that was necessary before the eligibility for participation in the RCT was established (only in UMC Utrecht) which was perceived to be risky, and the extra anxiety or stress that actual participation would entail, stemming from a fear of the pessary itself or the possible consequences of the device (e.g. excessive secretion, or stress of having the pessary). With regard to their risk-benefit assessment, most pregnant women indicated that they perceived the APOSTEL VI study to pose zero risk (n=12) because enrolment would not negatively impact the development or growth of their child whereas they found the burdens relatively small[30].

Healthcare professionals confirmed the reasons that pregnant women mentioned about their enrolment decision, thereby emphasising that they perceive pregnant women's altruistic reasons to be secondary to motivations of potential individual benefit. Additionally, healthcare professionals voiced concerns about the risks of the APOSTEL VI study and additional concerns with regard to the actual working mechanism of the pessary, the pessary itself and the extra internal exam[30]. Despite these concerns, most healthcare professionals mentioned that as the APOSTEL VI study was not perceived to be harmful, they were generally positive about inclusion of pregnant women in the APOSTEL VI study.

## Theme 2. Gatekeeping

In light of pregnant women's reported uncertainty with regard to participation in the APOSTEL VI study, most pregnant women (n=12) mentioned that they consulted with others about their enrolment decision and said that third party advise was important to them. A decision was usually made in deliberation with at least the partner, and sometimes

included additional conversations with other family members or healthcare professionals. Pregnant women mentioned that in these conversations with others, they perceived their partners as well as society in general to be particularly protective towards them and their future child. In interviews with other stakeholders, it appeared that the main reason why stakeholders are reluctant to include pregnant women in clinical research stems from this felt need to protect the woman and her foetus and not overburden her during her pregnancy. In other contexts, this phenomenon has been called gatekeeping. To illustrate, healthcare professionals reported that they sometimes decide not to ask pregnant women to participate in clinical research because they perceive a study not to be in their patient's interest; they believe the number of studies their patient is participating in is already sufficient and do not want to overload them; or they do not want to overburden their patients in relation to their personal situation (such as living circumstances or being a single parent) or simply overburden them in general. REC members and regulators furthermore mentioned the responsibility they felt for protection of pregnant women and their foetuses.

When asked about underlying reasons for the protective attitude towards pregnant women, a noticeable element that a number of respondents kept referring to was pregnant women's decision-making capacity, especially with regard to risk assessment. As mentioned above, doubts about their decision-making capacities were also mentioned by pregnant women themselves ("feeling too unstable to make the right decision"), who, possibly in light of their own doubts about being able to make the right decision, mentioned that they more often looked for third party advice. There appeared to be a general feeling among interviewees that there might be moments when the decision-making capacity of pregnant women might be threatened due to for example "being very emotional" or "completely stuffed with hormones", and that they might need protection for that reason. Another reason that was mentioned was the societal idea of "being a perfect mother" and "having a blind spot for the baby", which respondents felt could influence the behaviour of pregnant women, both in relation to daily life as well as to participation in clinical research.

## Theme 3. Counselling

The interviews with healthcare professionals showed that the recruitment process in obstetric research is focused around what they call the "counselling" conversation. As such, when a pregnant woman is found to be eligible for participation in the APOSTEL VI study, the first step is to initiate a counselling conversation in which she is informed about the study. The counselling conversation appeared to be decisive for pregnant women who said that they based their understanding of the APOSTEL VI study primarily on the conversation rather than patient information forms. Healthcare professionals confirmed the importance of the counselling conversation and specified that they perceived the counselling for the APOSTEL VI study to be simple because a) the potential

participants really want something and you have something to offer, b) APOSTEL VI is one of the easiest studies to explicate, c) it is a relatively innocent study because you can always remove the pessary without any harm and d) the logistics are easy since the women are already hospitalised and there is time for a conversation. Counselling for the APOSTEL VI study was thus found to be straightforward and feasible.

Healthcare professionals, in their role as researchers, reported a clear notion of the concept of counselling: the conversation should be objective and all eligible pregnant women should be asked to participate. When asked about counselling of their own patients, some healthcare professionals seemed to deviate from the described notion of counselling. To illustrate, counselling sometimes appeared to be used as a way to direct patients in a certain way regarding the decision whether or not to enrol in clinical research. For example, at times it may happen that healthcare professionals are hesitant to include their patients and make a conscious choice to "counsel negatively". As was mentioned in the previous theme, most reasons for negative counselling concerned a fear of overburdening their patients. However, another reason that was mentioned was the research interest itself, when the professionals for example believe that their patient is not the right candidate for the study or they believe that the study itself is not relevant. Counselling also appears in opposite direction, when the conversation is used to motivate patients to participate, referred to as "counselling positively", for example by negating or downplaying possible negative effects of research participation.

## Theme 4. Interest in (routine) inclusion

While the starting point of the interviews was the APOSTL VI study, respondents additionally articulated their views on research participation of pregnant women in clinical research in general. As such, the interviews demonstrated that all stakeholders are cautious when asked about inclusion of pregnant women in clinical research, and especially hesitant about routine inclusion. Since the term "routine" is undefined, we provided respondents with different examples where pregnant women could be included, thereby making a difference between obstetric and non-obstetric; interventional (e.g. experimental research or research about standard care practices) and observational research. We always specified that "routine" was not a universally agreed upon or currently practised term, but that we meant a general reference to having a default of inclusion of pregnant women unless there are scientific and ethical reasons for their exclusion[31].

Healthcare professionals reported an interest in inclusion of pregnant women in RCTs, as long as research participation would potentially be beneficial for the group or the individual or at least have no or no negative effect on the individual. REC members and regulators reported a preference for inclusion of pregnant women in observational research and mentioned that inclusion in RCTs should only be an option when it comprises research

with demonstrated necessity ("there are really no alternatives") and a real potential for improvement of the pregnancy outcome of the individual woman. To illustrate, they mentioned that if there is a new medication that might be better than known safe alternatives (including long time used off-label medications), they would not want a trial with the new medication because in a trial there would be a risk of taking a medication of which the safety is not entirely established, but rather continue with the (off-label) alternatives. Contrarily, if a medical treatment would be indicated and the effectiveness of different standard care practices needed to be proven, respondents found inclusion more acceptable because the risks would be known. Moreover, the respondents made a clear distinction between obstetric and non-obstetric research, arguing that inclusion in obstetric research was more "defendable" and added that women (in the Netherlands) who are ill are often already included in obstetric research performed by the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (NVOG consortium). With regard to further inclusion of pregnant women in clinical research, respondents mentioned that there was room for inclusion in specific cases, but that they had no desire to routinely include pregnant women in the way we had defined the term.

Most pregnant women (n=11) mentioned that they would only consider research participation during their pregnancy in case such research was imperative for their health condition. As an example, they mentioned having a certain illness for which research participation would offer high potential personal benefit. Especially with regard to invasive clinical research (which they characterised as being experimental; concerning medications or injections of some sort; or entailing the internal insertion of a medical device) there was no willingness to participate. With regard to non-invasive observational research, pregnant women mentioned that they would be willing to participate to help future pregnant women, as long as inconveniences such as time requirements were not too extensive. Additionally, pregnant women reported an interest in the development of registries in which pregnant women would automatically participate in order to increase the evidence-base, but they were reluctant with regard to routine inclusion in trials. To clarify, they mentioned that research on medical conditions for which there are really no treatment options and the risks of the condition for the woman and the foetus are very high would be understandable, but research on new medications for medical conditions for which there are safe alternatives (including off-label medications) would not be preferable.

## DISCUSSION

Our qualitative study shows that there are different reasons why pregnant women in the Netherlands are willing to participate in the APOSTEL VI study, a relatively conventional low-risk obstetrical RCT. In contrast to earlier hypothetical studies where altruism was identified as the primary motivator, our study indicates that women who are confronted with an actual recruitment scenario are primarily motivated by potential individual

benefit, while altruistic motives are secondary. Because of uncertainty about pregnant women's reasons for participation, there are assumptions that pregnant women may have different reasons for participation than non-pregnant participants[3,20,32]. Nevertheless, pregnant women in our study actually report similar reasons for participation as non-pregnant participants, where altruistic motivations were also said to be secondary to potential individual benefit[33,34]. With regard to altruism, it is particularly interesting that in our case, where pregnant women are fairly desperate and unsurprisingly mention potential individual benefit as a primary reason for participation, altruism is still cited as a secondary reason.

Similar to reports from earlier low-risk studies, one of the main reasons to refuse participation in the APOSTEL VI was physical inconvenience, in this case the required extra internal exam[35,36]. In that respect, the APOSTEL VI exemplifies the importance of managing practicalities. To illustrate, there was a clear difference in recruitment numbers between the two academic centres: UMC Utrecht: 18/40 persons included/not included versus AMC 49/15 included/not included. At the UMC Utrecht, healthcare professionals had voiced concerns about the APOSTEL VI study beforehand and may have (unconsciously) conveyed these concerns to potential research subjects. Moreover, the internal exam was, contrarily to the practice at the AMC, not part of standard care and thus became an extra invasive procedure which was considered to be a barrier for both pregnant women and healthcare professionals.

Furthermore, while bioethicists claim that inclusion of pregnant women in clinical research should be promoted or should even be routine, our qualitative study shows that stakeholders in the Netherlands are not necessarily interested in (routine) inclusion of pregnant women in clinical research, unless there are specific pressing cases in which the potential individual benefits are very high. Illustrative is the hesitance to conduct clinical research on new medications and the preference for continuing with long-time used off-label medications, which are arguably not well-researched or have long-term follow-up data. The underlying reason for the reluctance to include pregnant women seems to be a protective sentiment, which possibly explains the continuous underrepresentation and constant recruitment and delay struggles.

The protective sentiment relates to the theme of gatekeeping. First, on an individual level, healthcare professionals, RECs, regulators and possibly partners of pregnant women and pregnant women themselves appear to be resolved to shield women from any form of harm. Alarmingly, questions about pregnant women's competence to make decisions about research participation keep surfacing, questions that were also raised by pregnant women themselves. While finding a decision hard to make or consulting others for help are features of difficult decisions rather than an indication of issues with decision-making capacity, the particular questions concerned pregnant women's ability to make decisions throughout the pregnancy, noticeably exceeding the matter of merely finding a decision

hard to make. Second, on a professional level, our study confirms earlier findings that a sometimes paternalistic tendency for protection, demonstrated in the exclusion of possibly eligible pregnant women for their own good, hampers recruitment [21,37–39]. Gatekeeping by healthcare professionals could be facilitated by the current nature of the counselling process, which results in two problems. First, when healthcare professionals make an individual selection of patients instead of including every eligible patient, a bias is introduced in the research population, possibly infringing upon the scientific validity of clinical research. Second, patients' informed choice is threatened when clinicians steer patients in a direction they deem suitable.

Evidently, healthcare professionals should be entrusted to prevent individual patients from participating if they deem participation harmful. Nevertheless, the practice of gatekeeping on a structural level extends far beyond protection of an individual patient because it results in the exclusion of groups of possibly eligible pregnant women, which is problematic. Striking a balance between respecting pregnant women's competence to make an informed decision and not overly protecting them on the one hand, and safeguarding them from harm on the other is essential. Yet, protection can also mean *inclusion* in clinical research, thereby gathering evidence that may place fewer pregnant women and their foetuses at risk than the much larger number of pregnant women who will be exposed to the medications once they come to market[9]. The current lack of specific guidance for research with pregnant women, for example in the national legislation (WMO), may contribute to uncertainty about the preferred course of action with regard to inclusion of pregnant women. Providing specific guidance is therefore commendable.

Our qualitative study shows that research participation of pregnant women remains a charged topic and that it is unlikely that routine inclusion will become the norm overnight. Even with regard to our low-risk obstetric study, stakeholders were hesitant about inclusion of pregnant women. Imaginably, this hesitance is increased when it concerns non-obstetric research, the area where research is most problematically lacking interventions and medications that treat or prevent maternal and foetal illness during pregnancy. Following from these results, we may want to invest in additional ways to increase the evidence base for pregnant women. For example, solutions could be found in sharpening or adjusting the recruitment process, based on pregnant women's reasons for participation which, as the APOSTEL VI study exemplifies, are personal benefit and secondarily altruistic motives. Since reasons for participation are similar to those of non-pregnant research participants, lessons can be learned from recruitment strategies that have been used in these groups. Moreover, raising stakeholders' awareness on their protective attitude and the resulting negative effects may contribute to the promotion of pregnant women's decisional capacities. Another practical solution may be to capitalise on feasibility, for example by asking healthcare professionals beforehand to assess the logistics and potential risks and benefits of a study, thereby decreasing the risk of

delay and lack of equipoise which is often mentioned as a barrier for inclusion and which may have been the case in the APOSTEL VI[24,40,41].

## LIMITATIONS

This qualitative study has a number of limitations. First, we interviewed mostly highly educated stakeholders regarding only the Dutch situation and it is possible that the results are different in other countries, thus challenging the generalizability of the findings. Second, the saturation number of twenty interviews was reached on group level, but not always on sub-group level. As such, our inter-group comparisons are less valid than our group analyses. Third, we only included pregnant participants who were recruited for the APOSTEL VI study, a group that consists of women that become sick during their pregnancy and whom are recruited for a low-risk obstetric study. Future research should also aim to include research subjects from the group of sick women who become -or prepare to become- pregnant and participants recruited for high risk and non-obstetrical studies. We attempted to include women from the latter group, but all three trials we collaborated with were unfortunately cancelled, possibly another illustration of the gatekeeping tendency surrounding clinical research in pregnant women. Finally, we were unable to interview any representatives from a pharmaceutical company, since the seven organisations we contacted with a request to participate unfortunately did not respond or did not want to participate in our study.

## CONCLUSIONS

Our qualitative study shows that pregnant women are willing to participate in the relatively conventional low-risk obstetrical APOSTEL VI study for potential individual benefit and altruistic motives. But while pregnant women might be eligible and willing to participate, a protective sentiment seems to dominate the practice of the APOSTEL VI as well as clinical research in general. While bioethicists claim that inclusion of pregnant women in clinical research should be promoted or should even be routine, our study indicates that healthcare professionals, regulators, REC members and pregnant women themselves are not necessarily interested in inclusion unless there is a high potential for individual benefit. The underlying reason for the reluctance to include pregnant women appears to be a protective sentiment. This sentiment results in gatekeeping and directive counselling, threatening pregnant women's informed choice and hampering recruitment of eligible and potentially willing participants. Striking a balance between respecting pregnant women's autonomy and protecting them is essential.

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# FIGURES AND TABLES

**Table 1a.** Demographic characteristics pregnant women

| **Characteristics pregnant women** | **(n=14)** |
|---|---|
| **Age** | |
| <25 | 1 |
| 25–30 | 5 |
| 31–40 | 8 |
| **Parity** | |
| Nulliparous | 9 |
| Primiparous | 2 |
| Multiparous | 3 |
| **Gestational age (weeks)** | |
| 25–30 | 5 |
| 31–35 | 9 |
| **Education** | |
| Highschool | 3 |
| Lower vocational (MBO) | 3 |
| College (HBO/WO) | 4 |
| Graduate degree | 4 |
| **Partner** | |
| Married | 5 |
| Living together | 9 |
| Single | 0 |
| **Enrolment in study** | |
| Participating in Apostel VI | 8 |
| *Recruited from UMC Utrecht* | *3* |
| *Recruited from AMC* | *5* |
| Not participating in Apostel VI | 6 |
| *Recruited from UMC Utrecht* | *6* |
| *Recruited from AMC* | *0* |

**Table 1b.** Demographic characteristics professionals

| **Characteristics professionals** | **(n=26)[a]** |
|---|---|
| **Gender** | |
| Male | 11 |
| Female | 15 |
| **Age** | |
| 25–40 | 13 |
| 41–55 | 7 |
| > 55 | 6 |
| **Experience at present job (years)** | |
| <5 | 13 |
| 5–10 | 6 |
| 11–15 | 4 |
| 16 –20 | 3 |
| **Profession** | |
| Gynaecologist | 3 |
| Gynaecologist-in-training[b] | 6 |
| Midwife[c] | 5 |
| REC member[d] | 5 |
| Regulator/knowledge centre | 7 |

[a] 5 regulators from the focus group, 21 interviewees
[b] 1 gynaecologist-in-training was a gynaecologist-not-in-training (ANIOS)
[c] 3 research midwifes from academic hospitals
[d] 2 REC members were also gynaecologists

**Figure 1.** Flowchart of Inclusions

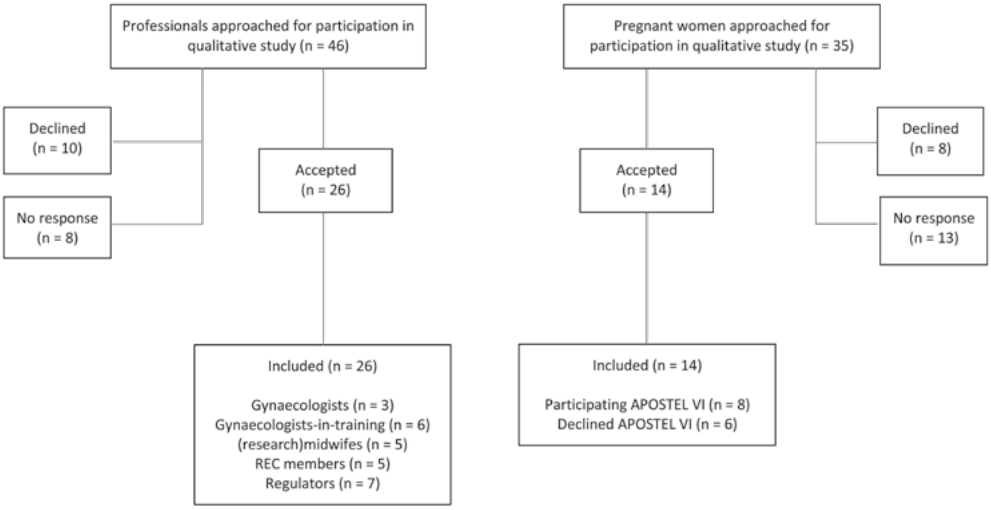


**Table 2.** General Topic List

| |
|---|
| Participation of pregnant women in clinical research; |
| Routine inclusion in clinical research; |
| Balancing risks and potential benefits; |
| Conflict of interest maternal-foetal benefit; |
| Whose interests should prevail; |
| Societal benefit versus therapeutic benefit; |
| Recruitment process at the medical centre; |
| Balancing risks and potential benefits in the APOSTEL VI; |
| Decision-making process in the APOSTEL VI. |

**Table 3.** Representative quotations

| Theme | Quotations* |
|---|---|
| Motivations for participation | **PW02, participating in APOSTEL VI**: I like to participate when it is positive for me, when participation makes me feel like I do something good, but that it is also positive for myself and that nothing can go wrong. |
| | **PW12, not participating in APOSTEL VI:** It depends whether participation is beneficial for yourself or whether it is purely for science. In this case, I considered it a valuable bonus that the pessary could potentially help to prolong my pregnancy. |
| | **PW13, not participating in APOSTEL VI**: [Healthcare professionals] did not want to perform internal examinations to prevent stimulation of the uterus. So I figured, if you insert a pessary, then you can also stimulate it. I was afraid of that. |
| | **HCP02, research midwife:** It is first and foremost herself and the baby. Saving the world comes secondary. |
| | **HCP04, gynaecologist-in-training:** Why would you do an intervention, why would we do something that has not been proven? I also wonder what the working mechanism of the pessary is, nobody can tell me, not even the big advocates. |
| Counselling | **HCP13, gynaecologist-in-training:** It is an easy study to recruit people for, because it involves people who really want something, and you have something to offer. |
| | **HCP05, gynaecologist:** You can only achieve fair inclusion when you ask each and every pregnant woman who potentially meets the inclusion criteria. |
| | **HCP10, research midwife:** If they are eligible, we ask them. In the following conversation I may determine that they are not suitable, for example because they do not understand it [the study]. We also have drug addicts here, where you decide that it is not a good idea because that lady doesn't belong to the group of women the study is interested in. |
| | **HCP08, midwife:** If there is a study where you think 'I'm not sure what I'm doing here', it is definitely a reason to counsel in the other direction. You try to counsel objectively, but we all know it is directive. |
| | **HCP13, gynaecologist-in-training:** Sometimes you know that it is not the right candidate. That it will be a mess. And then you counsel slightly more negatively. |
| Gatekeeping | **PW07, participating in APOSTEL VI:** I had so many doubts, I really didn't know. You are as mentally unstable as it can be when you lay there hospitalised so I couldn't make a good decision. Yes, many people where involved [in the decision-process]. |
| | **PW11, participating in APOSTEL VI:** I notice that you think different about things when you are pregnant, it may be hormonal or not, but you are surely different in terms of decisiveness in comparison to when you're not pregnant. |
| | **PW03, not participating in APOSTEL VI:** Sometimes I realise that I am less resolute in my decisions because I am pregnant. […] More doubtful and no completely following, like "oh no, what was it [that I missed]?". For that reason I turn to other people. |
| | **PW08, not participating in APOSTEL VI:** Everyone makes you aware of the fact that, as a pregnant woman, you are part of a weaker group. That you should be handled with great care. |

**Table 3.** (continued)

| Theme | Quotations* |
|---|---|
| | **HCP01, research midwife**: A dad finds it burdensome: 'there they are yet again with a study; she is already tired, she is sleeping, no, I don't think that she will participate'. |
| | **REC05, gynaecologist:** I notice that clinicians are protective towards patients, for example in that they do not mention ongoing scientific research. |
| | **HCP08, midwife:** Sometimes we ourselves decide that someone is not suitable. Because of the language, or when you wonder whether someone will understand it, or because someone is already participating in two other studies. |
| | **HCP03, gynaecologist-in-training**: The child cannot decide if he wants to participate in a potentially dangerous study. […and a pregnant woman] cannot estimate or oversee the risks for a child that may has to become 80 years old. |
| | **HCP14, gynaecologist:** Assuming that women may function differently during their pregnancy, also psychologically, you don't know if that does not influence their decision-making surrounding research participation. |
| | **HCP13, gynaecologist-in-training:** I think they [pregnant women] are behaviourally more vulnerable. I think they have some sort of black, blind spot: everything for the child. […] They are not sufficiently competent. |
| Interest in (routine) inclusion | **HCP05, gynaecologist:** Routine inclusion may be a little odd, but if you have the premise that there is a theoretical or practical basis to assume that a given therapy improves or can improve the pregnancy outcome, and you meet the strict guidelines of among others the REC and the WMO [Dutch regulation on the protection of human subjects], and you carefully register the outcome of the pregnancy and the side effects, I think that that would actually be very good. |
| | **HCP03, gynaecologist-in-training:** The question is whether there are no good alternatives. Is research really necessary? |
| | **REG01, MEB member:** Observational research has a different approach, where we do not intentionally expose pregnant women, but where women are already exposed and we try to collect data in the best way. |
| | **REC04, clinician:** You should not expose pregnant women to medications of which the effects on the baby are unknown, if you have an alternative. It's different if it is pregnancy-specific. In that case you don't have an alternative, and then I have fewer objections. |
| | **PW02, participating in APOSTEL VI:** I would not participate in a study where I have to take medications or where things are injected into me. I don't want to be a guinea pig for that. |
| | **PW12, not participating in APOSTEL VI:** If possible, I would not accept any research with risks. Why would you take risk if you don't have to, if there is no direct benefit? I wouldn't take that risk for science. |

* Quotations are sometimes slightly modified in order to enhance readability

## REFERENCES

1. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
2. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
3. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
4. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
5. EMA (European Medicines Agency). Guideline of the exposure to medicinal products during pregnancy: need for post-authorisation data. [Internet]. 2005 [cited 2016 Mar 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf
6. CIOMS & WHO. CIOMS draft guidelines [Internet]. 2016. Available from: http://www.cioms.ch/index.php
7. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
8. Zajicek A, Giacoia GP. Obstetric clinical pharmacology: coming of age. Clin. Pharmacol. Ther. 2007;81:481–2.
9. Macklin R. Enrolling pregnant women in biomedical research. Lancet. 2010;375:632–3.
10. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. Clin. Infect. Dis. 2014;59 Suppl 7:S400-7.
11. Levine RJ. IRB perspective on inclusion of pregnant women in clinical research. ORWH Work. Enrolling pregnant women Issues Clin. Res. An ORWH 20th Anniv. Event. Bethesda, MD: National Institutes of Health; 2011. p. 37–43.
12. Secretariat on Responsible Conduct of Research. Tri-Council Policy Statement (TCPS-2): Ethical conduct for research involving humans. [Internet]. [cited 2016 Mar 25]. Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf
13. Baylis F, Halperin SA. Research involving pregnant women: Trials and tribulations. Clin. Investig. (Lond). 2012;2:139–46.
14. Noah BA. The inclusion of pregnant women in clinical research barbara a. noah* a. 2014;353–89.
15. Lyerly AD, Namey EE, Gray B, Swamy G, Faden RR. Women's views about participating in research while pregnant. IRB Ethics Hum. Res. 2012;34:1–8.
16. Vecchi Brumatti L, Montico M, Russian S, Tognin V, Bin M, Barbone F, et al. Analysis of motivations that lead women to participate (or not) in a newborn cohort study. BMC Pediatr. 2013;13:53.
17. Rodger M a, Makropoulos D, Walker M, Keely E, Karovitch A, Wells PS. Participation of pregnant women in clinical trials: will they participate and why? Am. J. Perinatol. 2003;20:69–76.
18. Lavender T, Kingdon C. Primigravid women's views of being approached to participate in a hypothetical term cephalic trial of planned vaginal birth versus planned cesarean birth. Birth. 2009;36:213–9.
19. Oude Rengerink K, Logtenberg S, Hooft L, Bossuyt PM, Mol BW. Pregnant womens' concerns when invited to a randomized trial: a qualitative case control study. BMC Pregnancy Childbirth. 2015;15:207.
20. van der Zande ISE, van der Graaf R, Hooft L., van Delden JJM. . Facilitators and Barriers to Participation: a Systematic Review on the Willingness of Pregnant Women to Participate in Clinical Research. submitted.

21. Tooher RL, Middleton PF, Crowther CA. BMC Pregnancy and Childbirth A thematic analysis of factors influencing recruitment to maternal and perinatal trials. 2008;12:1–12.
22. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. Elsevier Inc.; 2013;23:e39–45.
23. Brandon AR, Shivakumar G, Inrig SJ, Sadler JZ, Craddock Lee SJ. Ethical Challenges in Designing, Conducting, and Reporting Research to Improve the Mental Health of Pregnant Women: The Voices of Investigators and IRB Members. AJOB Empir. Bioeth. 2014;5:25–43.
24. Madan A, Tracy S, Reid R, Henry A. Recruitment difficulties in obstetric trials: a case study and review. Aust. N. Z. J. Obstet. Gynaecol. 2014;54:546–52.
25. Haas DM, Wunder K, Wolf JG, Denne SC. Women's health care providers' attitudes toward research in pregnancy. J Reprod Med. 2010;55:108–14.
26. Charmaz K. Constructing Grounded Theory: A Practical Guide through Qualitative Analysis. Constr. Grounded Theory A Pract. Guid. Through Qual. Anal. 2006. p. SAGE Publications Ltd.
27. Braun V, Clarke V. Using thematic analysis in psychology. Qual. Res. Psychol. 2006;3:77–101.
28. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med. Res. Methodol. 2008;8:45.
29. QSR. NVivo 10 research software for analysis and insight [Internet]. www.qsr Int. 2014. Available from: http://www.qsrinternational.com/products_nvivo.aspx?utm_source=NVivo+10+for+Mac
30. van der Zande ISE, van der Graaf R, Oudijk MA, van Delden JJM. A qualitative study on acceptable levels of risk for pregnant women in clinical research. BMC Med. Ethics. 2017;18:35.
31. Halperin SA. Research involving pregnant women : trials and tribulations. 2012;2:139–46.
32. Mohanna K, Tunna K. Withholding consent to participate in clinical trials: decisions of pregnant women. Br. J. Obstet. Gynaecol. 1999;106:892–7.
33. Edwards SJL, Lilford RJ. The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals. BMJ. 1998;
34. McCann SK, Campbell MK, Entwistle V a. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. Trials. 2010;11:31.
35. van Delft K, Schwertner-Tiepelmann N, Thakar R, Sultan a H. Recruitment of pregnant women in research. J. Obstet. Gynaecol. 2013;33:442–6.
36. Mihrshahi S, Vukasin N, Forbes S, Wainwright C, Krause W, Ampon R, et al. Are you busy for the next 5 years? Recruitment in the Childhood Asthma Prevention Study (CAPS). Respirology. 2002;7:147–51.
37. Helmreich RJ, Hundley V, Norman A, Ighedosa J, Chow E. Research in pregnant women: the challenges of informed consent. Nurs. Womens. Health. 2007;11:576–85.
38. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. Clin. Infect. Dis. 2014;59 Suppl 7:S400-7.
39. Mccauley-elsom K, Gurvich C, Lee S, Elsom S, Connor MO, Kulkarni J. Vulnerable populations and multicentred research. 2009;108–15.
40. Turner CE, Young JM, Solomon MJ, Ludlow J, Benness C, Phipps H. Willingness of pregnant women and clinicians to participate in a hypothetical randomised controlled trial comparing vaginal delivery and elective caesarean section. Aust. New Zeal. J. Obstet. Gynaecol. 2008;48:542–6.
41. Mohanna K, Tunna K. Withholding consent to participate in clinical trials: decisions of pregnant women. Br. J. Obstet. Gynaecol. 1999;106:892–7.

# CHAPTER 9

# TOWARDS AN APPROPRIATE FRAMEWORK TO FACILITATE RESPONSIBLE INCLUSION OF PREGNANT WOMEN IN DRUG DEVELOPMENT PROGRAMS

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## ABSTRACT

Evidence based treatment for pregnant women will ultimately require research conducted in the population of pregnant women. Currently, few scholars have addressed the issue of responsible inclusion pregnant women in drug research. Because of additional risks associated with including pregnant women in drug research and the altered ways in which drugs are processed by the pregnant body, pregnant women cannot be treated as an ordinary subgroup in the various phases of drug development. Instead, responsible inclusion of pregnant women requires a careful design and planning of research for pregnant women specifically. Knowledge about these aspects is virtually non-existent. In this paper, we present a practical framework for planning responsible inclusion of pregnant women in drug development. We suggest that the framework consists of using a question based approach with five key questions in combination with three prerequisites which should be addressed when considering inclusion of pregnant women in drug research. The five questions are:

*Question A: Can we consider the drug safe (enough) for first exposure in pregnant women and fetuses?*

*Question B: In which dose range (potentially depending on gestational age) can the drug be considered to remain safe in pregnant women?*

*Question C: At what dose (regimen, within the range considered safe) can we expect efficacy in pregnant women?*

*Question D: Can efficacy be confirmed at the target dose, either similar to the initial population or different?*

*Question E: Can clinical safety be confirmed at a sufficiently acceptable level at the target dose for pregnant women as well as their fetus, so as to conclude a positive benefit risk ratio?*

Combining questions and prerequisites leads to a scheme for appropriate timing for responsible inclusion of pregnant women in drug research. Accordingly, we explore several research design options of including pregnant women in drug trials that are feasible within the framework. Ultimately, the framework may lead to i) earlier inclusion of pregnant women in drug development, ii) ensuring that key prerequisites such as proper dosing, are addressed before more substantial numbers of pregnant women are included in trials, and iii) optimal use of safety and efficacy data from the initial (non-pregnant) population throughout drug development.

## BACKGROUND

Over the past decades, bioethicists, pharmacologists, regulators and researchers have called attention to the inclusion of pregnant women in clinical research in order to improve the evidence-base underlying maternal and fetal health[1–5]. During pregnancy, women may suffer from serious acute and chronic obstetric or non-obstetric illnesses that require drug treatment in the interest of both the mother and the fetus, for example mental disorders, hypertension, asthma, diabetes, cancer and autoimmune disorders[1,2]. It is estimated that 84 – 99% of women take medications during pregnancy, for which there are no substantial data on safety, efficacy or fetal risk[6–9]. The lack of a sound evidence base leads to suboptimal care or even under-treatment of pregnant women.

To bridge the knowledge gap regarding safe and effective drug use in pregnant women, various stakeholders have taken up the challenge of inclusion. Already in 1994, the Institute of Medicine stated that pregnant women are presumed to be eligible for participation in clinical research, a view that was later endorsed by others[1,4,10]. In 2009, the Second Wave Initiative was launched, a collaborative academic initiative to find ethically and scientifically responsible means to increase the knowledge base for the treatment of pregnant women with medical illness[1,11]. Additionally, the United State Food and Drug Administration (FDA) recently replaced its traditional pregnancy categories for drug-use in pregnant women by the Pregnancy and Lactation Labelling Rule (PLLR, Final Rule), which is expected to provide further incentives for the development and conduction of more clinical research in pregnant women[12]. Despite these attempts to respond to the call for inclusion, the underrepresentation and exclusion of pregnant women from clinical research remains common practice[5,13]. There are various reasons for the continuing status quo, such as a fear of harming the fetus, numerous liability concerns and the question whether pregnant women would be willing to participate even if they were found to be eligible[14–16]. Moreover, one unresolved, yet very essential element, is the challenge of designing studies that warrant responsible inclusion of pregnant women in drug research. Since pregnancy can alter the ways that drugs are processed by the body and the ways that drugs act on the body in a fashion difficult to predict from the pharmacokinetics (PK) and pharmacodynamics (PD) in men and non-pregnant women, answering PK and PD questions for pregnant women requires the development of different or new research designs for drug research[1,17,18].

Francoise Baylis and colleagues have been the first to address ethically responsible inclusion of pregnant women by proposing alternative approaches towards including pregnant women in drug research. They argue for a particular type of routine inclusion of pregnant women in clinical studies of drug safety and effectiveness, except when there are compelling scientific or ethical reasons to exclude them[3,19]. They start from the assumption that it is ethically preferable to a) expose a limited number of pregnant women and their fetuses to a new drug in very well controlled conditions at an early stage first, compared to b) not

doing so and instead having to rely on information from exposure of large numbers post-market authorization in less well-controlled conditions. Although we do not underwrite routine inclusion, we sympathize with the work of Baylis and colleagues and their attempt to take on the challenge of research design for pregnant women. However, their proposal can be further strengthened. What is particularly missing in the current discussion on the inclusion of pregnant women in drug trials, and what we will address in this paper, are i) thoughts about the level of evidence needed from pregnant women to ensure safe and effective drug use, ii) guidance to help decide on appropriate timing (in the development course of a drug), if at all, for the inclusion of pregnant women in drug trials, and iii) more extensive exploration of research designs that can facilitate inclusion.

The aim of our paper is to present a practical framework for planning responsible inclusion of pregnant women in drug development. Our paper further suggests directions for trial design that support safe and efficient inclusion of pregnant women in different stages of drug development. First, we introduce the practical framework which consists of a question based approach in combination with prerequisites, providing a rational and efficient method for the design of a drug development program in the form of a scheme[20,21]. Second, we evaluate the proposal of Baylis and colleagues in light of our framework. Third, we extend the discussion beyond the scope of Phase I trials and use the framework to explore practical suggestions for key (statistical) design features of clinical studies to deal with potential safety concerns, thereby placing the contributions of Baylis and colleagues in a broader context. Finally, we discuss the practical implications of our proposal. Our scope encompasses non-obstetrical illnesses and the development of new drugs for these conditions. Note, we do not aim to provide a conclusive answer regarding specific trials, but instead aim to prompt methodological discussion on the inclusion of pregnant women in drug trials.

## FRAMEWORK: QUESTION BASED APPROACH AND PREREQUISITES

Traditionally, the timing and sequential order of clinical research studies for new drugs is in four phases: first exposure in humans and primary safety (Phase I), establishing the efficacious and safe dose (Phase II), confirming efficacy and safety in a broader population (Phase III) and additional studies post market authorization (Phase IV). The current paradigm in drug development splits the pre-marketing drug development process in roughly two larger phases: "Learning" and "Confirming"[22]. Given the (unknown) risks and possible serious consequences for pregnant woman and fetus, including pregnant women as an ordinary subgroup in the regular phases is often unwarranted. Instead, an approach is needed that ensures an adequate level of evidence of safety and efficacy for inclusion of pregnant women. We suggest a question based approach for inclusion of pregnant women in drug trials.

Similar to the traditional four phase approach, a question based approach assumes that a clinical drug development program ultimately aims to answer pertinent questions about a new drug, from fundamentals about the mechanism of action and its effects in the human body, up to clinical efficacy and safety[20,21]. A question based approach specifically acknowledges that different types of questions may require different clinical research designs, and that the right order of addressing the questions may increase the relevance and safety of the information and efficiency of decision making[20,21]. As such, the principle starting point is that these questions do not differ between the initial population (here and hereafter referring to: men and *non-pregnant* women or non-pregnant women only) and pregnant women, but essentially that pregnancy adds complexity and additional safety concerns. A question-based approach can clarify in which phase which question should be answered before pregnant women can be enrolled. An important advantage of looking at the situation from a question based perspective rather than (only) Phase I - IV based is that the research question is made explicit and all options to obtain an appropriate answer can be considered. This may very well prevent unnecessary clinical studies in pregnant women, as we will argue below.

Applying a question based approach to pregnant women in clinical studies for new drug treatments, we assume that for a specific drug a complete development plan in the initial population is already foreseen. Since we are particularly concerned with clinical efficacy and safety, we suggest that the key questions to (potentially) address for pregnant women are:

*Question A: Can we consider the drug safe (enough) for first exposure in pregnant women and fetuses?*

*Question B: In which dose range (potentially depending on gestational age) can the drug be considered to remain safe in pregnant women?*

*Question C: At what dose (regimen, within the range considered safe) can we expect efficacy in pregnant women?*

*Question D: Can efficacy be confirmed at the target dose, either similar to the initial population or different?*

*Question E: Can clinical safety be confirmed at a sufficiently acceptable level at the target dose for pregnant women as well as their fetus, so as to conclude a positive benefit risk ratio?*

Questions A to C fall under "Learning". To arrive at a negative answer, usually in terms of safety, research in the initial population or even only in animals may suffice. Hence, answering questions A to C may not always necessitate clinical research in pregnant women. Questions D and E are confirmatory, and would need research in the target

population of pregnant women. Of course, different questions can be addressed within the same study; most clinical studies will address both efficacy and safety questions. Combining learning and confirming questions within the same study is more controversial[23], but can be realized with an adaptive clinical trial design[24]. So the questions that are specifically targeting pregnant women could be answered with a separate trial, but also with a trial in which pregnant women constitute a subgroup, among the initial population.

Generally agreed upon prerequisites for clinical trials in pregnant women are threefold[25]. First, adequate pre-clinical and early clinical data pertinent to pregnancy must be available before first exposure in pregnant women. If possible, these data would include pharmacokinetic data from non-pregnant women, animal data including data from pregnant animals, pre-clinical and in-vitro models of placenta transfer and, if possible, placental transport, metabolism and endocrine function[25]. Second, clinical exposure in pregnant women should preferably start once basic clinical safety data in the initial population are known and can be used to assess potential risks for pregnant women[3,19]. Third, clinical efficacy should preferably be established to a sufficient extent in the initial population, before exposing larger numbers of pregnant women, so as to avoid exposure to a potentially non-effective drug. Combining a question based approach in which the five clinical questions are addressed with the three prerequisites, leads to a scheme for acceptable options for inclusion of pregnant women in a drug development program (as portrayed in Table 1).

In Table I, it is assumed that for a clinical trial addressing confirmatory questions D and E, questions A-C have already been answered adequately (by means of a clinical trial

**Table 1.** Proposed admissible timing scheme

| **Acceptability of inclusion of pregnant women** | **Development phase in the initial population** | | | |
|---|---|---|---|---|
| | **Learning** | | **Confirming** | |
| **Question for pregnant women** | **Phase I** | **Phase II** | **Phase III** | **Phase IV** |
| A First exposure | | AB II | AB III | AB IV |
| B Safe dose | | | | |
| C Efficacious dose | | | C III | C IV |
| D Confirm efficacy | | | D III | D IV |
| E Confirm safety | | | | E IV |

Proposed admissible timing scheme for question based inclusion of pregnant women relative to the different phases of drug development in the initial population

= not acceptable = potentially acceptable = acceptable

or otherwise). Furthermore, gestational age is likely to impact pharmacokinetics of drugs[25], and should thus be included in all design considerations. It is worth noting that inclusion of pregnant women at different gestational ages may impact the total sample size, depending on the disease and duration of exposure. Additionally, we assume that follow-up of fetuses and children is part of every trial with pregnant women. Subsequently, the framework (i.e. the scheme resulting from the combination of a question based approach and the prerequisites), enables us to assess potential design options for inclusion of pregnant women in drug trials more systematically.

## APPLYING THE FRAMEWORK TO BAYLIS' AND HALPERIN'S PROPOSAL

Baylis and Halperin have considered two modes of conducting Phase I trials in pregnant women during Phase II and Phase III trials in the initial population[19]. One proposed alternative is to run a separate Phase I trial in pregnant women parallel with Phase III in the general population, the other proposal is to embed the Phase I trial features (including intensive safety monitoring) for pregnant women within a late Phase II or Phase III trial. As Baylis and Halperin explicate, the primary advantage of timing a Phase I in pregnant women during a Phase III in the initial population is that efficacy and safety data can be evaluated prior or concurrently to the initial population and information from earlier drug trials can better inform researchers about potential risks and benefits of that same drug in pregnant women. As such, the Phase I trial in pregnant women (separate or embedded) may avoid unnecessary testing of drugs in pregnant women that are proven insufficiently safe in the initial population.

In our proposed framework, the two proposed designs by Baylis and Halperin presumably aim to answer question A (safety), and potentially also B (effective dose). It appears that Baylis and Halperin assume that question A (is the drug safe enough for first exposure in pregnant women) was answered positively, based on the pre-clinical and clinical research in the initial population. However, it is not clear how an appropriate dose range for pregnant women is subsequently achieved (question B). If Phase I is embedded in Phase III, there will most likely be evidence generated of efficacy and clinical safety in pregnant women (questions C – E), presumably in the sense of evaluating consistency of efficacy and safety with the general population, but this is not specifically mentioned. Additionally, Baylis and Halperin do not address (statistical) design features that may provide further safeguards for pregnant women and their fetuses. In the following, we will extend the ideas of Baylis and Halperin by addressing ideas on clinical research design options in more detail.

# APPLYING THE FRAMEWORK FURTHER: EXTENDED DESIGN OPTIONS AND CONSIDERATIONS FOR TRIALS

We will now put our framework (Table 1) into context. We will discuss each of the five questions, address the important issue of timing of answering these questions and provide practical guidance for research design wherever possible.

## Design options during Phase II, addressing questions A and B (AB II)

*Question A: can we consider the drug safe (enough) for first exposure in pregnant women and fetuses?*

*Question B: in which dose range (potentially depending on gestational age) can it be considered to remain safe in pregnant women?*

In most cases, it is too early to address questions A and B in pregnant women in parallel with a Phase II in the initial population because Phase I data from the initial population is insufficiently informative on the appropriate (safe and effective) dose for pregnant women and Phase II safety data from the initial population (typically laboratory data and adverse experiences) is missing. However, as it is crucial to determine appropriate dosing for pregnant women in light of their specific physiology, in some cases we could imagine careful first exposure of pregnant women at this stage. For question A, the pre-clinical and Phase I data in the initial population might in some cases be considered adequate, if only a limited dose range in pregnant women is evaluated subsequently during Phase II. This limited dose range can provide important pharmacokinetic information on dosing in pregnant women, possibly preventing safety risks later on in the drug development program. Question B could (partially) be answered early (in parallel with Phase II in the initial population), by gathering data in pregnant women at (very) low doses of the new drug that would allow extrapolation from the exposure in the initial population (e.g. obtained in Phase I) to exposure in pregnant women, possibly at different gestational ages.

A stepwise adaptive trial could be considered to support model-based extrapolation to a proper dose in pregnant women for a future trial. When planned after the Phase I in the initial population, essential human pharmacokinetic properties are known (linear or non-linear kinetics, dose exposure relations), as well as some pharmacodynamics. A (small) trial could be designed involving pregnant women of different gestational ages. The objective would be to optimize an extrapolation model of existing pharmacokinetics (PK) to pregnant women, to enable the selection of an appropriate dose for therapeutic trials. First exposure would be at (very) low doses, and would assess, and subsequently carefully increase, PK, based on a translational model from the available and new PK data to "match" the exposure as observed in the initial Phase I PK. As such, the trial

can be used to optimize the extrapolation model of PK to pregnant women, whilst remaining in a sufficiently safe dose range. It will thus be able to answer question B (at least approximately) and provide estimated potentially effective doses for future trials, extrapolated with the model from data of pregnant women (at low doses) and initial Phase I data. Furthermore, the risk, which exists in absence of the extrapolation data, of exposing pregnant women to a potentially unsafe high dose at a later stage would be reduced.

## Design options during Phase III, addressing questions A and B (AB III)

*Question A: can we consider the drug safe (enough) for first exposure in pregnant women and fetuses?*

*Question B: in which dose range (potentially depending on gestational age) can it be considered to remain safe in pregnant women?*

Answering questions A and B for pregnant women concurrent with a phase III in our framework is in line with Baylis and Halperin's proposal for a Phase I study in pregnant women parallel to a Phase III study in the initial population.

A phase I study in pregnant women in parallel with a Phase III study in the initial population would entail a more traditional Phase I study, including escalating doses which are guided by PK and safety considerations. Dose escalation then needs to be done up to the level that exposure is expected to be therapeutic in pregnant women. Pregnant women of different gestational ages would need to be included. Moreover, the above described PK extrapolation approach is needed here as well, in order to determine an appropriate and safe dose escalation scheme.

## Design options during Phase III, addressing questions C and D (C III – D III)

*Question C: at what dose (regimen, within the range considered safe) can we expect efficacy in pregnant women?*

*Question D: can efficacy be confirmed at the target dose, either similar to the initial population or different?*

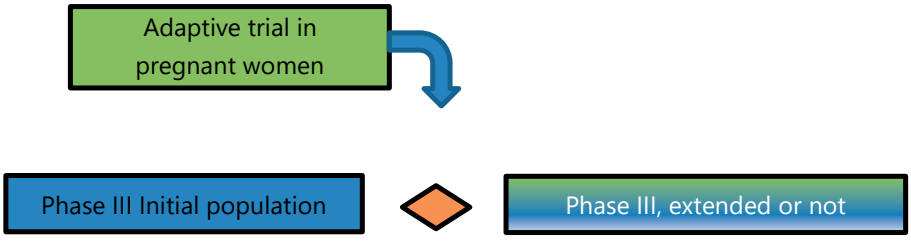
Answering questions C and D in our framework is in line with Baylis and Halperin's earlier explained proposal to embed the Phase I trial for pregnant women in the Phase III trial for the initial population. But in contrast to Baylis and Halperin, we argue that answering questions C and D for pregnant women extends well beyond embedding a Phase I trial in a Phase III trial. To provide an answer, not only Phase I data for pregnant women would

need to be generated within the context of the Phase III trial, also more pertinent data is needed. For instance, data on clinical efficacy or safety over a relevant treatment period given the disease. And in all cases, pregnant women and to the extent possible their fetuses need to be monitored intensively from a safety perspective, in line with Phase I/ First in Human studies, even if it is not the first exposure. Furthermore, before considering enrolling pregnant women in a Phase III and reflecting on the potential objectives for doing so, it is worthwhile to consider additional prerequisites that would have to be taken into account. First, a minimum prerequisite for considering the new treatment efficacious in pregnant women is that efficacy is demonstrated in the initial population. Second, when enrolling pregnant women in a Phase III simultaneously with the initial population, a prerequisite is that the safety of the dose(s) used in pregnant women should be optimal. Hence, the scenario of addressing questions C and D concurrent with the regular Phase III would require some kind of Phase I study in pregnant women at an earlier stage (so that question B is addressed specifically for pregnant women), or reliable extrapolation data based on data from the initial population.

There are a number of potential design considerations for addressing questions C and D in Phase III. One important consideration is that the subgroup of pregnant women would typically not be large enough to stand on its own. Following our proposed prerequisites, exposing larger numbers of pregnant women would only be justified if efficacy is sufficiently established in the initial population. Additional safeguards can be built in, based on pre-planned interim analyses. In a Phase III trial in which pregnant women would enroll from the start, interim analyses would include early stopping for safety or efficacy reasons. With respect to the latter, interim analyses can analyze whether efficacy in pregnant women is (considerably) less promising as compared to the initial population, which would allow early stopping of the group of pregnant women, thus avoiding risks where there might not be benefit.

Finally, when there is substantial residual uncertainty at the start of a Phase III, an adaptive approach is worth considering. The Phase III trial can already start without including pregnant women. An interim decision can be made in Phase III to extend recruitment

**Figure 1.** Adaptive Phase III trial with interim extension of recruitment based on adaptive trial in pregnant women



to pregnant women (see Figure 1), based on results of an adaptive trial in pregnant women to arrive at a proper and safe dose (following the adaptive design as described above). The statistical approach for such a design could be based on the methodology of Bauer and Köhne which can be applied to the group of non-pregnant women to establish confirmatory evidence of efficacy on the combined date before and after the adaptation[24]. The subgroup of pregnant women can be evaluated separately (albeit with limited power), and consistency of treatment effect estimates between pregnant and non-pregnant women can be assessed similar to other subgroup evaluations[26].

## Design options during Phase IV, addressing all questions (AB IV – E IV)

*Question A: can we consider the drug safe (enough) for first exposure in pregnant women and fetuses?*

*Question B: in which dose range (potentially depending on gestational age) can it be considered to remain safe in pregnant women?*

*Question C: at what dose (regimen, within the range considered safe) can we expect efficacy in pregnant women?*

*Question D: can efficacy be confirmed at the target dose, either similar to the initial population or different?*

*Question E: Can clinical safety be confirmed at a sufficiently acceptable level at the target dose for pregnant women as well as their fetus, so as to conclude a positive benefit risk ratio?*

Addressing questions A to E in Phase IV would mean that a new treatment is marketed, before pregnant women have participated in clinical trials. At this point, efficacy and safety in the initial population are sufficiently established. If questions for pregnant women are answered at all, they are generally answered through case-studies of pregnant women using the drugs off-label. Currently, off-label use is the most common situation. However, there are many challenges that require similar safeguards as in the clinical trial designs that were introduced above. To illustrate, a proper dose for pregnant women needs to be established, requiring Phase I type trials and a careful stepwise evaluation of safety. This includes the non-clinical safety investigations that are needed. As the opportunity to include pregnant women in a Phase III trial in the initial population is currently not used, in most cases this means that a separate efficacy and safety study in pregnant women is (still) needed in order to address questions A and B.

In this scenario, delay is an obvious negative consequence of requiring a Phase I study before allowing pregnant women in phase IV studies. And if we do not require a Phase I study but depend on observational data we are faced with a similar timeframe, since it

may take years before sufficient observational data is collected[27]. Because of these delay issues, we propose that there are cases where pregnant women could already be included in phase IV trials even when questions A – E are not answered in trials for pregnant women. Depending on the general safety profile and the results of a Phase I type study in pregnant women (PK and dosing), close monitoring based on an observational registry in which data is systematically gathered might suffice.

## DISCUSSION

Including pregnant women in regular drug development programs is unwarranted due to the often unknown risks and potential serious consequences for pregnant women and fetuses. Instead of considering pregnant women an 'ordinary subgroup' for which the traditional four phases approach towards drug development could apply, we proposed a practical framework for planning inclusion of pregnant women in drug development, in the form of a question based approach in combination with prerequisites. Specifically, we formulated five key clinical research questions and complemented the questions with three generally agreed upon prerequisites in order to determine concurrent with what phase of the traditional development program the questions should be answered for pregnant women. Based on the combination of questions and prerequisites, a scheme for responsible inclusion of pregnant women in drug trials could be drafted (Table 1). Accordingly, in our framework we argued that question A and B first need to be answered positively for pregnant women (parallel/embedded with Phase II or Phase III initial population), with establishing proper safe dosing as a key prerequisite, before question C – E can be answered by including pregnant women (parallel or embedded in Phase III or Phase IV general population). Consequentially, we proposed that in most cases a Phase I trial, in which data on drug safety and drug dose range is collected, should always be conducted before including pregnant women in later phases. By indicating which information needs to be addressed at what time, we demonstrated different possibilities of responsibly including pregnant women at an earlier time in the drug development process.

The planning of including pregnant women in drug programs is a relatively unexplored field and there are a number of additional aspects that need exploration in order to determine the viability of our framework. One such aspect involves the monitoring of safety and follow-up of pregnant women and fetuses, which should have a place in any scenario. Presently, there are requirements for monitoring and, if possible, follow-up[8], but these requirements seem insufficient because they do not stipulate the method for monitoring or follow-up. Some countries have experience with compulsory pregnancy registries (for example the Swedish Medical Birth Register), which enables the collection of large numbers of maternal medication data even though such registries have their own

challenges. Further research into adequate monitoring and follow-up is necessary, but is outside the scope of our paper.

It could be argued that our framework, which requires the establishment of safety and dose range in a Phase I trial may delay inclusion of pregnant women in drug research. Nevertheless, delay could be partly avoided if pre-clinical data combined with Phase I data in the initial population would allow exposure at low doses of pregnant women, combined with extrapolation from the initial population to pregnant women. Moreover, our paper actually emphasizes the different options of including pregnant women at an earlier phase in order to increase the possibilities to conduct research in pregnant women. By indicating the appropriate time when inclusion of pregnant women can be safe and therefore acceptable, we remove design barriers that have hindered inclusion of pregnant women in drug trials. We challenge the current underrepresentation and we support the idea that including a smaller group of pregnant women in a well-controlled setting is preferable to exposing the whole population of pregnant women to unknown risks. We hope that our discussion on the appropriate timing and the different design options for the responsible inclusion of pregnant women will ultimately contribute to the development of specific trial designs for pregnant women.

## LIMITATIONS

This paper has some limitations. First, the current exploration does not include a full practical application and the actual proof would be a fully developed protocol and evidence of feasibility through adequate recruitment and conduct. Second, our proposal assumes that funding agencies and manufacturers are willing to include pregnant women in clinical research. Further research should explore if funding agencies and manufacturers are indeed willing to include pregnant women in our proposed design options. Third, irrespective of the design, intense monitoring and long follow-up of women, fetuses and newborns is essential. While we did not address the issue, of monitoring and long-term follow-up, the present limitations in physiological and medical follow-up of the fetus and newborns may still be a serious hurdle to include pregnant women, which cannot be overcome by clinical trial methodology alone.

## CONCLUSIONS

In this paper we have argued that a practical framework for the inclusion of pregnant women in drug research could consist of the combination of a question based approach with prerequisites for drug development for pregnant women. The framework includes a scheme for the safe and appropriate timing of inclusion of pregnant women concurrent with the regular drug development program. Ultimately, our framework may lead

to i) earlier inclusion of pregnant women in drug development, ii) ensuring that key prerequisites such as proper dosing, are addressed before more substantial numbers of pregnant women are included in trials, and iii) optimal use of safety and efficacy data from the initial (non-pregnant) population throughout the development program. Our paper thus emphasizes the different options of including pregnant women at an earlier phase in order to increase the possibilities to conduct research in pregnant women. By indicating the appropriate time when inclusion of pregnant women can be safe and therefore acceptable, we aim to remove design barriers that have hindered inclusion of pregnant women in drug trials. We challenge the current underrepresentation and we support the idea that including a smaller group of pregnant women in a well-controlled setting is preferable to exposing the whole population of pregnant women to unknown risks. We further hope that our discussion will support the development of specific trial designs for pregnant women and thereby contribute to increasing the evidence-base for pregnant women and fetuses.

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## REFERENCES

1. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
2. Little M, Lyerly A, Faden R. Pregnant women and medical research: a moral imperative. Bioethica Forum. 2009;2:60–5.
3. Baylis F. Pregnant women deserve better. Nature. 2010;465:689–90.
4. CIOMS & WHO. CIOMS draft guidelines [Internet]. 2016. Available from: http://www.cioms.ch/index.php
5. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet. Gynecol. 2013;122:1077–81.
6. Haas DM, Gallauresi B, Shields K, Zeitlin D, Clark SM, Hebert MF, et al. Pharmacotherapy and pregnancy: Highlights from the third international conference for individualized pharmacotherapy in pregnancy. Clin. Transl. Sci. 2011;4:204–9.
7. Lupattelli a, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby a C, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4:e004365.
8. EMA (European Medicines Agency). Guideline of the exposure to medicinal products during pregnancy: need for post-authorisation data. [Internet]. 2005 [cited 2016 Mar 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf
9. Noah BA. The inclusion of pregnant women in clinical research barbara a. noah* a. 2014;353–89.
10. ORWH (United States. Department of Health and Human Services, Public Health Service, National Institutes of Health O of R on WH. Enrolling pregnant women: Issues in clinical research. 2011.
11. The Second Wave Initiative [Internet]. [cited 2017 Mar 20]. Available from: http://secondwaveinitiative.org/
12. ACOG Statement on FDA Pregnancy Labeling Final Rule - ACOG [Internet]. [cited 2016 May 24]. Available from: http://www.acog.org/About-ACOG/News-Room/Statements/2014/ACOG-Statement-on-FDA-Pregnancy-Labeling-Final-Rule
13. Cain J, Lowell J, Thorndyke L, Localio a R. Contraceptive requirements for clinical research. Obstet. Gynecol. 2000. p. 861–6.
14. van der Zande ISE, van der Graaf R, Browne JL, van Delden JJM. Fair Inclusion of Pregnant Women in Clinical Research: A Systematic Review of Reported Reasons for Exclusion. In: F Baylis, A Ballantyne. ., editor. Clin. Trials Involv. Pregnant Women. 2016. p. 65–94.
15. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. Elsevier Inc.; 2013;23:e39–45.
16. Frew PM, Saint-Victor DS, Isaacs MB, Kim S, Swamy GK, Sheffield JS, et al. Recruitment and retention of pregnant women into clinical research trials: an overview of challenges, facilitators, and best practices. Clin. Infect. Dis. 2014;59 Suppl 7:S400-7.
17. Little BB. Pharmacokinetics during pregnancy: Evidence-based maternal dose formulation. Obstet. Gynecol. 1999. p. 858–68.
18. Mattison D, Zajicek A. Gaps in knowledge in treating pregnant women. Gend. Med. 2006;3:169–82.
19. Halperin SA. Research involving pregnant women : trials and tribulations. 2012;2:139–46.
20. de Visser SJ. A question based approach to drug development. 2003.

21. de Visser S.J. , B. Tuk JMA van G and AFC. Drug development project management by a new question based approach and decision analysis support. Scrip Mag. 2003;
22. Sheiner LB. Learning versus confirming in clinical drug development*. Clin. Pharmacol. Ther. 1997;61:275–91.
23. EMA. Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned With an Adaptive Design. Reproduction. 2007;
24. Bauer P, Köhne K. Evaluation of experiments with adaptive interim analyses. Biometrics. 1994;50:1029–41.
25. Sheffield JS, Siegel D, Mirochnick M, Heine RP, Nguyen C, Bergman KL, et al. Designing drug trials: Considerations for pregnant women. Clin. Infect. Dis. 2014;59:S437–44.
26. Grouin JM, Coste M, Lewis J. Subgroup analyses in randomized clinical trials: Statistical and regulatory issues. J. Biopharm. Stat. 2005;15:869–82.
27. Briggs GG, Polifka JE, Wisner KL, Gervais E, Miller RK, Berard A, et al. Should Pregnant Women be Included in Phase IV Clinical Drug Trials? Am. J. Obstet. Gynecol. Elsevier Ltd; 2015;

# CHAPTER 10

## GENERAL DISCUSSION
## A NORMATIVE FRAMEWORK FOR INCLUSION OF PREGNANT WOMEN IN CLINICAL RESEARCH

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*Submitted*

## THE NEED FOR A WAY FORWARD

Including pregnant women in clinical research inevitably leads to a paradox: we want to protect pregnant women and foetuses from harm and therefore intuitively prefer to exclude them from clinical research; but by protecting them we may subject pregnant women and foetuses to harm because in daily clinical practice they are exposed to medications and treatments for which there is a lack of evidence, which can only be gathered by research in the population of pregnant women. In the last decades, protection through inclusion has been promoted, based on the idea that evidence gathered under rigorous scientific conditions that place pregnant women and their foetuses at risk, is preferred over exposing the population of pregnant women to non-evidence based medications once they come to market[1–3]. Yet, increasing the evidence base through inclusion of pregnant women is a complex issue and at present, pregnant women remain underrepresented in clinical research for a variety of reasons **(Chapter 2)**.

This thesis identified and evaluated four ethical issues relative to the inclusion of pregnant women in clinical research. The findings indicated a need for guidance on a way forward. In the General Discussion, we present a normative framework in which we specify under which conditions pregnant women may be included in clinical research. The framework is based on the main findings of this thesis and aims to challenge the underrepresentation of pregnant women. The framework consists of four normative considerations and a number of specific recommendations for stakeholders who are actively involved in the inclusion of pregnant women in clinical research. A visual illustration of the ethical issues and the normative framework is depicted in the Infographic.

## NORMATIVE CONSIDERATIONS AND PRACTICAL RECOMMENDATIONS

Four normative considerations should be taken into account in relation to including pregnant women in clinical research. Additionally, healthcare professionals, Research Ethics Committee (REC) members, researchers and pharmacologists, methodologists, sponsors and regulators (national regulators as well as regulatory authorities such as the FDA and EMA) have a shared responsibility to realise the inclusion of pregnant women. For each consideration we therefore indicate specific recommendations for different stakeholders. Neither the list of stakeholders nor the recommendations are exhaustive, yet they provide an overview of potential actions that may follow from the proposed normative considerations.

## Consideration I. Acceptable levels of risk for pregnant women should be formulated through a deliberative process balancing risks and benefits and the outcome of the process should henceforth be respected

Rational deliberation on acceptable levels of risks and subsequently acceptance of such established risk classifications should be the rule. The Council of International Organizations of Medical Sciences (CIOMS) has recently revised its guidelines for health-related research involving humans. The guideline on research with pregnant women has clarified the level of acceptable risks. According to the guideline, risks must be minimised and outweighed by the prospect of individual benefit for potentially beneficial research. In addition, the guideline stipulates that for research with no potential individual benefit, the risks must either be minimised and more than minimal, or, when the social value is compelling, a minor increase above minimal risk is acceptable (CIOMS 2016, Guideline 19[4]). The guideline appears to contradict the views of healthcare professionals, RECs, regulators and pregnant women in the Netherlands. These stakeholders are risk adverse to the point where they propose an upper limit of risk in potentially beneficial clinical research, in order to protect the foetus and the pregnant woman from harm. Yet, a risk threshold for potentially beneficial research is not even set in research with persons who are unable of giving informed consent **(Chapter 3)**.

Moreover, healthcare professionals make individual judgments about risks and they sometimes perceive minimal risk studies as posing higher risk. This distorted perception of risk relates to the precautionary principle, for pregnant women often interpreted in the strong version "*in dubio abstine*". The word "pregnant" automatically triggers a precautionary sentiment in daily life which is also extrapolated to clinical research. Here, "pregnant" is often linked to halting any study in which pregnant women may face risks, even when there are also benefits. The argument behind a strong version of the precautionary principle is that if there is a possibility that research participation can result in serious adverse effects for the foetus, the precautionary action should be to exclude pregnant women from clinical research. We argue that when risk-benefit analyses are made, the precautionary principle should be applied in a weak rather than a strong version **(Chapter 4)**. A weak version requires an overall shift in thinking where potential harms of a precautionary measure itself are also taken into account. Additionally, it is important to realise that there is not always risk or that risks are minimal when pregnant women are included; or that risk is inevitable, especially regarding pregnant women who are already at risk due to chronic non-obstetric or (a history of) obstetric illness. Evidently, clinical research in pregnant women never concerns healthy pregnant women or foetuses, but always involves research in pregnant women that are or have become ill during pregnancy.

### Recommendations for healthcare professionals

Individual judgements about potential risks of a study or clinicians' potential lack of personal equipoise despite evidence may hamper the recruitment of potentially eligible and willing pregnant women and thereby challenge the success of the study[5,6]. Ambiguity on the risks or the reason for a study should therefore be avoided. We recommend aligning risk classifications by involving healthcare professionals from the start of a research project. For example, by asking healthcare professionals to assess the logistics and potential risks and benefits of a study in advance, thereby decreasing the risk of delay and lack of personal equipoise. Aligning risk classifications upfront is a practice that is currently introduced in the Dutch NVOG consortium, via the Scientific Research Agenda[7]. Another recommendation is to collaborate with patient representative organisations to align views on risks and optimise recruitment procedures. Patient collaboration has proven beneficial in other fields, where including the perspective of patients' experiential knowledge has been related to for instance a broadening of the research agenda, more efficient trials, and better recruitment and retention rates[8–11]. However, even though collaboration between healthcare professionals, patients and industry is at times achieved and increasingly required by funders[12], the practice is still exception rather than rule.

### Recommendations for RECs

When making risk-benefit assessments, REC members should apply a weak interpretation of the precautionary principle. A weak interpretation sustains the ethical consideration that foetal wellbeing is an important value to protect, but it also takes alternatives into account. As such, a weak interpretation of the precautionary principle requires a clear definition of the threat and a balance between costs and benefits of inclusion and exclusion, thereby taking a broad scope of harms and possible alternatives into account. Moreover, a weak version also necessitates that the harms of the precautionary measure itself are taken into account, in order to prevent counter-productivity[13,14]. Finally, a weak interpretation leaves room for contextualisation of a situation instead of automatically linking the word 'pregnant' to extreme precaution.

## Consideration II. Pregnant women should only be deemed vulnerable when they encounter a higher exposure to risk due to a lack of scientific knowledge

Pregnant women are often automatically deemed to be a vulnerable population, even when the notion of vulnerability is not clearly defined. Nevertheless, there is consensus about some aspects of vulnerability, summarised in Samia Hurst's definition which states that someone can be vulnerable when she encounters an identifiably increased likelihood of incurring additional or greater wrong[15] **(Chapter 5)**. When we tested our in

the literature found features of pregnant women's alleged vulnerability to the definition, it transpired that pregnant women are only vulnerable because a higher exposure to risk due to a lack of scientific knowledge for their population comprises an increased wrong. In most instances, there is a lack of scientific research, which means that pregnant women may in most cases be vulnerable in clinical research. Because their vulnerability consists of a lack of scientific knowledge, special protection should, paradoxically, be focused on the inclusion of pregnant women in order to increase the evidence-base and thereby decrease their vulnerability. Other reasons for pregnant women's alleged vulnerability that were raised in the literature as well as by stakeholders (including pregnant women themselves), included concerns about pregnant women's ability to provide informed consent, their susceptibility to coercion and the vulnerability of the foetus **(Chapter 5, Chapter 8)**. However, these reasons are invalid and special protection should not be directed towards these aspects.

### Recommendations for RECs

We recommend to raise awareness among REC members to not automatically classify pregnant women as a vulnerable population. Moreover, RECs need to be informed that including pregnant women in clinical research can in fact decrease their vulnerability and may therefore be viewed as a form of protection.

### Recommendations for RECs and healthcare professionals

We recommend changing the perception of pregnant women's decisional capacities by raising awareness that pregnant women are only potentially vulnerable in the sense that they are increasingly exposed to higher risks in clinical research, and that they are not vulnerable because of a lack of informed consent or susceptibility to coercion. Accordingly, pregnant women are competent to make decisions about research participation. Healthcare professionals can play a role in the empowerment of pregnant women by stimulating them in the belief that they are able to make decisions during pregnancy, be it in relation to clinical research or to other aspects of clinical care.

## Consideration III. Fair inclusion of pregnant women implies that separate trials in pregnant women should be promoted and that prioritising their research interests is the shared responsibly of all actors involved in the research process

Fair inclusion of pregnant women means i) that pregnant women who are eligible are not excluded solely for being pregnant, and ii) that the research interests of pregnant women are prioritised **(Chapter 6)**. The first component should not be mistaken for routine inclusion in every trial, instead, there are three phase III research scenarios where

fair inclusion has methodological limitations and exclusion can be justified for scientific reasons. First, when *we know that intervention effects for pregnant women differ* from those for non-pregnant women, pregnant women should not be included in phase III research that consists of non-pregnant women, instead, separate trials should be initiated or phase IV and post-marketing studies should be conducted. Second, when *we know that no differences exist* between intervention effects for pregnant and non-pregnant women, conducting post-marketing studies or establishing registries is preferable. And when *we assume rather than know that there are no differences*, we should refer back to the default of the first scenario. Third, when *we are uncertain whether differences exist due to insufficient prior information,* it may also be preferable to return to the first scenario. Contrarily, in the case when *there is prior information but the information does not indicate either differences or no differences*, inclusion of pregnant women in phase III trials should at least be sufficient (i.e. not simply enrolling a few pregnant women in a trial).

Furthermore, fair inclusion requires addressing the inclusion of pregnant women in clinical research, primarily the set-up of separate trials. The establishment of separate trials cannot and should not be bestowed upon individual researchers and RECs at the moment of ethical review of already designed research projects. Instead, it has to be realised at the earliest phases of research involving pregnant women, at three different levels. First, at a national level, sponsors and regulators should from a corrective justice perspective stimulate inclusion, because scientific evidence for the group of pregnant women is relatively underrepresented. Second, at the level of research design and review of individual research projects, researchers and pharmacologists and RECs should justify the exclusion of pregnant women from clinical research, based on reasons of equity and corrective justice.

Third, at the level of enrolling pregnant women in clinical research, healthcare professionals should fairly include pregnant women and not resort to gatekeeping. Pregnant women seem willing to participate for personal and altruistic motivations **(Chapter 7)** and healthcare professionals in their role as researcher also report a willingness to advance inclusion of pregnant women. However, at least in the Dutch clinical practice, it turns out that healthcare professionals are reluctant to include pregnant women because of a protective and risk-adverse attitude. In their role as caretakers, healthcare professionals sometimes resort to gatekeeping, where they do not ask all patients that fulfil the inclusion criteria to participate, or where they direct patients in a certain direction during the counselling conversation **(Chapter 8)**. To prevent bias and to treat all pregnant women equally, healthcare professionals should provide information about research participation to all patients who are potentially eligible for research participation.

## Recommendations for sponsors and regulators

Based on a notion of corrective justice, we first recommend that sponsors and regulators take up the responsibility for inclusion of pregnant women in clinical research at an (inter) national level. For instance by requiring researchers to provide appropriate justification for the exclusion of pregnant women or by requiring pharmaceutical companies to conduct separate trials in pregnant women. Such initiatives currently exist in paediatric research (respectively the NIH Policy Inclusion of Children and the EU Paediatric Regulation), and could also be applied to research involving pregnant women. Next to that, we recommend national regulators to invest in mandatory pregnancy registries. Even though such registries have their own challenges, they enable the collection of large numbers of maternal medication data for scientific purposes. Lessons can be learned from countries that have experience with pregnancy registries, for example the mandatory Swedish Medical Birth Register or the recently established voluntary pREGnant register in the Netherlands[16,17]. Second, we recommend a policy wherein sponsors prioritise clinical research in pregnant women by including at least one grant for research in this population per each application round or by providing financial incentives to generate data on pregnant women by granting a three-month period of market exclusivity for drug companies that invest in research in this population (similar to the paediatric setting[18]). Third, we recommend that agreements about liability are made, for example sharing or shifting liability[19,20], in order to overcome liability fears of manufacturers.

## Recommendations for RECs and researchers and pharmacologists

RECs and researchers and pharmacologists should justify exclusion. RECs are charged with the task to assess research protocols. Although they may argue that their main responsibility is the protection of persons who are already included in the research proposal by the researcher, we recommend that they take up their role in a broader way and also actively demand justifications for the exclusion of pregnant women. Asking researchers to justify exclusion (and thereby focusing on inclusion) is in fact a form of protection. However, RECs are only involved at a late stage in the research process and by that time it might be too late to compel researchers and pharmacologists to include pregnant women in order to reduce the knowledge gap. Therefore, justifying exclusion is also especially important for researchers and pharmacologists themselves. We recommend that these stakeholders report and discuss their reasoning regarding the exclusion criteria in their research proposals.

## Recommendations for healthcare professionals

We recommend healthcare professionals to adjust the counselling conversation to ensure more objectivity. A first step could be to provide education on non-directive counselling and to raise awareness on the way in which healthcare professionals in their role as

caretakers may (unconsciously) influence their patients' decisions. A second step could be to contact patient representative organisations and discuss the way to address potential research participants in a way that is most beneficial for both the individual patient and the overall advancement of clinical care. An area of particular interest may be that of preconception care. Especially for women with chronic non-obstetric conditions or women with obstetric problems in prior pregnancies, the preconception period can be used for counselling, thereby preparing women for potential recruitment questions and increasing time for informed choices.

## Consideration IV. Pregnant women may be early included in the drug development process, provided that prerequisites and safety and efficacy data are adequately addressed and safeguarded throughout the process

Because of additional risks associated with including pregnant women in clinical research and the altered ways in which drugs are processed by the pregnant body, methodologically pregnant women cannot be treated as an ordinary subgroup in the various phases of traditional drug development. Instead, we propose that a practical framework for inclusion of pregnant women is better suited. The framework consists of using a question based approach with five key clinical questions in combination with three prerequisites that should be addressed when considering inclusion of pregnant women in drug research **(Chapter 9)**. Combining questions and prerequisites leads to a scheme for appropriate timing for responsible inclusion of pregnant women in drug research (Table 1, Chapter 9). Ultimately, the framework may result in i) early inclusion of pregnant women in drug development, ii) ensuring that key prerequisites, such as proper dosing, are addressed before more substantial numbers of pregnant women are included in trials, and iii) optimal use of safety and efficacy data from the initial (non-pregnant) population throughout the drug development process. By demonstrating when pregnant women can be safely included, design barriers that previously hindered inclusion of pregnant women in clinical research are removed.

### Recommendations for researchers and pharmacologists and methodologists

Our proposed framework for inclusion of pregnant women in drug research requires that questions are asked differently and at different times. The application of this approach requires further discussion relative to the precise ethically optimised research design and matters such as monitoring and long-term follow-up of women, foetuses and new-borns. We recommend researchers and pharmacologists to take up this discussion with methodologists and ethicists and eventually invest in the development of a full research protocol in order to realise practical application and actual proof of the concept.

## CONCLUSIONS

There are ways forward with respect to the apparent paradox pertaining the inclusion of pregnant women in clinical research. In our normative framework we specify four normative considerations under which pregnant women may be included in clinical research:

i. Acceptable levels of risk for pregnant women should be formulated through a deliberative process balancing risks and benefits and the outcome should henceforth be respected;

ii. Pregnant women should only be deemed vulnerable when they encounter a higher exposure to risk due to a lack of scientific knowledge;

iii. Fair inclusion of pregnant women implies that separate trials in pregnant women should be promoted and that prioritising their research interests is a shared responsibility of all actors involved in the research process;

iv. Pregnant women may be early included in the drug development process, provided that prerequisites and safety and efficacy data are adequately addressed and safeguarded throughout the process.

Our normative framework is an addition to the ever increasing body of bioethical literature on inclusion of pregnant women in clinical research. The reasons *why* pregnant women should be included were previously convincingly addressed. Our proposed considerations and stakeholder recommendations provide further guidance on ethical issues that underlie the *how* of fair inclusion. For instance, by specifying the cases where risks may be acceptable and by stimulating a change in the perception of pregnant women's vulnerability and decision-making capacities. And, similarly, by showing that it can be permissible to include pregnant women early in the drug development process and that especially separate trials for pregnant women should be prioritised. As fundamental ethical issues are progressively answered, the way forward requires a focus on practical application. In our normative framework we attempt to activate different stakeholders and simultaneously stimulate a collaborative partnership between partners that may be key to the practical application of fair inclusion. Ethicists can be the connecting factor. For example by linking agencies that can determine the research agenda to pharmaceutical companies who run into ethical questions regarding liability; or by connecting methodologists who are willing to develop innovative research designs to researchers who are willing to implement the design and thereby encounter ethical questions regarding the recruitment procedure. Connecting stakeholders in this way will be essential to further the discussion on and application of inclusion of pregnant women. Ultimately, we hope that our normative framework can contribute to the fair inclusion of pregnant women in clinical research, for research is the only way to increase the evidence base, which is imperative to improve foetal and maternal health.

# Fair Inclusion of Pregnant Women in Clinical Research

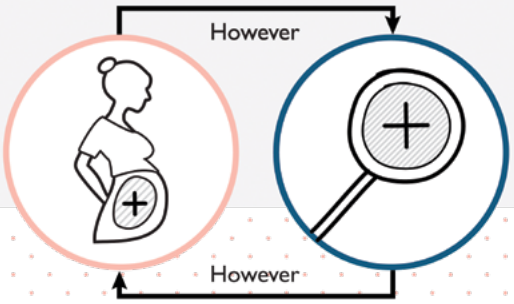
## Research Paradox

WHY

We intuitively prefer to exclude pregnant women from clinical research.

Exclusion leads to harm: 9/10 pregnant women take medications while > 90% of approved medications has an undetermined risk for use in pregnancy.

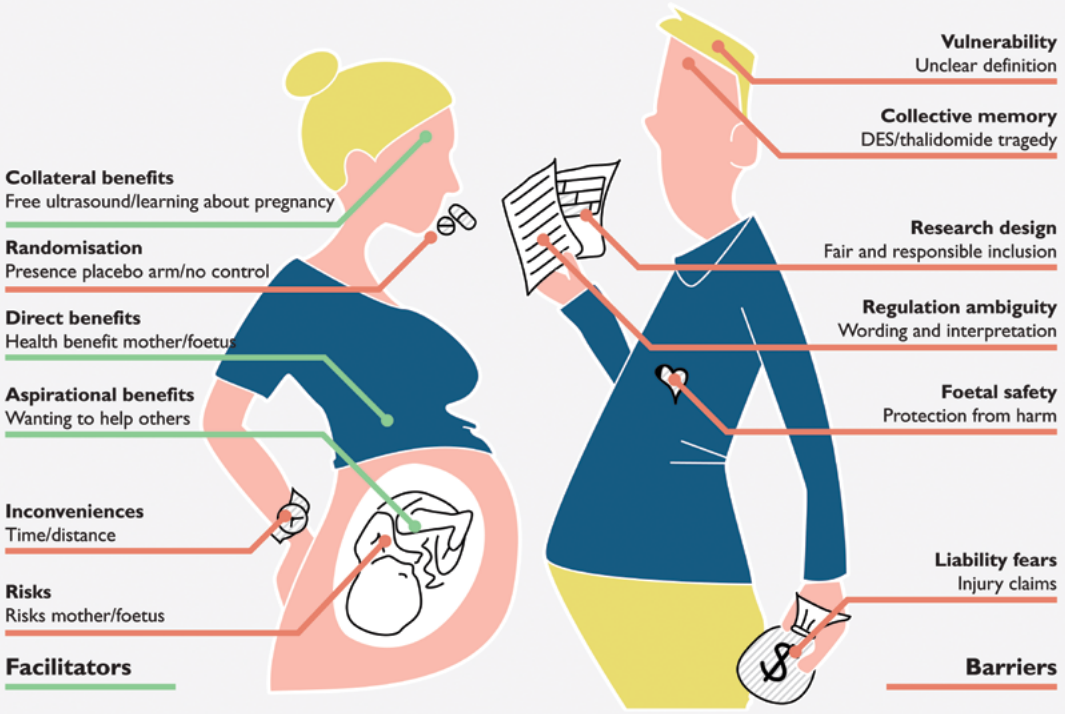
We want to protect pregnant women and foetuses from harm.




Sound evidence can only be gathered through fair inclusion of pregnant women in research.

## Facilitators and Barriers

WHAT



## Normative Considerations

HENCE

1. Acceptable levels of risk for pregnant women should be formulated through a deliberative process balancing risks and benefits and the outcome should henceforth be respected.

2. Pregnant women should only be deemed vulnerable when they encounter a higher exposure to risk due to a lack of scientific knowledge.

3. Fair inclusion of pregnant women implies that separate trials in pregnant women should be promoted and that prioritising their research interests is a shared responsibility of all actors involved in the research process.

4. Pregnant women may be early included in the drug development process, provided that prerequisites and safety and efficacy data are adequately addressed and safeguarded throughout the process.

## Recommendations

HOW

### Acceptable risk

Stakeholders have a distorted perception of risk, leading to extreme precaution and individual risk judgements. Acceptance of established risk classifications should be stimulated.

- Apply weak version precautionary principle
- Collaborate with patient groups
- Align risk classifications

### Vulnerability

Despite concerns in literature and by stakeholders, pregnant women are not vulnerable because of autonomy related issues such as informed consent or susceptibility to coercion.

- Stop automatic classification as vulnerable
- Awareness: inclusion decreases vulnerability
- Change perception on decisional capacities

### Fair inclusion

The establishment of separate trials has to be realised at the earliest phases of research, by all actors involved. Pregnancy cannot be the sole reason for exclusion, yet there are scenarios with methodological limitations where exclusion can be justified for scientific reasons.

- Require justifications for exclusion
- Require establishment of separate trials
- Invest in mandatory registries
- Provide financial incentives
- Organise liability agreements
- Ensure objectivity in counselling

### Early inclusion

Pregnant women cannot be treated as a regular subgroup in drug development; a question based approach is better suited to indicate the time for responsible (early) inclusion.

- Collaborate with patient groups
- Address monitoring and follow-up
- Develop ethically optimised research designs
- Provide proof of concept

WHO

Apply weak version precautionary principle

Collaborate with patient groups

Align risk classifications

Stop automatic classification as vulnerable

Awareness: inclusion decreases vulnerability

Change perception on decisional capacities

Require justifications for exclusion

Require establishment of separate trials

Invest in mandatory registries

Provide financial incentives

Organise liability agreements

Ensure objectivity in counselling

Collaborate with patient groups

Address monitoring and follow-up

Develop ethically optimised research designs

Provide proof of concept

**Research Ethics Committees**

**Healthcare professionals**

**Researchers, Pharmacologists, Methodologists**

**Sponsors and Regulators**

## Stakeholders

## Conclusions

THUS

It is possible to escape the research paradox. The way forward requires a focus on ethical issues that underlie the *how* rather than the *why* of fair inclusion of pregnant women. Stakeholder collaboration is essential in order to further the discussion on and application of inclusion of pregnant women.

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ZonMw

*Design by:*

STICKY VISUALS

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## REFERENCES

1. Macklin R. Enrolling pregnant women in biomedical research. Lancet. 2010. p. 632–3.
2. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton J a. Enrolling Pregnant Women: Issues in Clinical Research. Women's Heal. Issues. 2013;23:e39-45.
3. Lyerly AD, Little MO, Faden R. The second wave: Toward responsible inclusion of pregnant women in research. Int. J. Fem. Approaches Bioeth. 2008;1:5–22.
4. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-Related Research Involving Humans. Geneva, Switzerland: Council for International Organizations of Medical Sciences. [Internet]. 2016. Available from: http://www.cioms.ch/ethical
5. Madan A, Tracy S, Reid R, Henry A. Recruitment difficulties in obstetric trials: a case study and review. Aust. N. Z. J. Obstet. Gynaecol. 2014;54:546–52.
6. Cook C, Sheets C. Clinical equipoise and personal equipoise: two necessary ingredients for reducing bias in manual therapy trials. J Man Manip Ther. 2011;19:55–57.
7. NVOG kennisagenda 2017 - 2020 [Internet]. [cited 2017 Aug 10]. Available from: http://www.nvog.nl//Sites/Files/0000005146_NVOG kennisagenda 2017-2020.pdf
8. de Wit M, Abma T, Koelewijn-van Loon M, Collins S, Kirwan J. Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences. BMJ Open. 2013;3:1–12.
9. Edwards V, Wyatt K, Logan S, Britten N. Consulting parents about the design of a randomized controlled trial of osteopathy for children with cerebral palsy. Heal. Expect. 2011;14:429–38.
10. Patient Partner Consortium. Patient Involvement in Research. A guide for Patient Organisations and Patient Representatives [Internet]. [cited 2017 Aug 10]. Available from: https://www.geneticalliance.org.uk/media/1602/patientspartnerforpatientorgs.pdf.
11. Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, et al. Patient Engagement in Research: A Systematic Review. BMC Health Serv. Res. 2014;14:89.
12. Visser L, de Boer MA, de Groot CJM, Nijman TAJ, Hemels MAC, Bloemenkamp KWM, et al. Low dose aspirin in the prevention of recurrent spontaneous preterm labour – the APRIL study: a multicenter randomized placebo controlled trial. BMC Pregnancy Childbirth. 2017;17:223.
13. Koen Kramer., Hans L. Zaaijer MFV. The Precautionary Principle and the Social Institution of Blood Donation. Am. J. Bioeth. 2017;17:52–4.
14. Wilson K, Atkinson K. Toward Neo-Precaution: A New Approach to Applying the Precautionary Principle to Public Health. Am. J. Bioeth. 2017;17:44–6.
15. Hurst S a. Vulnerability in research and health care; Describing the elephant in the room? Bioethics. 2008. p. 191–202.
16. pREGnant [Internet]. [cited 2017 Jul 22]. Available from: https://www.pregnant.nl/
17. Swedish Medical Birth Register [Internet]. [cited 2017 Aug 10]. Available from: http://www.socialstyrelsen.se/register/halsodataregister/medicinskafodelseregistret/inenglish
18. Donley G. Encouraging Maternal Sacrifice: How Regulations Governing the Consumption of Pharmaceuticals During Pregnancy Prioritize Fetal Safety over Maternal Health and Autonomy. Rev. Law Soc. Change. 39:45–88.
19. Kaposy C, Lafferty L. Overcoming liability concerns in vaccine trials involving pregnant women. Account. Res. 2012;19:156–74.
20. Mariner W. Compensation for Research Injuries. In: A. Matroianni, R. Faden, D. Federman ., editor. Women Heal. Res. Ethical Leg. Issues Incl. Women Clin. Stud. Vol. 2 Work. Comm. Pap. Washington, D.C.: National Academies Press; 1999.

# APPENDICES &

**TOPIC LISTS**
**SUMMARY**
**SAMENVATTING**
**LIST OF PUBLICATIONS**
**CURRICULUM VITAE**
**DANKWOORD**

# TOPIC LISTS

## Topic list pregnant women[1]

What are the views of pregnant women regarding their participation in clinical research?

### Participation in APOSTEL VI

Recruitment

- You were recently asked to participate in this trial; can you go to the moment the trial was first mentioned to you?
- Can you explain how you experienced the course of the following process?
- Can you tell me the aim of the study?
- What motivations played a role in your decision to participate/decline?
- What motivation was ultimately decisive?
- How decisive was your decision?
- Who were involved in your decision? How important was their opinion?

Risks

- What are your reasons to say that this trial poses no or any risks?
- What are your views regarding the potential risks?
- I imagine that you made a certain calculation concerning the potential benefits and risks of participating in this trial. How did you do this?
- Can you hypothesise about your decision about this trial if there would not have been potential benefit for your baby, but it would only have been potentially beneficial for future patients?

### Participation of pregnant women in general

There are different opinions regarding research participation of pregnant women. Some argue that we should not include pregnant women at all, while others argue that we should include pregnant women more often. Some even argue for a type of routine inclusion. Although there is no accepted definition of this term, it could mean a default of inclusion in research, unless there are scientific or ethical reasons for exclusion.

- What is your opinion regarding the inclusion and the routine inclusion of pregnant women?
- On what grounds would you consider participation in a trial?
- What is your opinion about a) observational research, b) interventional research, c) drug trials, d) obstetric versus non-obstetric research involving pregnant women?

[1] We performed this qualitative study as part of a larger study. The same research population and topic list was therefore used to answer two different research questions: stakeholders' views on acceptable levels of risk (Chapter 3) and stakeholder's views on inclusion of pregnant women in the APOSTEL VI (Chapter 8).

- What are your reasons to say there is or there isn't a difference between a drug trial and the trial you are currently enrolled in/you were asked to participate in?
- Have you previously been asked to participate in clinical research or other types of scientific research?
- What were your reasons to participate/decline at that time?

Risks

- What is your opinion about clinical research in pregnant women that poses potential risk for the mother and/or the foetus?
- Do you experience a difference between research that poses only risks for you and none for your baby; and research that poses risks for the both of you?
- In some trials there is a risk threshold that is called "minimal risk"; this means that the risks in the trial are comparable to risks in daily life or in standard clinical care (e.g. blood draws). What is your opinion about this "minimal risk" threshold for research in pregnant women?
- What is your opinion about trials where the risks are more than minimal? How much more?
- There is a difference between research where the research participant may benefit from participating, and research where the research participant has no benefit but it may be beneficial for future patients. Do you think the level of acceptable risks should differ between these types of research?

Vulnerability

Vulnerability is a term that is sometimes used in clinical research in relation to groups or persons who are at an increased risk of being harmed, for example because they are less able to protect their own interests. Some argue that pregnant women are vulnerable in research in comparison with other research participants and that they need special protection because of their vulnerability.

- What is your opinion on pregnant women's vulnerability in clinical research?
- What is your opinion on pregnant women's vulnerability outside of clinical research?

## Topic list healthcare professionals[2]

What are the views and experiences of healthcare professionals regarding participation of pregnant women in clinical research?

### Research experience

APOSTEL VI

- What is the aim of the study?
- What are the potential risks and benefits for the mother and the foetus?
- What is your assessment of these risks (high/low) in comparison with the potential benefits?
- What are your views on reaching the sample size?
- What is your role in the study?
- Can you describe the recruitment and consent procedure and your role in the process?
- Can you recall times and reasons for not informing a pregnant woman who was eligible for participation about the study?
- In your opinion, what are the motivations of pregnant women to participate or decline?

In general

- Can you tell me about your role and the types of research you are involved in?
- What are the differences and similarities between recruitment and consent procedures of different studies?
- Can you recall times and reasons for not informing a pregnant woman who was eligible for participation about a study?
- What are your considerations when assessing or designing a research protocol?
- Do you recall times and reasons why a research protocol received a negative assessment?
- How do you weigh potential benefits against potential risks?
- Do you recall decisions where the interest of the pregnant woman had priority over the interest of the foetus, or the other way around?
- How do research participants view risks of participating in your experience?
- What is your role in relation to participants' views on risks?

### Participation of pregnant women in general

There are different opinions regarding research participation of pregnant women. Some argue that we should not include pregnant women at all, while others argue that we

[2] We performed this qualitative study as part of a larger study. The same research population and topic list was therefore used to answer two different research questions: stakeholders' views on acceptable levels of risk (Chapter 3) and stakeholder's views on inclusion of pregnant women in the APOSTEL VI (Chapter 8).

should include pregnant women more often. Some even argue for a type of routine inclusion. Although there is no accepted definition of this term, it could mean a default of inclusion in research, unless there are scientific or ethical reasons for exclusion.

- What is your position in the debate regarding (routine) inclusion of pregnant women?
- What is your opinion about a) observational research, b) interventional research, c) drug trials (off-label/new medication), d) obstetric versus non-obstetric research involving pregnant women?
- What is your experience and view on pregnancy registries?
- What are your thoughts on including pregnant women in the different phases or research?
- What are your thoughts on including pregnant women during different phases of pregnancy?
- What is your opinion on prioritising research in pregnant women?

Risk

- Do you have suggestions on how to balance risks and benefits?
- What do you view as a minimal risk or a minor increase over minimal risk?
- In some trials there is a risk threshold that is called "minimal risk"; this means that the risks in the trial are comparable to risks in daily life or in standard clinical care (e.g. blood draws). What is your opinion about this "minimal risk" threshold for research in pregnant women?
- What is your opinion about trials where the risks are more than the minimal risk standard?
- Is there a maximum of acceptable risk for a pregnant woman or foetus in research?
- How do research risks that are allowed in research with children play a role?
- There is a difference between research where the research participant may benefit from participating, and research where the research participant has no benefit but it may be beneficial for future patients. Do you think the level of acceptable risks should differ between these types of research?

Vulnerability

Vulnerability is a term that is sometimes used in clinical research in relation to groups or persons who are at an increased risk of being harmed, for example because they are less able to protect their own interests. Some argue that pregnant women are vulnerable in research in comparison with other research participants and that they need special protection because of their vulnerability.

- What is your opinion on pregnant women's vulnerability in clinical research?
- What are your suggestions regarding potential special protection?
- What is your opinion on pregnant women's vulnerability outside of clinical research?

# SUMMARY

There has always been a reluctance to include pregnant women in clinical research, due to a fear of harm to the foetus. At the same time, there is a need for evidence-based information on medications and treatments for pregnant women who are or become ill during their pregnancy, which can only be gathered through research in the population of pregnant women. For this reason, inclusion of pregnant women has been promoted in the last decades by bioethicists, pharmacologists, regulators and researchers. Yet despite efforts to include pregnant women in clinical research, they are still underrepresented. There are a number of open issues and it is likely that there are ethical reasons underlying the continuous underrepresentation of pregnant women. These ethical reasons need to be discussed in order to change the status quo. The four main issues that are addressed in this thesis are: 1) acceptable level of risk, 2) vulnerability, 3) fair inclusion, and 4) research design. By addressing these four open ethical issues, we aim to encourage the responsible inclusion of pregnant women in clinical research. As such, the main objective of this thesis is to challenge the underrepresentation of pregnant women by developing a normative framework specifying the conditions under which pregnant women could be included in clinical research.

In **Chapter 2,** we conduct a systematic review of literature relevant to the inclusion of pregnant women in clinical trials. In particular, we address barriers to fair inclusion that we identified within the literature. The 31 articles that were reviewed discuss the exclusion of pregnant women from clinical trials. Reasons given for such exclusion were grouped under several themes, including: foetal safety, collective memory or social controversies, liability, regulations, Research Ethics Committee interpretations, research design, willingness to participate and consent. We find that barriers to fair inclusion of pregnant women in clinical research interact. While there are practical solutions for surmounting some barriers, others require further discussion.

**Chapter 3** presents a prospective qualitative study in which we explore what healthcare professionals, Research Ethics Committee members (RECs), regulators and pregnant women recruited for the APOSTEL VI case-study deem an acceptable level of risk for pregnant women in clinical research. We establish four themes: i) continuum of acceptable risks in general, ii) desirability of clinical research in pregnant women in general, iii) interest in an upper limit of acceptable risk, and iv) perceived risks of APOSTEL VI study. We conclude that healthcare professionals, RECs, regulators and pregnant women are all risk adverse in practice, possibly explaining the continuing underrepresentation of pregnant women in clinical research. Determining the acceptable levels of risk on a universal level alone is insufficient, because the individual *perception* of risk also influences behaviour towards pregnant women in clinical research. Therefore, bioethicist and researchers might be interested in changing the perception of risk, which could be achieved by education and awareness about the actual benefits and harms of inclusion and exclusion of pregnant women.

In **Chapter 4** we explore through conceptual analysis *whether* and if so *how* the precautionary principle should apply to pregnant women. We argue that the precautionary principle is a decision-making strategy which can underlie risk-benefit decisions in clinical research and we establish that, as such, the precautionary principle can be applied to pregnant women in clinical research. However, the current application of the precautionary principle to the population of pregnant women is a strong one, leading to the promotion of two extremes: absolute exclusion or, less often, absolute inclusion of pregnant women. The current interpretation is thus paralysing the situation. In order to change the current situation, a shift towards weak precautionary thinking is necessary. A weak interpretation leaves room for contextualisation of situations, it takes a broad scope of harms and alternatives into account, it requires a clear definition of a threat and it necessitates that the harms of the precautionary measure itself are taken into account.

**Chapter 5** discusses *whether* and if so *to what extent* pregnant women are vulnerable as research subjects. A conceptual analysis supports Samia Hurst's definition of vulnerability. Consequently, we argue that pregnant women are vulnerable if they encounter an identifiably increased likelihood of incurring additional or greater wrong. According to the literature, this increased likelihood could exist of four alleged features of pregnant women's vulnerability: i) informed consent, ii) susceptibility to coercion, iii) higher exposure to risk due to lack of knowledge, iv) vulnerability of the foetus. Testing the four features against Hurst's definition, it becomes clear that the only reason why pregnant women are potentially vulnerable is to the extent that they are increasingly exposed to higher risks due to a lack of scientific knowledge. Research Ethics Committees have a responsibility to protect the vulnerable, but a higher exposure to risk due to lack of scientific knowledge is a much broader issue and also needs to be addressed by other stakeholders.

In **Chapter 6** we provide a conceptual ethical and methodological analysis and evaluation of fair inclusion in order to determine when research with pregnant women can be considered as fair and what constitutes scientific reasons for exclusion. We argue that fair inclusion of pregnant women means i) that pregnant women who are eligible are not excluded solely for being pregnant and ii) that the research interests of pregnant women are prioritised, meaning that they ought to receive substantially more attention. Fairness does not imply that pregnant women should be included in virtually every research project, as including only a few pregnant women in a population consisting of women will not help to determine the effectiveness and safety of a treatment in pregnant women. Separate trials in pregnant women may be preferable once we assume, or know, that effects of interventions in pregnant women differ from the effects in other subpopulations, or when we assume, or know, that there are no differences. In the latter case, it may be preferable to conduct post-marketing studies or establish registries. If there is no conclusive evidence indicating either differences or equivalence of effects between

pregnant and non-pregnant women, yet is seems unlikely that major differences or exact equivalence exists, inclusion of pregnant women should be sufficient. We conclude that fair inclusion of pregnant women in research implies that separate trials in pregnant women should be promoted and that stakeholders have a joint responsibility to realise the inclusion of pregnant women at the earliest phases of the research process.

**Chapter 7** presents a systematic review of articles regarding pregnant women's reasons for participation in clinical research, thereby distinguishing between facilitators and barriers. The 30 articles that were reviewed discuss facilitators and barriers. Themes classified as facilitators are: aspirational benefits, collateral benefits, direct benefits, third party influence and lack of inconvenience. Themes classified as barriers are: inconveniences, risks, randomisation, lack of trust in research enterprise, medical reasons and third party influence. We find that pregnant women report mostly altruistic and personal reasons for their willingness to participate in clinical research, while barriers primarily relate to inconveniences. It furthermore appears that pregnant women's described reasoning is similar to the described reasoning of non-pregnant research subjects.

**Chapter 8** presents a prospective qualitative study in which we aim to identify what healthcare professionals, Research Ethics Committee members (RECs), regulators and pregnant women recruited for the APOSTEL VI case-study think about research participation of pregnant women in regular pregnancy-related research. We establish four themes: i) motivations for participation, ii) counselling, iii) gatekeeping, and iv) interest in (routine) inclusion. We conclude that pregnant women are willing to participate in the APOSTEL VI study for potential individual benefit and altruistic motives. However, an underlying protective sentiment, resulting in gatekeeping and directive counselling, sometimes hampers recruitment in the APOSTEL VI study as well as in clinical research in general. While bioethicists claim that inclusion of pregnant women should be customary, our study indicates that healthcare professionals, regulators, RECs and pregnant women themselves are not necessarily interested in inclusion. Advancing the situation and increasing the evidence-base for pregnant women and foetuses may require additional measures such as investing in the recruitment and feasibility of randomised controlled trials (RCTs) and stimulating pregnant women's decisional capacities.

In **Chapter 9** we propose a practical framework for planning responsible inclusion of pregnant women in drug development. We suggest that the framework consists of using a question based approach with five key questions in combination with three prerequisites which should be addressed when considering inclusion of pregnant women in drug research. Combining questions and prerequisites leads to a scheme for appropriate timing for responsible inclusion of pregnant women in drug research. Accordingly, we explore several research design options of including pregnant women in drug trials that are feasible within the framework. Ultimately, the framework may lead to i) early inclusion of pregnant women in drug development, ii) ensuring that key prerequisites, such as proper

dosing, are addressed before more substantial numbers of pregnant women are included in trials, and iii) optimal use of safety and efficacy data from the initial (non-pregnant) population throughout drug development.

Finally, we present our normative framework for fair inclusion of pregnant women in **Chapter 10**. The framework was established through reflection on the four ethical issues and the main findings of this thesis. In the normative framework, we specify four normative considerations under which pregnant women may be included in clinical research: i) acceptable levels of risk for pregnant women should be formulated through a deliberative process balancing risks and benefits and the outcome should henceforth be respected, ii) pregnant women should only be deemed vulnerable when they encounter a higher exposure to risk due to a lack of scientific knowledge, iii) fair inclusion of pregnant women implies that separate trials in pregnant women should be promoted and that prioritising their research interests is a shared responsibility of all actors involved in the research process, and iv) pregnant women may be early included in the drug development process, provided that prerequisites and safety and efficacy data are adequately addressed and safeguarded throughout the process. As fundamental ethical issues concerning the *why* of fair inclusion are progressively answered, the way forward primarily requires a focus on the *how* of fair inclusion. Our normative framework encourages a collaborative partnership between stakeholders that may be key to the practical application of fair inclusion, in which ethicists can be the connecting factor. Ultimately, we express our hope that the normative framework can contribute to the fair inclusion of pregnant women in clinical research.

# SAMENVATTING

Er is altijd terughoudend geweest ten aanzien van het includeren van zwangere vrouwen in medisch-wetenschappelijk onderzoek, voornamelijk ingegeven door angst om de foetus schade te berokkenen. Tegelijkertijd is er behoefte aan evidence-based informatie over medicijnen en behandelingen voor zwangere vrouwen die ziek zijn of ziek worden tijdens hun zwangerschap. Deze evidence-based informatie kan alleen worden verkregen door onderzoek te verrichten onder zwangere vrouwen. Om deze reden wordt het betrekken van zwangere vrouwen bij onderzoek de laatste decennia aangemoedigd door bioethici, farmacologen, regelgevers en onderzoekers. Ondanks verschillende pogingen om zwangere vrouwen in medisch-wetenschappelijk onderzoek te includeren blijft deze groep ondervertegenwoordigd. Er zijn verschillende open vraagstukken en het is waarschijnlijk dat er onderliggende ethische redenen zijn voor de blijvende ondervertegenwoordiging van zwangere vrouwen. Deze mogelijk ethische redenen moeten worden besproken om een verandering in de huidige situatie te bereiken. De vier vraagstukken die in dit proefschrift worden behandeld zijn: 1) acceptabele hoogte van risico, 2) kwetsbaarheid, 3) rechtvaardige inclusie en 4) onderzoekdesign. Door deze vier open ethische vraagstukken te behandelen streven we ernaar om het verantwoord betrekken van zwangere vrouwen in medisch-wetenschappelijk onderzoek te bevorderen. Het doel van dit proefschrift is om op grond van het bovenstaande de bestaande ondervertegenwoordiging van zwangere vrouwen te veranderen door het schetsen van een normatief kader waarin de condities beschreven zijn waaronder zwangere vrouwen in medisch-wetenschappelijk onderzoek geïncludeerd kunnen worden.

In **Hoofdstuk 2** voeren we een systematische review uit van de literatuur die relevant is voor de inclusie van zwangere vrouwen in klinische studies. We bespreken in het bijzonder de barrières voor rechtvaardige inclusie die uit de literatuur naar voren komen. De 31 artikelen die werden opgenomen in de review behandelen de uitsluiting van zwangere vrouwen in klinische studies. Redenen voor uitsluiting werden gecategoriseerd in verschillende thema's, waaronder: veiligheid van de foetus; collectief geheugen over sociale controversies; aansprakelijkheid; regelgeving; interpretatie door Medisch Ethische Toetsingscommissies (METCs); onderzoekdesign; bereidheid om deel te nemen en geïnformeerde toestemming. We zien dat er een wisselwerking is tussen de barrières ten aanzien van rechtvaardige inclusie van zwangere vrouwen in medisch-wetenschappelijk onderzoek. Terwijl er praktische oplossingen zijn voor sommige barrières, vereisen andere uitgebreidere discussie.

**Hoofdstuk 3** beschrijft een prospectieve kwalitatieve studie waarin we onderzoeken wat gezondheidsmedewerkers, leden van METCs, regelgevers en zwangere vrouwen geworven voor de APOSTEL VI casestudie een acceptabele hoogte van risico vinden voor zwangere vrouwen in medisch-wetenschappelijk onderzoek. We constateren dat er vier thema's zijn: i) continuüm van acceptabele risico's in het algemeen, ii) wenselijkheid van medisch-

wetenschappelijk onderzoek met zwangere vrouwen in het algemeen, iii) interesse in een bovengrens van acceptabel risico, en iv) verondersteld risico van de APOSTEL VI studie. We concluderen dat gezondheidsmedewerkers, METCs, regelgevers en zwangere vrouwen in de praktijk allen risicomijdend zijn, wat mogelijk de voortdurende ondervertegenwoordiging van zwangere vrouwen in medisch-wetenschappelijk onderzoek verklaart. Het is niet voldoende om op universeel niveau te bepalen wat een acceptabel hoogte van risico is, omdat de persoonlijk *veronderstelling* van risico medebepalend is voor het gedrag ten aanzien van zwangere vrouwen in medisch-wetenschappelijk onderzoek.

In **Hoofdstuk 4** verrichten we een conceptuele analyse waarin we bestuderen *of* en zo ja *hoe* het voorzorgsprincipe (precautionary principle) op zwangere vrouwen van toepassing is. We beargumenteren waarom het voorzorgsprincipe een besluitvormingsstrategie is die ten grondslag ligt aan risico-baten beslissingen in medisch-wetenschappelijk onderzoek. We constateren dat het voorzorgsprincipe op zwangere vrouwen in medisch-wetenschappelijk onderzoek kan worden toegepast. De huidige toepassing is echter "sterk", wat leidt tot het stimuleren van twee extremen: absolute uitsluiting of, minder vaak, absolute inclusie van zwangere vrouwen. De huidige interpretatie van het voorzorgsprincipe verlamt hierdoor de situatie en om die te veranderen is een beweging naar "zwak" voorzorgsbeginsel-denken nodig. Een zwakke interpretatie biedt ruimte voor het contextualiseren van een situatie, houdt rekening met een breed scala aan schade en alternatieven, vereist een heldere definitie van een mogelijke dreiging en verlangt daarnaast het meewegen van de schade veroorzaakt door de voorzorgsmaatregel.

**Hoofdstuk 5** beschrijft *of* en zo ja *in welke mate* zwangere vrouwen als deelnemers aan onderzoek kwetsbaar zijn. Een conceptuele analyse ondersteunt Samina Hurt's definitie van kwetsbaarheid. Om die reden beargumenteren we dat zwangere vrouwen kwetsbaar zijn wanneer zij aantoonbaar grotere kans op meer of groter onrecht lopen. Uit de literatuur blijkt dat er verschillende redenen zijn waarom zwangere vrouwen kwetsbaar geacht worden. Deze redenen zijn: i) informed consent, ii) ontvankelijkheid voor dwang, iii) hogere blootstelling aan risico door onvoldoende wetenschappelijk bewijs en iv) de kwetsbaarheid van de foetus. Wanneer we deze vier redenen toetsen op de definitie van Hurst, wordt de enige reden waarom zwangere vrouwen mogelijk kwetsbaar zijn duidelijk: de mate is waarin ze meer aan hogere risico's blootgesteld worden vanwege onvoldoende wetenschappelijk bewijs. METCs hebben een verantwoordelijkheid om de kwetsbaren te beschermen. Tegelijkertijd is een hogere blootstelling aan risico vanwege onvoldoende wetenschappelijk bewijs een veel breder probleem dat ook door andere stakeholders moet worden opgepakt.

In **Hoofdstuk 6** presenteren we een conceptuele ethische en methodologische analyse en evaluatie van rechtvaardige inclusie, om te bepalen wanneer onderzoek met zwangere vrouwen als rechtvaardig beschouwd kan worden en welke de wetenschappelijke redenen voor uitsluiting zijn. We beargumenteren dat rechtvaardige inclusie van

zwangere vrouwen betekent dat: i) zwangere vrouwen die in aanmerking komen voor deelname aan onderzoek niet worden uitgesloten op basis van hun zwangerschap en ii) de onderzoeksbelangen van zwangere vrouwen worden geprioriteerd. Dit betekent dat ze substantieel meer aandacht behoeven. Rechtvaardigheid betekent niet dat zwangere vrouwen in virtueel elk onderzoeksproject meegenomen zouden moeten worden, want het meenemen van alleen een paar vrouwen in een populatie van niet-zwangere vrouwen zal niet helpen om de effectiviteit en veiligheid van een behandeling voor zwangere vrouwen te bepalen. Afzonderlijke studies met zwangere vrouwen hebben de voorkeur wanneer we ervan uitgaan, of weten, dat interventie effecten in zwangere vrouwen verschillen van de effecten in andere subpopulaties, of wanneer we ervan uitgaan, of weten, dat er geen verschillen zijn. In het laatste geval gaat de voorkeur wellicht uit naar post-marketing studies of het opzetten van registers. Wanneer er geen doorslaggevend bewijs is voor verschillen in dan wel identieke effecten tussen zwangere en niet-zwanger vrouwen, maar het onwaarschijnlijk is dat er grote verschillen of precieze overeenkomsten zijn, dan zou het includeren van zwangere vrouwen in studies sufficiënt moeten zijn. We concluderen dat rechtvaardige inclusie van zwangere vrouwen in onderzoek betekent dat afzonderlijke studies met betrekking tot zwangere vrouwen bevorderd zouden moeten worden en dat stakeholders een gezamenlijke verantwoordelijkheid hebben om het includeren van zwangere vrouwen in de eerste fases van het onderzoeksproces te realiseren.

**Hoofdstuk 7** is een systematische review van artikelen die de redenen van zwangere vrouwen om deel te nemen aan medisch-wetenschappelijk onderzoek behandelen, waarbij een verschil wordt gemaakt tussen bevorderende en belemmerende factoren. De 30 artikelen die werden geïncludeerd in de review bespreken bevorderende en belemmerende factoren. Thema's gecategoriseerd als bevorderende factoren zijn: altruïstisch voordeel; gemeenschappelijke voordeel; direct voordeel; advies van een derde partij en het ontbreken van ongemak. Thema's gecategoriseerd als belemmerende factoren zijn: ongemak; risico's; randomisering; gebrek aan vertrouwen in de onderzoekswereld; medische redenen en advies van een derde partij. We zien dat zwangere vrouwen voornamelijk altruïstische en persoonlijke redenen aangeven voor hun bereidheid tot deelname aan medisch-wetenschappelijk onderzoek, terwijl belemmerende factoren voornamelijk aan het onderwerp ongemak gerelateerd zijn. Daarnaast blijkt dat de redenering die zwangere vrouwen hierbij aangeven vergelijkbaar is met de redenering van niet-zwangere onderzoekdeelnemers.

**Hoofdstuk 8** beschrijft een prospectieve kwalitatieve studie waarin we onderzoeken wat gezondheidsmedewerkers, regelgevers, METC-leden en zwangere vrouwen geworven voor de APOSTEL VI casestudie denken van onderzoek deelname van zwangere vrouwen aan regulier zwangerschaps-gerelateerd onderzoek. We stellen vier thema's vast: i) motivaties voor deelname, ii) counseling, iii) gatekeeping, en iv) interesse in

(routinematige) inclusie. We concluderen dat zwangere vrouwen bereid zijn om deel te nemen aan de APOSTEL VI studie vanwege potentieel individueel voordeel en altruïstische motieven. Echter, een onderliggend beschermend sentiment, wat resulteert in gatekeeping en directief counselen, belemmert soms de werving voor de APOSTEL VI studie en de werving in medisch-wetenschappelijk onderzoek in het algemeen. Terwijl bioethici beweren dat inclusie van zwangere vrouwen gangbaar zou moeten zijn geeft onze studie aan dat gezondheidsmedewerkers, regelgevers, METCs en zwangere vrouwen zelf niet per se geïnteresseerd zijn in deelname. Om de huidige situatie te bevorderen en de evidence-base voor zwangere vrouwen en foetussen te vergroten zijn verdere maatregelen nodig, zoals het investeren in de werving en de haalbaarheid van studies, of het stimuleren van het beslisvermogen van zwangere vrouwen.

In **Hoofdstuk 9** stellen we voor een praktisch kader voor, voor het plannen van verantwoorde inclusie van zwangere vrouwen in het geneesmiddelenontwikkelingsproces. We beargumenteren dat het kader bestaat uit een vraag gestuurde benadering met vijf essentiële vragen in combinatie met drie voorwaarden die aan de orde moeten komen wanneer inclusie van zwangere vrouwen in geneesmiddelenonderzoek wordt overwogen. Het combineren van die vragen en voorwaarden leidt tot een schema met passende timing voor verantwoorde inclusie van zwangere vrouwen in geneesmiddelenonderzoek. Vervolgens verkennen we verschillende onderzoekdesign opties voor het includeren van zwangere vrouwen in geneesmiddelenstudies die haalbaar zijn binnen het praktische kader. Uiteindelijk kan het kader leiden tot: i) vroege inclusie van zwangere vrouwen in geneesmiddelenonderzoek, ii) de verzekering dat essentiële voorwaarden, zoals adequate dosering, zijn afgehandeld voordat substantiëlere aantallen zwangere vrouwen in studies worden geïncludeerd, en iii) het optimaal gebruik van veiligheids- en werkzaamheidsdata van de initiële (niet-zwangere) populatie gedurende het geneesmiddelenontwikkelingsproces.

Tot slot presenteren we ons normatieve kader voor rechtvaardige inclusie van zwangere vrouwen in **Hoofdstuk 10.** Het normatieve kader werd vastgesteld door reflectie op de vier ethische vraagstukken en de belangrijkste bevindingen van dit proefschrift. In het normatieve kader specificeren we vier normatieve overwegingen waaronder zwangere vrouwen in medisch-wetenschappelijk onderzoek geïncludeerd kunnen worden: i) het acceptabele hoogte van risico voor zwangere vrouwen moet worden geformuleerd op basis van een weloverwogen proces waarin risico's-baten gebalanceerd worden, en de uitkomst moet vervolgens worden aanvaard, ii) zwangere vrouwen moeten alleen kwetsbaar worden geacht wanneer ze vanwege een gebrek aan wetenschappelijk onderzoek aan hogere risico's blootgesteld worden, iii) rechtvaardige inclusie van zwangere vrouwen impliceert dat afzonderlijke studies voor zwangere vrouwen bevorderd moeten worden en dat het prioriteren van hun onderzoeksbelangen een gezamenlijke verantwoordelijkheid is van alle actoren die betrokken zijn in het onderzoeksproces,

en iv) zwangere vrouwen kunnen eerder in het geneesmiddelenontwikkelproces geïncludeerd worden, mits aan de voorwaarden en veiligheid- en werkzaamheidseisen zijn voldaan en worden gegarandeerd gedurende het proces. Naarmate fundamentele ethische vraagstukken omtrent het *waarom* van rechtvaardige inclusie beantwoord worden, vereist de toekomst en de weg ernaartoe bovenal aandacht voor het *hoe* van rechtvaardige inclusie. Ons normatieve kader stimuleert samenwerkingsverbanden tussen stakeholders die belangrijk zijn voor praktische toepassing van rechtvaardige inclusie, waarbinnen ethici de verbindende factor kunnen zijn. Uiteindelijk hopen we dat ons normatieve kader bijdraagt aan de rechtvaardige inclusie van zwangere vrouwen in medisch-wetenschappelijk onderzoek.

# LIST OF PUBLICATIONS

**Indira S.E. van der Zande**, Rieke van der Graaf, Joyce L. Browne, Johannes J.M. van Delden. Fair Inclusion of Pregnant Women in Clinical Research: A Systematic Review of Reasons for Exclusion. In: F. Baylis and A. Ballantyne (eds) Clinical Research Involving Pregnant Women 2016; Research Ethics Forum, volume 3. doi: 10.1007/978-3-319-26512-4_5

**Indira S.E. van der Zande**, Rieke van der Graaf, Martijn A. Oudijk, Johannes J.M. van Delden. A Qualitative Study on Acceptable Levels of Risk for Pregnant Women in Clinical Research. BMC Medical Ethics 2017; 18:35. doi: 10.1186/s12910-017-0194-9

**Indira S.E. van der Zande**, Rieke van der Graaf, Martijn A. Oudijk, Johannes J.M. van Delden. How Should the Precautionary Principle Apply to Pregnant Women in Clinical Research? *(submitted)*

**Indira S.E. van der Zande**, Rieke van der Graaf, Martijn A. Oudijk, Johannes J.M. van Delden. Vulnerability of Pregnant Women in Clinical Research. Journal of Medical Ethics 2017; 43:10. doi: 10.1136/medethics-2016-103955

Rieke van der Graaf, **Indira S.E. van der Zande**, Hester M. den Ruijter, Martijn A. Oudijk, Johannes J.M. van Delden, Katrien Oude Rengerink, Rolf H.H. Groenwold. Fair Inclusion of Pregnant Women in Clinical Trials: Ethical and Methodological Considerations. *(submitted)*

**Indira S.E. van der Zande**, Rieke van der Graaf, Lotty Hooft, Johannes J.M. van Delden. Facilitators and Barriers to Participation: a Systematic Review on the Willingness of Pregnant Women to Participate in Clinical Research. *(submitted after revisions)*

**Indira S.E. van der Zande**, Rieke van der Graaf, Martijn A. Oudijk, Elsbeth H. van Vliet- Lachotzki, Johannes J.M. van Delden. A Qualitative Study on Stakeholders' views on Inclusion of Pregnant Women in the APOSTEL VI study: a low-risk obstetrical RCT. *(submitted after revisions)*

Kit C.B. Roes, **Indira S.E. van der Zande**, Maarten van Smeden, Rieke van der Graaf. Towards an Appropriate Statistical Design to Facilitate Ethically Responsible Inclusion of Pregnant Women in Drug Development. *(submitted)*

**Indira S.E. van der Zande**, Rieke van der Graaf, Martijn A. Oudijk, Elsbeth H. van Vliet-Lachotzki, Johannes J.M. van Delden. A Normative Framework for Inclusion of Pregnant Women in Clinical Research. *(submited)*

# CURRICULUM VITAE

Indira Samantha Elisabeth was born on 18 November 1989, in New Delhi, India. In 2007, she graduated from secondary school *Da Vince College Kagerstraat* in Leiden, having participated in a pre-university programme for outstanding students in year 5 and year 6.

In 2007, Indira started her bachelor in Liberal Arts and Sciences at University College Utrecht. She studied at the University of California in Santa Cruz for an exchange semester and successively conducted various research internships in the Netherlands and abroad. In 2012, she obtained her MA in Applied Ethics and her MSc in International Development Studies, both from Utrecht University. Following, she worked as Project Manager at non-profit organisation *Health[e] Foundation*.

In October 2014, Indira started at the *Julius Center for Health Sciences and Primary Care*, University Medical Center Utrecht, on the research project that is presented in this thesis (PREGMETHICs: ETHICally sound inclusion of PREGnant women in MEdical research). She was supervised by prof. dr. J.J.M. van Delden, dr. R. van der Graaf and dr. M.A. Oudijk. During her PhD-research she taught ethics at the medical school and obtained her University Teaching Qualification.

As of March 2017, Indira works as Education Coordinator at the University of Groningen/ Campus Fryslân. In addition, she became a member of the Research Ethics Committee of Isala Zwolle.

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