Monitoring of fetal heart rate and uterine activity

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Monitoring of fetal heart rate and uterine activity

Registreren van foetale hartfrequentie en weeënactiviteit

(met een samenvatting in het Nederlands)

Proefschrift

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Elisabeth Margo Graatsma

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Co-promotoren	Dr. E.J.H. Mulder Dr. Ir. B.C. Jacod

Content

Chapter 1

Introduction

Introduction

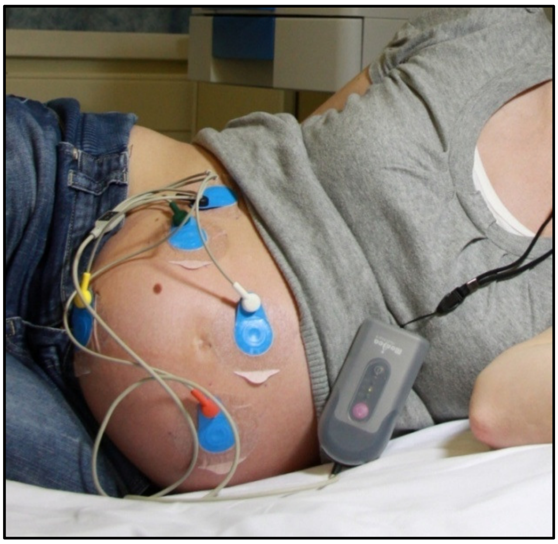
While most pregnancies have an uncomplicated character and result in healthy newborns, changes in demographics (rising maternal age and pre-pregnancy weight) and environment (food intake, intoxications) account for a growing number of complicated pregnancies. Frequent complications are hypertensive disorders, (with accompanying) intra uterine growth restriction, obesity, (pre-) gestational diabetes, and chromosomal and/or congenital abnormalities. For timely recognition of complications in these pregnancies, monitoring of the maternal and fetal condition during pregnancy and labour have become of increasing importance.

Throughout pregnancy the fetal condition can be assessed with a variety of tests, mainly based on the ultrasound technique. Ultrasonography for measurement of fetal biometry; real-time ultrasonography for observations of fetal movements and behavior[1-4]; Doppler velocity waveforms for measurements of the resistance to flow of uterine, placental and fetal arterial and venous circulation[5,6]; and Doppler cardiotocography (CTG) for assessment of fetal heart rate (FHR) and its variation[7]. In order to achieve optimal outcome of labour in complicated pregnancies, both the fetal condition and maternal uterine activity are assessed by FHR monitoring and external tocography or intauterine pressure recording, respectively.

Although FHR monitoring during pregnancy and monitoring of uterine activity during labour are known to have limitations[8-11], their use is widely adopted. An alternative technique for monitoring of FHR as well as uterine activity is the measurement of the electromyography (EMG) as recorded from the maternal abdomen. This EMG-technique has been studied in the past, but was hampered due to technical difficulties[8,12-14]. Improvements in technology, an increasing desire for a true non-invasive technique, and awareness of the limitations of the traditional monitoring techniques for uterine activity and FHR have led to the renewed interest in EMG measurements for fetal and uterine monitoring. The recorder used for FHR - and uterine activity-monitoring in this thesis is displayed in Figure 1.

Part I of this thesis will outline the validation of FHR monitoring using the fetal ECG (fECG) signal. Furthermore, the use of the fECG-technique in pregnancies complicated with intra uterine growth restriction and (pre)gestational diabetes will be described. Part II will focus both on the validation and the potential clinical benefits of contraction monitoring using uterine EMG during labour.

Figure 1: AN24 - fetal ECG and uterine contraction monitor. (Monica Healthcare, Nottingham, UK)



PART I

Monitoring of the fetal condition using fetal electrocardiography

Antepartum fetal surveillance constitutes an essential component of the standards of care in managing high risk pregnancies. Ultrasound examination (growth, amniotic fluid index and Doppler flow velocimetry) and FHR monitoring are the most commonly used antepartum fetal surveillance tests. In current obstetrical practice, both techniques are used for short durations at regular intervals, although long-term monitoring could help to improve clinical management in some cases. To date, this is only possible using ultrasound based cardiotocography (CTG)[15]. However, its use for a prolonged period both in the hospital and in the home-environment remains cumbersome due to discomfort and poor signal quality in prolonged recordings[8]. Moreover, it exposes the fetus to prolonged ultrasound insonation[16]. An alternative is the continuous monitoring of fetal heart rate through the measurement of the electrical signal of the fetal heart (fetal ECG; fECG). Originally hampered by technical difficulties[8], the method now seems ready for clinical use.

In obese women fetal monitoring is difficult because the body fat layer interferes with all traditional surveillance modalities. Ultrasound is attenuated, thereby hampering simple biometry, CTG monitoring, Doppler velocimetry, and visualization of the fetus. This is demonstrated in the literature by an increase in the rate of suboptimal ultrasound visualization of fetal cardiac structures by 50% and of craniospinal structures by 31%[17]. Since the prevalence of obesity among women of reproductive age has reached epidemic proportions[18,19], clinicians can benefit from an alternative technique to adequately

monitor the fetus' condition in pregnancies complicated by obesity. As FHR monitoring using the fECG signal utilizes a fundamentally different modality, it may overcome the limitations of Doppler FHR monitoring in obese women.
While evaluating the validation of the improved fECG monitoring technique in terms of signal quality in the (obese) pregnant population, next step will be to study the 'true' FHR data in pathological pregnancies, for example in uterine growth restricted fetuses and in diabetic pregnancy.

Although fetal monitoring using CTG and Doppler measurements is commonly used in pregnancies complicated by intra uterine growth restriction (IUGR), decision making based on the test results towards expectant management or indicated (preterm) delivery remains difficult. In IUGR fetuses chronic oxygen and food deprivation is thought to lead to a delayed maturation of the sympathetic nervous system, as confirmed by the frequently found reduction in accelerations of FHR and reduced short term variability (STV)[20]. The parasympathetic nervous system (cardio-inhibitory) does not seem to be affected in the same extent since the presence and duration of decelerations of FHR are comparable to that in normal pregnancy. Separate analysis of the sympathetic and parasympathetic nervous system using Phase Rectified Signal Averaging (PRSA) has proven to provide a better prediction of survival in adults suffering from myocardial infarction[21]. Currently also in fetal medicine the PRSA technique is gaining interest. A pilot study indicated that differentiation between the contributions of the sympathetic and parasympathetic branches of the nervous system on FHR regulation may offer a more specific assessment of the growth restricted fetus[22,23]. Although the first studies using PRSA in fetal medicine have been executed using FHR as recorded with CTG, the fECG technique measures FHR with an accuracy of 1 ms and may therefore provide even more specific assessment of fetal cardiovascular (patho-) physiology in pregnancies complicated by IUGR.

In diabetic pregnancy most major complications (macrosomia, sudden intra uterine death, congenital malformations and neonatal hypoglycaemia) seem associated with intermittent hyperglycaemia of the mother during pregnancy. While a previous study in women with type 1 diabetes demonstrated that high day-to-day glucose variability exists mainly in the first trimester of pregnancy[24], it is unclear whether this high variability persists at individual level in the second and third trimesters of pregnancy. Fetal exposure to large fluctuations in maternal glucose levels may partly explain the ten-fold increased risk for sudden unexplained intrauterine deaths in diabetic pregnancy compared to the normal population[25-27]. Difficulties are encountered in the recognition of the fetus at risk of intra uterine death, since routine FHR monitoring during euglycaemia can falsely reassure clinicians. Doppler velocity waveform patterns of the umbilical artery have also failed to be of diagnostic importance[28]. FHR monitoring during prolonged excursions in glucose levels might offer insight into the fetal compensatory mechanisms. Novel techniques offer the possibility to perform simultaneous and long term FHR - and glucose monitoring using a portable fECG monitor and a continuous glucose monitoring system (CGMS), and thus to observe the fetal response to spontaneous fluctuations in maternal glucose levels.

Aims of part I of the thesis

- To evaluate the quality of prolonged antenatal FHR recordings obtained with abdominal ECG electrodes in the second half of gestation. In addition, to study the accuracy of antenatal fetal ECG recordings by comparing the abdominal FHR recordings with scalp electrode measurements using intrapartum FHR recordings (Chapter 2).
- To study the quality of antenatal fetal ECG recordings in obese women. (Chapter 3)
- To describe the normal development of FHR, STV and the sympathetic - and parasympathetic components of FHR throughout normal gestation, and to perform a preliminary comparison of these FHR parameters between normal and IUGR fetuses. (Chapter 4)
- To observe the extent and evaluation of day-to-day variability throughout pregnancy in type 1 diabetes. (Chapter 5) To describe the fetal responses to spontaneous glucose excursions monitored using simultaneous continuous measurements of FHR and maternal glucose levels in the second half of gestation in women with (pre-) gestational diabetes. (Chapter 6)

PART II

Monitoring uterine contractions using electrohysterography

Labour can be defined as the presence of regular, painful uterine contractions resulting in cervical changes (effacement and dilation)[29]. To achieve progress of labour adequate uterine activity is a prerequisite. Labour progression can be monitored by a combination of digital examination of the cervix and engagement of the presenting fetal part, and by measurements of uterine activity using external tocodynamometry or internal monitoring using intra-uterine pressure catheters (IUPC). Unfortunately, both external tocodynamometry and IUPC have disadvantages. Intra-uterine pressure catheters are invasive and have, in rare cases, been associated with intra-uterine infection, perforation and placental abruption[9,30-33]. Tocodynamometry is non-invasive and easy to use but its recording quality depends on correct positioning of the sensor on the maternal abdomen and is influenced by maternal movements and BMI[9,33,34]. Additionally, the use of tocodynamometry is limited to the frequency of contractions only, with no information regarding force or efficiency[35]. Finally, a recent randomized trial has demonstrated that none of the current techniques of contraction monitoring improved labour outcome[36]. The search for an alternative has led to the investigation of methods measuring the uterus' electrical activity. This approach, denoted either uterine electromyography (uterine EMG) or electrohysterography (EHG) has been known for more than fifty years[12,13,37]. It is recently experiencing a renewed surge of interest thanks to technical improvements and because of data indicating that it could be able to discriminate between efficient and inefficient contractions. This distinction is particularly relevant in the context of threatened preterm labour[38-42]. Although promising results have been obtained on this issue, EHG is a method that is still under development. Studies focusing on signal analysis have shown that the EHG signal could be made to agree with IUPC measurements using algorithms of varying complexity[43-47]. Only few studies, however, have compared the performance of EHG to other methods of uterine activity monitoring under conditions representative of clinical practice[39,48].

Where the possibilities with IUPC and external tocodynamometry are limited, EHG can be used for more than the determination of contraction frequency, duration and amplitude. The acquired uterine activity can be analyzed using standard signal analysis techniques such as the power density spectrum. The additional information following this analysis might help in the understanding of the biological or pathological pathways leading to dysfunctional contractility.

Aims of part II of the thesis

- To consolidate the validation of EHG during labour by comparing it to the method of reference, the intrauterine pressure catheter. (Chapter 7)
- To examine whether non-invasive monitoring of uterine activity using electrohysterography can help to differentiate between normal and dysfunctional term labour in nulliparous women. (Chapter 8)

Reference List

1. Nijhuis IJ, Ten Hof J, Nijhuis JG, Mulder EJ, Narayan H, Taylor DJ, et al. Temporal organization of fetal behavior from 24-weeks gestation onwards in normal and complicated pregnancies. Dev.Psychobiol. 1999 05;34(0012-1630; 4):257-268.
2. Visser GH, Poelmann-Weesjes G, Cohen TM, Bekedam DJ. Fetal behavior at 30 to 32 weeks of gestation. Pediatr.Res. 1987 12;22(0031-3998; 6):655-658.
3. Visser GH. Fetal health assessment. Curr.Opin.Obstet.Gynecol. 1991 04;3(1040-872; 2):242-247.
4. Visser GH. Fetal behaviour and the cardiovascular system. J.Dev.Physiol. 1984 06;6(0141-9846; 3):215-224.
5. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackeloer BJ, Kok HJ, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet.Gynecol. 2001 12;18(0960-7692; 6):564-570.
6. Hecher K, Campbell S, Snijders R, Nicolaides K. Reference ranges for fetal venous and atrioventricular blood flow parameters. Ultrasound Obstet.Gynecol. 1994 Sep 1;4(5):381-390.
7. Visser GH. Antenatal cardiotocography in the evaluation of fetal well-being. Aust.N.Z.J.Obstet.Gynaecol. 1984 05;24(0004-8666; 2):80-85.
8. Peters M, Crowe J, Pieri JF, Quartero H, Hayes-Gill B, James D, et al. Monitoring the fetal heart non-invasively: a review of methods. J.Perinat.Med. 2001;29(0300-5577; 5):408-416.
9. Bakker PC, Zikkenheimer M, van Geijn HP. The quality of intrapartum uterine activity monitoring. J.Perinat.Med. 2008;36(3):197-201.
10. Dawes GS, Moulden M, Redman CW. Limitations of antenatal fetal heart rate monitors. Am.J.Obstet.Gynecol. 1990 Jan;162(1):170-173.
11. Pieri JF, Crowe JA, Hayes-Gill BR, Spencer CJ, Bhogal K, James DK. Compact long-term recorder for the transabdominal foetal and maternal electrocardiogram. Med.Biol.Eng.Comput. 2001 01;39(0140-0118; 1):118-125.
12. Steer CM, Hertsch GJ. Electrical activity of the human uterus in labor; the electrohysterograph. Am.J.Obstet.Gynecol. 1950 Jan;59(1):25-40.
13. Wolfs GM, van Leeuwen M. Electromyographic observations on the human uterus during labour. Acta Obstet.Gynecol.Scand.Suppl. 1979;90:1-61.
14. den Exter T, van Eykern L, de Kreek J., Mulder EJH., Peuscher JHJ., Visser GHA. Simultaneous recording of fetal ECG and uterine activity by transcutaneous electrodes: A new way for non-invasive cardiotocography. Fetal Neonatal Phys Measur 1989.
15. Kuhnert M, Hellmeyer L, Stein W, Schmidt S. Twenty-four-hour CTG monitoring: comparison of normal pregnancies of 25-30 weeks of gestation versus 36-42 weeks of gestation. Arch.Gynecol.Obstet. 2007 06;275(0932-0067; 6):451-460.

16. Visser GH, de Vries JI, Mulder EJ, Ververs IA, van Geijn HP. Effects of frequent ultrasound during pregnancy. Lancet 1993 11/27;342(0140-6736; 8883):1359-1360.
17. Hendler I, Blackwell SC, Bujold E, Treadwell MC, Wolfe HM, Sokol RJ, et al. The impact of maternal obesity on midtrimester sonographic visualization of fetal cardiac and craniospinal structures. Int.J.Obes.Relat.Metab.Disord. 2004 12;28(0307-0565; 12):1607-1611.
18. Chu SY, Kim SY, Bish CL. Prepregnancy obesity prevalence in the United States, 2004-2005. Matern.Child Health J. 2009 Sep;13(5):614-620.
19. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006 Apr 5;295(13):1549-1555.
20. Snijders RJ, Ribbert LS, Visser GH, Mulder EJ. Numeric analysis of heart rate variation in intrauterine growth-retarded fetuses: a longitudinal study. Am.J.Obstet.Gynecol. 1992 01;166(0002-9378; 1):22-27.
21. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Makikallio T, Ulm K, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006 May 20;367(9523):1674-1681.
22. Huhn EA, Phasengleichgerichtete Signalmittelung der Kardiotokographie bei intrauteriner Wachstums-retardierung. Munchen, Germany: Frauenklinik der Technischen Universität München Klinikum rechts der Isar; 2007.
23. Lobmaier SM, Pildner von Steinburg S, Müller A, Schuster T, Ortiz J, Huhn EA, Schneider KTM, Schmidt G. Phase-rectified signal averaging as a new method for surveillance of growth restricted fetuses, a prospective observational study. Munchen, Germany: Frauenklinik, Abt. Perinatalmedizin, TU München.
24. Kerssen A, de Valk HW, Visser GH. Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. BJOG 2004 09;111(1470-0328; 9):919-924.
25. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004 04/17;328(1468-5833; 7445):915.
26. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006 Jul 22;333(7560):177.
27. Penney GC, Mair G, Pearson DW, Scottish Diabetes in Pregnancy Group. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. BJOG 2003 Mar;110(3):315-318.
28. Salvesen DR, Higueras MT, Mansur CA, Freeman J, Brudenell JM, Nicolaides KH. Placental and fetal Doppler velocimetry in pregnancies complicated by maternal diabetes mellitus. Am.J.Obstet.Gynecol. 1993 Feb;168(2):645-652.

29. Norwitz ER, Robinson JN, Challis JR. The control of labor. N.Engl.J.Med. 1999 Aug 26;341(9):660-666.
30. Bakker PC, van Geijn HP. Uterine activity: implications for the condition of the fetus. J.Perinat.Med. 2008;36(1):30-37.
31. Chan WH, Paul RH, Toews J. Intrapartum fetal monitoring. Maternal and fetal morbidity and perinatal mortality. Obstet.Gynecol. 1973 Jan;41(1):7-13.
32. Trudinger BJ, Pryse-Davies J. Fetal hazards of the intrauterine pressure catheter: five case reports. Br.J.Obstet.Gynaecol. 1978 Aug;85(8):567-572.
33. Miles AM, Monga M, Richeson KS. Correlation of external and internal monitoring of uterine activity in a cohort of term patients. Am.J.Perinatol. 2001 May;18(3):137-140.
34. Vanner T, Gardosi J. Intrapartum assessment of uterine activity. Baillieres Clin.Obstet.Gynaecol. 1996 Jun;10(2):243-257.
35. Schlembach D, Maner WL, Garfield RE, Maul H. Monitoring the progress of pregnancy and labor using electromyography. Eur.J.Obstet.Gynecol.Reprod.Biol. 2009 May;144 Suppl 1:S33-9.
36. Bakker JJ, Verhoeven CJ, Janssen PF, van Lith JM, van Oudgaarden ED, Bloemenkamp KW, et al. Outcomes after internal versus external tocodynamometry for monitoring labor. N.Engl.J.Med. 2010 Jan 28;362(4):306-313.
37. Devedeux D, Marque C, Mansour S, Germain G, Duchene J. Uterine electromyography: a critical review. Am.J.Obstet.Gynecol. 1993 Dec;169(6):1636-1653.
38. Maner WL, Garfield RE. Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. Ann.Biomed.Eng. 2007 Mar;35(3):465-473.
39. Maul H, Maner WL, Olson G, Saade GR, Garfield RE. Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery. J.Matern.Fetal.Neonatal Med. 2004 May;15(5):297-301.
40. Garfield RE, Maner WL. Physiology and electrical activity of uterine contractions. Semin.Cell Dev.Biol. 2007 Jun;18(3):289-295.
41. Maner WL, Garfield RE, Maul H, Olson G, Saade G. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet.Gynecol. 2003 Jun;101(6):1254-1260.
42. Garfield RE, Maner WL, Maul H, Saade GR. Use of uterine EMG and cervical LIF in monitoring pregnant patients. BJOG 2005 Mar;112 Suppl 1:103-108.
43. Maner WL, MacKay LB, Saade GR, Garfield RE. Characterization of abdominally acquired uterine electrical signals in humans, using a non-linear analytic method. Med.Biol.Eng.Comput. 2006 Mar;44(1-2):117-123.

44. Jezewski J, Horoba K, Matonia A, Wrobel J. Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach. Physiol.Meas. 2005 Oct;26(5):753-767.
45. Skowronski MD, Harris JG, Marossero DE, Edwards RK, Euliano TY. Prediction of intrauterine pressure from electrohysterography using optimal linear filtering. IEEE Trans.Biomed.Eng. 2006 Oct;53(10):1983-1989.
46. Euliano T, Skowronski M, Marossero D, Shuster J, Edwards R. Prediction of intrauterine pressure waveform from transabdominal electrohysterography. J.Matern.Fetal.Neonatal Med. 2006 Dec;19(12):811-816.
47. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW. Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. Physiol.Meas. 2008 Jul;29(7):829-841.
48. Euliano TY, Nguyen MT, Marossero D, Edwards RK. Monitoring contractions in obese parturients: electrohysterography compared with traditional monitoring. Obstet.Gynecol. 2007 May;109(5):1136-1140.

Chapter 2

Fetal electrocardiography: feasibility of long term fetal heart rate recordings

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Fetal electrocardiography: feasibility of long term fetal heart rate recordings

Abstract
The feasibility and accuracy of long-term transabdominal fetal-ECG recordings throughout pregnancy were studied using a portable fetal-ECG monitor. Fifteen-hour recordings of fetal heart rate (FHR) were performed in 150 pregnant women at 20–40 weeks' gestation, and one-hour recordings were performed in 22 women in labour and compared to simultaneous scalp-electrode recordings. When ≥60% of fECG-signals was present the recording was defined as good. 82% (123/150) of antenatal recordings were of good quality. This percentage increased to 90.7% (136/150 recordings) when only the night part (11pm-7am) was considered. Trans-abdominal measurement of FHR and its variability correlated well with scalp-electrode recordings ($r=0.99, p<0.01$; $r=0.79, p<0.01$, respectively). We demonstrated the feasibility and accuracy of long-term transabdominal fetal-ECG monitoring.

Introduction
Antepartum fetal surveillance constitutes an essential component of the standards of care in managing high risk pregnancies, including maternal hypertensive disorders, intra-uterine growth restriction (IUGR) and other maternal and fetal pathophysiological conditions. Ultrasound examination (growth, Doppler flow velocimetry) and fetal heart rate (FHR) monitoring are the most commonly used antepartum fetal surveillance tests. In current obstetrical practice, both techniques are used for short durations at regular intervals, although long-term monitoring could help improve clinical management in some cases[1]. To date, this is only possible using ultrasound based cardiotocography (CTG)[1]. However, its use for a prolonged period both in the hospital and in the home-environment remains cumbersome due to discomfort and poor signal quality in prolonged recordings[2]. Moreover, it exposes the fetus to prolonged ultrasound insonation. An alternative is the continuous monitoring of fetal heart rate through the measurement of the electrical signal of the fetal heart (fetal electrocardiogram, fECG). Originally hampered by technical difficulties[2], the method seems now ready for clinical use. The primary aim of the present study was to evaluate the quality of prolonged antenatal FHR recordings obtained with abdominal ECG electrodes in the second half of gestation. In addition, the accuracy of trans-abdominal recordings was evaluated by comparing to scalp electrode measurements in a smaller set of intrapartum recordings.

Material and methods

The antenatal group consisted of 150 pregnant women at 20 – 40 weeks of gestation. Exclusion criteria were multiple gestation and congenital malformations. Women were recruited for a single overnight recording, either at home (n=110) or during admission at the obstetrics ward (n=40). Maternal mobility was not restricted while being attached to the monitor. Recordings were performed during 15 hours (5pm – 8am), mostly overnight to minimize abdominal muscle activity that could result in distortion of the fECG signal[2]. Fetal presentation was determined by ultrasound examination before starting the recording. Table 1 summarizes patient distribution according to gestational age periods, fetal presentation (cephalic, breech and transverse), and fetal-maternal complications. The intrapartum group consisted of 22 women in labour at term recruited in the labour ward of our tertiary centre. Trans-abdominal and scalp electrode recordings were performed simultaneously for one hour in the first stage of labour. Medians of FHR and short term variability (according to Dawes et al.[3]) were calculated as variables for accuracy. The median and ranges for gestational age and BMI of the patients are summarized in Table 1.

Signal processing

The recordings were performed with the AN24 fetal ECG monitor (Monica Healthcare, Nottingham, UK). The electrophysiological signal, recorded using 5 disposable electrodes placed on the maternal abdomen, contains the maternal ECG (mECG), fetal ECG and noise. Maternal and fetal ECG complexes were used to calculate beat-to-beat (R-R) pulse intervals, which correspond to the maternal (MHR) and fetal heart (FHR) rates, respectively. The methodology used for signal extraction and analysis has been described in detail by Pieri et al[4]. The five disposable electrodes were placed on the maternal abdomen in a standardized manner, independent of fetal positioning; two electrodes along the midline (at the side of the uterine fundus and above the symphysis), one at each side of the uterus and the ground electrode on the left flank. Skin impedance was reduced before placing the electrodes using abrading paper at the electrode placement site. Skin impedance was below 5 kΩ in all recordings. Data was analysed off line after computer download.

Quality assessment of fECG recordings

Signal loss was defined as the proportion of epochs (in %) during which no valid data were available (after data reduction over 3.75s epochs)[3]. Instead of signal loss, we will use the term recording quality (RQ; 100% – signal loss), with RQ ≥ 60% to indicate a successful record based on Dawes et al[3].

Table 1: Study population characteristics

Gestational age	$20^{+0} – 25^{+6}$ N=20 (13%)	$26^{+0} – 31^{+6}$ N=45 (30%)	$32^{+0} – 34^{+6}$ N=30 (20%)	$35^{+0} – 37^{+6}$ N=28 (18%)	$\geq 38^{+0}$ N=27 (18%)
Fetal Presentation (%)					
Cephalic	10 (50)	28 (62.2)	27 (90)	28 (100)	26 (96.3)
Breech	4 (20)	7 (15.6)	2 (6.7)	0	1 (3.7)
Transverse	6 (30)	10 (22.2)	1 (3.3)	0	0
Fetal-maternal condition (%)					
None	14 (70)	18 (40)	18 (60)	17 (60.7)	24 (88.9)
PE/PIH[1]	0	3 (6.7)	4 (13.3)	2 (7.1)	3 (11.1)
IUGR[2]	0	5 (11.1)	5 (16.7)	3 (10.7)	0
PPROM[3]	1 (5)	5 (11.1)	0	0	0
PTL[4]	1 (5)	4 (8.9)	0	0	0
DM/GDM[5]	2 (10)	3 (6.7)	0	2 (7.1)	0
VBL[6]	0	5 (11.1)	1 (3.3)	0	0
Others[7]	2 (10)	2 (4.4)	2 (6.7)	4 (14.3)	0
Recording location (%)					
Home	18 (90)	23 (51.1)	23 (76.7)	22 (78.6)	24 (88.9)
Hospital	2 (10)	22 (48.9)	7 (23.3)	6 (21.4)	3 (11.1)

Intrapartum Recordings

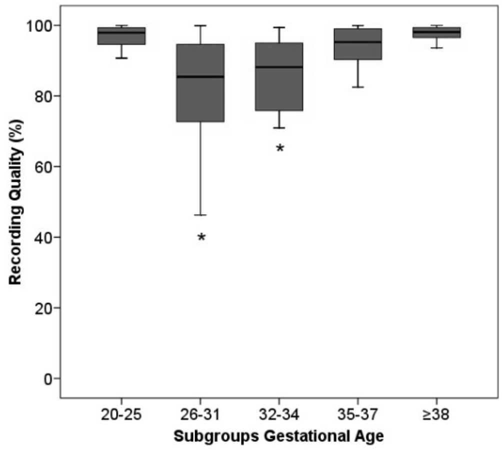
	Median	Range
Gestational age	40^{+1}	$37^{+2} – 42^{+2}$
BMI (kg/m^2)	24.5	16.9 – 40.4

Table legend: 1:Pre-eclampsia or Pregnancy induced hypertension; 2: Intra uterine growth retardation; 3: Prelabour premature rupture of membranes; 4: Preterm Labour; 5: Diabetes Mellitus or Gestational Diabetes Mellitus; 6: Vaginal blood loss; 7: Others include: fetal arrhythmias, antidepressants, polyhydramnious, and Morbus Graves.

Statistics

SPSS for Windows (version 12.01, SPSS Inc., Chicago, Ill.) was used for statistical analysis. Results were summarized with the use of standard descriptives for non-parametric tests: medians, and (interquartile) ranges. Groups were compared with the Kruskal-Wallis test with post hoc analysis where appropriate, and Spearman correlation was used to evaluate the effect of potential confounders.

Figure 1: Recording quality (median; interquartile range, p2.3 and p97.7) in five distinct gestation periods (night recordings, n= 150). Boxes marked with an asterisk indicate p < 0.05 as compared to the 20-25, 35-37, and ≥38 weeks subgroups.



Results

Antenatal group: 82% (123/150) of the recordings were considered of sufficient quality (i.e. RQ ≥ 60%) when total recording time (5pm - 8am) was studied. There was a wide variation in RQ during the early evening probably due to maternal activity. From 9 pm onwards the median RQ increased gradually to a maximum of 100% from about 12 pm until 6 am. The proportion of recordings with sufficient quality reached 90.7% (136/150) during the night part (11pm - 7am) which will serve as the basis for the analyses presented further. RQ was high at 20-26 weeks gestation, followed by lower values and wider variation at 26-34 weeks, with a gradual improvement thereafter, see Figure 1. This trend was tested using Kruskal Wallis test, and was shown to be significant (H(4) statistic = 41.52, p<0.01). RQ did not differ statistically between the home recordings (median RQ 95%, interquartile range 85.0–98.4%) and recordings made in the hospital (median 91.9%, interquartile range 77.9 – 97.8%, respectively, p = 0.15). Recording quality was not significantly affected by fetal positioning (median RQ 94.7%, 89%, and 92.2% for cephalic, breech and transverse position, respectively (H(2) statistic: 5.9, p = 0.06; Kruskal Wallis test), nor by the body mass index (median 27.1; range 16.0 – 43.8, R = 0.01 Spearman's test, p = 0.89).

Intrapartum group: 77.3% (17/22) of the recordings were of good quality (i.e. RQ ≥ 60%). The median fetal heart rate and median STV (short term variability) found in the 17 recordings using transabdominal fECG and scalp electrodes were: FHR 140.6 bpm (range 127.9–155.4) vs 141.4 bpm (range 128.5–156.2), r=0.998, p<0.01, and STV 8.0 ms (range 4.8–10.1) vs 8.1 ms (range 4.5–9.0), r=0.79, p<0.01 respectively.

Side effects

After removal of the electrodes 30 out of the 150 women (20%) complained of skin irritation. In most cases, irritation consisted of transient redness of the skin and itchiness on the site where we had abraded the skin. Almost all of these women were in late gestation and had no history of skin irritation. When asked whether they would like to use the monitor again, they replied not to mind in case there would be an indication for fetal monitoring. Overall, women did not experience any other discomfort while using the monitor.

Discussion

This study evaluated the feasibility and accuracy of an improved FHR monitoring technique using the external fECG signal. This technique is an alternative to ultrasound for long-term antenatal fetal monitoring. To date, all studies on long-term fetal monitoring are based on FHR data acquired in a hospital setting[1,5-7]. They used either transabdominally placed needle electrodes[6], transabdominally placed "sucking-cup" electrodes[7], or ultrasound heart rate monitors[1,5]. Since the quality of Doppler CTG recordings is dependent on fetal movements, long-term monitoring requires frequent repositioning, while the woman is restricted to a fixed position. The current method, being truly ambulatory, can perform long-term recordings also in the home environment. We showed that it can obtain approximately eight hours of qualitatively good FHR records without the necessity of interference of any care-givers from 20 weeks of gestation onwards. There is a slight decrease in recording quality between 26 and 34 weeks of gestation but the signal quality remains acceptable. The 25th percentile of the night RQ remained far above the required minimum of 60% in this subgroup of gestational age. A subset analysis comparing pregnancies with fetal-maternal complications with healthy pregnancies found no significant difference in the magnitude of this effect. This is thus unlikely to be due to the occurrence of fetal-maternal complications at this stage of gestation and is probably related to the formation of the vernix caseosa at this gestational age as suggested by others[2]. Interestingly, the quality of fECG recordings was not influenced by maternal obesity as our results show no decline of RQ with increasing BMI.

The findings were validated in a smaller set of intrapartum recordings by comparing fetal heart rate and STV to measurements performed with the actual gold standard, the scalp electrode. Both methods were found to correlate well. The correlation was similar to the values reported in previous comparisons in the literature between non-invasive methods and scalp electrodes[8,9]. Trans-abdominal fetal ECG, therefore seems to be a valid and accurate substitute for other non-invasive fetal heart rate monitoring techniques. The fECG technique has the advantages that its true ambulatory character enables long-term recordings, that the quality of its recording is not influenced by the patient's BMI, which is becoming of increasing importance, and that the technique is purely noninvasive. Transabdominal fECG recording is, however, probably more than an adequate substitute for current methods given its potential for true beat-to-beat heart rate, variability, and ECG complex analysis. At this point, however, the technology available to the researchers did not allow for the computation of true beat-to-beat interval variability and fetal ECG morphology. Following adult cardiology standards an abdominal signal sample rate of 1000Hz is required in order to calculate a true measure of beat-to-beat variability and follow changes in fECG morphology. The current version of this fECG monitor has a sample frequency of 300Hz. This will be increased to 1000Hz in subsequent research devices. It is worth noting that modern conventional fetal monitors only provide an accuracy of +/- 1 beat per minute and update the FHR every 250ms (a sample of 4Hz).

Conclusion

Our findings demonstrate the feasibility and accuracy of an improved fetal monitoring technique using the externally obtained fetal ECG signal. Quality was optimal when the recording was performed overnight. Fetal ECG monitoring will be most applicable in high risk pregnancies that require extended fetal monitoring.

Acknowledgement

The authors would like to thank Monica Healthcare Ltd (Biocity, Pennyfoot street , Nottingham NG1 1GF, UK, www.monicahealthcare.com) for the provision of the FECG holter systems and support during this study.

Reference List

1. Kuhnert M, Hellmeyer L, Stein W, Schmidt S. Twenty-four-hour CTG monitoring: comparison of normal pregnancies of 25-30 weeks of gestation versus 36-42 weeks of gestation. Arch Gynecol Obstet 2007; 275(6):451-460.
2. Peters M, Crowe J, Pieri JF, Quartero H, Hayes-Gill B, James D et al. Monitoring the fetal heart non-invasively: a review of methods. J Perinat Med 2001; 29(5):408-416.
3. Dawes GS, Houghton CR, Redman CWG, Visser GHA. Pattern of the normal human fetal heart rate. Br J Obstet Gynaecol 1982; 89(4):276-284.
4. Pieri JF, Crowe JA, Hayes-Gill BR, Spencer CJ, Bhogal K, James DK. Compact long-term recorder for the transabdominal foetal and maternal electrocardiogram. Med Biol Eng Comput 2001; 39(1):118-125.
5. De Vries JIP, Visser GHA, Mulder EJH, Prechtl HFR. Diurnal and other variations in fetal movement and heart rate patterns at 20-22 weeks. Early Hum Dev 1987; 15(6):333-348.
6. Patrick J, Campbell K, Carmichael L, Natale R, Richardson B. Daily relationships between fetal and maternal heart rates at 38 to 40 weeks of pregnancy. Can Med Assoc J 1981; 124(9):1177-1178.
7. Visser GHA, Goodman JD, Levine DH, Dawes GS. Diurnal and other cyclic variations in human fetal heart rate near term. Am J Obstet Gynecol 1982; 142(5):535-544.
8. Kariniemi V, Hukkinen K, Katila T, Laine H. Quantification of fetal heart rate variability by abdominal electrocardiography. J Perinat Med 1979; 7(1):27-32.
9. Solum T, Ingemarsson I, Nygren A. The accuracy of abdominal ECG for fetal electronic monitoring. J Perinat Med 1980; 8(3):142-149.

Chapter 3

Maternal Body Mass Index does not affect performance of fetal electrocardiography

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Maternal Body Mass Index does not affect performance of fetal electrocardiography

Abstract

Objective The obesity epidemic challenges traditional antenatal fetal heart rate (FHR) monitoring technologies. Doppler signals in particular are attenuated. We sought to evaluate whether the performance of a novel transabdominal fetal-ECG (fECG) device (AN24, Monica Healthcare) is influenced by Body Mass Index (BMI).

Study Design Prospective observational study of singleton pregnancies (gestational age; GA; 20–41 weeks) monitored overnight with fECG. Recording quality (RQ; %) of both the best hour and the total recording time of the FHR-record were related to BMI.

Results 204 women were monitored. BMI ranged from 16.0–50.7 (median BMI 26.9). The correlation coefficient (r; with 95% confidence interval (CI)) between BMI and RQ was -0.35 (CI -0.60; -0.03) for the gestational age group 20^{+0}-25^{+6} weeks, -0.08 (CI -0.28; 0.13) for GA 26^{+0}-33^{+6} weeks, and -0.20 (CI -0.40; 0.03) for GA group $\geq 34^{+0}$ weeks. Median RQ in obese women (BMI ≥30kg/m2) was 97.4%, 98.9% and 100%, respectively.

Conclusion BMI has no clinically significant influence on recording quality of FHR monitored with fECG. It can therefore be considered a good method for monitoring the fetal condition in pregnancies of obese women.

Introduction

Obesity in pregnancy is associated with a higher incidence of complications, including spontaneous abortions, fetal malformations, fetal macrosomia, preeclampsia, (gestational) diabetes, preterm birth, stillbirth, induction of labour, and instrumental delivery[1,2]. The incidence of complications increases with the degree of obesity. Further the prevalence of obesity among women of reproductive age has reached epidemic proportions[3,4]. Fetal monitoring is difficult in obese women because the body fat layer interferes with all traditional surveillance modalities. Ultrasound is attenuated, hampering simple biometry, fetal heart rate (FHR) monitoring, and Doppler velocimetry. This is demonstrated in the literature by an increase in the rate of suboptimal ultrasound visualization of fetal cardiac structures by 50% and of craniospinal structures by 31%[5].

An alternative to traditional Doppler ultrasound based cardiotocography (CTG) is the transabdominal fetal electrocardiogram (fECG). With this technique intra-abdominal electrical activity is recorded using skin electrodes on the maternal abdomen. The signals derived from the fetal heart are then extracted to display a continuous record of the fetal heart rate. The validity and feasibility of this technique using a novel portable five electrode system, (AN24, Monica Healthcare, Nottingham, UK) has been described elsewhere[6]. Because the fECG utilizes a fundamentally different modality, it may overcome the limitations of Doppler FHR monitoring in obese women. We studied the influence of BMI on the performance of this novel fetal ECG device in the second half of pregnancy.

Materials and Methods

A prospective observational study was conducted at the University Medical Center Utrecht, The Netherlands, and at the University of Maryland, Baltimore, United States. The study was approved by the local medical ethical committees. Women appearing for fetal assessment with singleton pregnancies between 20 – 42 weeks of gestation were eligible. Exclusion criteria were multiple gestation and congenital malformations. Women were recruited for a single overnight recording, either at home (low risk pregnancies) or in the hospital (high risk pregnancies). After informed consent was obtained, recordings were performed overnight, during sleep, to minimize maternal abdominal muscle activity that can distort the fECG signal. Using the AN24, the fECG signal was extracted from the electrophysiological signal measured over the maternal abdomen using five disposable electrodes. The electrodes were placed on the abdomen in a standardized manner, independent of fetal positioning[6]. As recording begins, the AN24 indicates receipt of a valid electrical signal. Maternal mobility was not restricted during monitoring. After recording is completed, the electrodes are removed and the data are downloaded from the portable device into the computer. The derived fECG signal is converted into continuous FHR (Figure 1). The computer output of the data is identical to the FHR pattern derived from standard, Doppler derived, electronic fetal monitoring techniques. The methodology used for the signal extraction and analysis has been described in detail by Pieri et al[7].

Quality Analysis

Recording quality (RQ) was defined as the percentage of continuous fECG data per hour of monitoring. During the period between 11pm – 7am, each one hour epoch of the tracing was analyzed and median RQ for total recording time was calculated. As well, the hour with the highest RQ within each recording was defined as the “best hour”.

Previous research described differences in RQ in relation to gestational age probably due to the formation of the vernix caseosa[6,8]. As the lowest quality was found between 26-34 weeks gestation, data in this study were analyzed in three gestational age subgroups (20^{+0} – 25^{+6} weeks, 26^{+0}–33^{+6} weeks and 34^{+0} weeks – term). The Body mass Index (BMI) was calculated using the maternal weight and height at the time of recording.

Figure 1: Computer output of fetal heart rate (FHR; upper trace) and maternal heart rate (MHR; lower trace) are displayed in the users preferred 'paper speed'. The lower frame shows the compressed data for trend analysis.

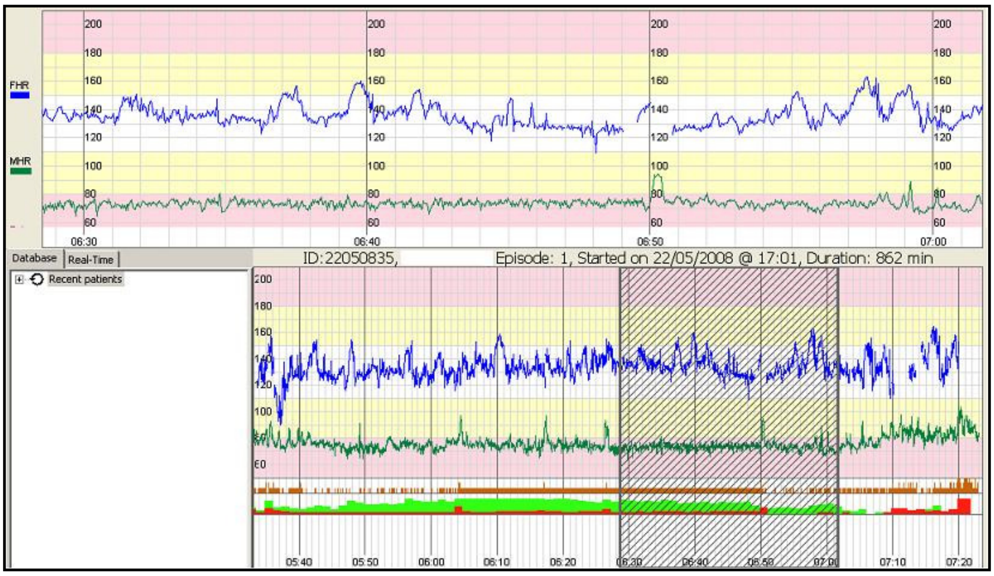


Table 1: Study population characteristics

Gestational Age	$20^{+0} - 25^{+6}$ N=38 (19%)	$26^{+0} - 33^{+6}$ N=92 (45%)	34^{+0} – term N=74 (36%)	Total N=204
Median GA	23^{+6}	30^{+6}	36^{+4}	31^{+3}
BMI (kg/m^2)				
Median	26.7	26.0	28.3	26.9
Range	(22.1–50.7)	(19.4–42.2)	(16.0–41.1)	(16.0–50.7)
BMI Subgroups (n; %)				
≤ 24.9 kg/m^2	15 (39)	37 (40)	17 (23)	69
25.0 – 29.9 kg/m^2	15 (39)	35 (38)	41 (55)	91
≥ 30.0 kg/m^2	8 (22)	20 (22)	16 (22)	44

Abbreviations: GA: gestational age; BMI: body mass index.

Statistics

Results were summarized with the use of standard descriptives for non-parametric tests: medians, and (interquartile) ranges. Spearman correlation (r; 95% confidence interval) was used to evaluate the relationship between BMI and recording quality. For the main analysis BMI is analysed as a continuous variable. For descriptive purposes BMI is described as categorical value. (Table 1: BMI; normal weight ≤24.9 kg/m2, overweight 25.0 – 29.9 kg/m2, obesity ≥ 30.0 kg/m2). The distribution of RQ values relative to gestational age groups was compared with the Kruskal-Wallis test. SPSS for Windows (version 15.01, SPSS Inc., Chicago, III.) was used for statistical analysis. Significance was defined as a p value <0.05.

Results

Two hundred and four women underwent a single overnight fECG recording. One hundred and sixteen low-risk women were recorded at home, and 88 women with maternal or fetal complications of pregnancy were recorded in the hospital. BMI of patients ranged from 16-50.7 kg/m^2. The medians and ranges of BMI in each gestational age subgroup are described in Table 1.

For the total analyzed recording time (11pm-7am) the median recording quality was 92.3% (interquartile range; IQR = 79.4% - 97.9%). Neither fetal position nor fetal- or maternal condition affected RQ. A significant difference in RQ between subgroups for gestational age was found for both the total recording time, and the 'best hour' of recording (Table 2; Kruskal-Wallis: H(3) = 31.96, p<0.001, H(3) = 13.1, p= 0.001, respectively). Therefore, further analysis was done for the gestational age subgroups independently. The median RQ for the 'best hour' within all recordings was 100% (IQR: 97.8%–100%). For an indirect comparison with standard practice, where the analysis is based on the best 'readable CTG trace', the 'best hour' of fECG recording will be used in further analyses rather than the RQ values of the total recording. The RQ 'best hour' values for the GA subgroups are displayed in Table 2 and Figures 2a-2c.

Recording quality did correlate negatively with BMI in the periviable group (20^{+0} – 25^{+6} weeks; r= -0.35, CI [-0.60; -0.03], p=0.04), but not in later gestation (Table 2). However, RQ for the 'best hour' reached high values, even in obese women (BMI≥30 kg/m2). In early gestation (20^{+0} – 25^{+6} weeks) the median 'best hour' RQ was 97.4%, increasing to 98.9% and 100% in the next gestational age windows (Table 2). Given the fact that most results are close to 100% and the distribution along the effect was quite small, the effect of BMI categories on RQ per GA group was also analysed using a non parametric test (Kruskal-Wallis; Table 2).

In 4/44 women with a BMI ≥ 30 kg/m2 the RQ of the 'best hour' did not reach 60%; three of them were in the GA subgroup 26^{+0}–33^{+6} weeks.

Table 2: Results for recording quality (RQ) and BMI per subgroup of gestational age (GA)

Gestational Age	20^{+0} – 25^{+6} N=38 (19%)	26^{+0} – 33^{+6} N=92 (45%)	34^{+0} – term N=74 (36%)	Total N=204
Recording quality % (IQR)				
RQ Median 11pm-7am	94.9 (89.1–98.8)	83.8 (70.0–94.5)*	96.1 (88.0–98.7)	92.3(79.4–97.9)
RQ Median "best hour"	100 (99.4-100)	99.6 (91.7-100)**	100 (99.4-100)	100 (97.8–100)
BMI ≤ 24.9 kg/m²	100 (100–100)	100 (94.1–100)	100 (99.9–100)	
BMI 25.0 – 29.9 kg/m²	100 (99.5–100)	99.1 (87.5–100)	100 (99.3–100)	
BMI ≥ 30.0 kg/m²	97.4 (90.8–100)	98.9 (80.9–100)	100 (97.4–100)	
Kruskal-Wallis H(3) (P value)	6.92 (0.03)	1.67 (0.43)	1.9 (0.38)	
BMI & Median RQ 11pm-7am				
Spearman r [95% CI]	-0.08 [-0.40; 0.25]	-0.13 [-0.33; 0.08]	-0.06 [-0.29; 0.18]	
P-value	0.63	0.22	0.62	
BMI & 'Best hour' RQ				
Spearman r [95% CI]	-0.35[-0.60; -0.03]	-0.08 [-0.28; 0.13]	-0.20[-0.40; 0.03]	
P-value	0.04	0.46	0.09	

*Table legend: *Kruskal-Wallis H(3)= 31.96, p < 0.001, ** H(3)=13.1, p= 0.001. Abbreviations: BMI: body mass index; GA, gestational age; IQR: interquartile range (p25-p75); RQ: recording quality.*

Discussion

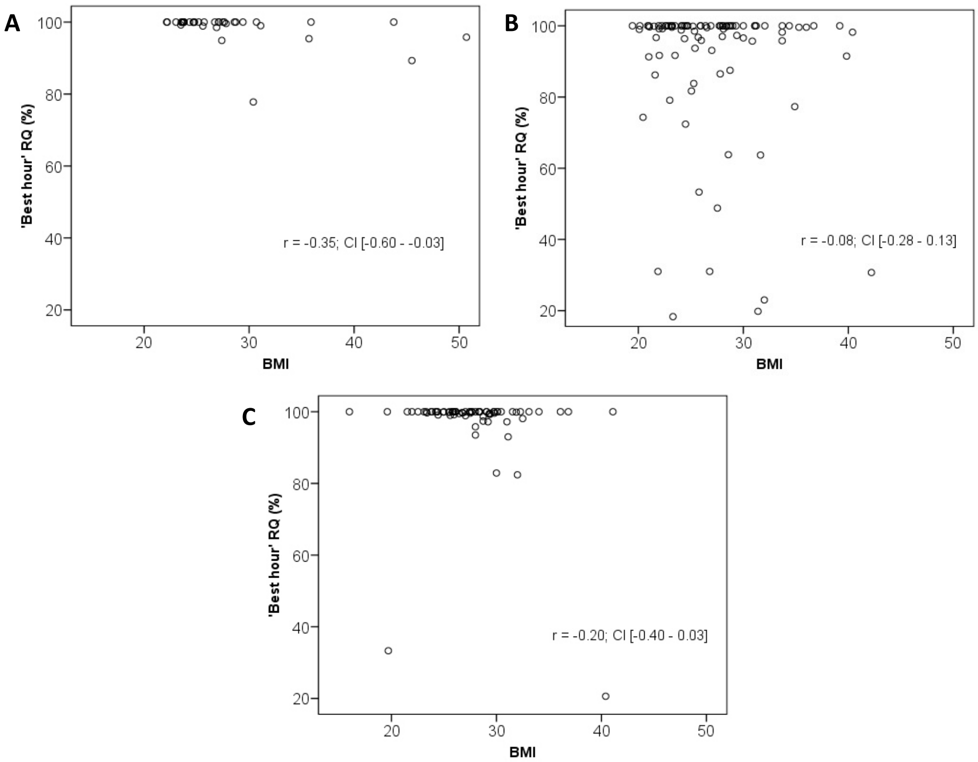
We evaluated the effect of BMI on transabdominal fetal ECG monitoring. In a population of women with a wide range of BMI (16-50.7 kg/m^2) we performed 204 overnight monitoring sessions between 20-41 weeks gestation. We looked at the relationship between recording quality and BMI in three gestational age epochs: periviable, early preterm and late preterm-term. Obesity had no significant effect on recording quality of the fetal heart rate when the AN24 monitor was used beyond the periviable period.

There are no prior studies systematically evaluating the effect of maternal obesity on attenuation of the fetal ECG signal. In previous studies, lower conductivity of the fetal ECG signal in the GA period between 26 and 34 weeks has been attributed to interference from the vernix caseosa and relatively increased amniotic fluid volume[6,8,9]. One author suggested that increased fetal movements may also contribute to signal loss. When these factors were accounted for, the influence of adipose tissue was assumed to be unimportant[9] - maternal obesity was not evaluated.

As a benchmark for fetal heart rate recording quality, FHR acquisition of 60% or more is considered adequate[10]. This cut-off value was set with the introduction of the Doppler technique for FHR-monitoring, and might be considered out-dated. However, presuming the technique has improved over time, new cut-off values are lacking. RQ in the current study was not influenced by fetal positioning, maternal condition, or recording location,

even in obese women. This suggests that the technology may be widely applicable and technically feasible for resting patients.
BMI has no significant effect on RQ except in the periviable period. The reason for this gestational age effect is unclear. Because FHR monitoring is uncommon this early in pregnancy, and the overall recording quality is high, we consider this finding not clinically relevant.
Basing the analysis on the 'best hour' of recording may introduce bias, as this does account for the total time required to obtain one best hour. However, our recordings were all performed at fixed (overnight) times and an effect of BMI on median RQ (total recording time) was absent (Table 2). Furthermore, the start-times for the best hours were defined by the clock rather than determined by the best RQ in a moving window of 60 minutes. Finally, in our study, the AN24 fECG monitor was applied and the recording was completed before RQ was assessed.

Figure 2: 'Best hour' RQ per recording and BMI with Spearman r and 95% confidence interval for gestational age subgroups 20^{+0}-25^{+6} weeks (figure A: n=38), 26+0-33+6 weeks (figure B: n=92), and > 34+0 weeks (figure C: n=74).



If monitoring with the AN24 fECG monitor was inadequate, there was no opportunity for adjustment as there was no real time display. Finally, there is no literature available evaluating the effect of obesity on Doppler-CTG monitoring.
The fECG technique still bears some limitations as the attenuation of the fECG by abdominal muscle activity may limit clinical situations where the AN24 can be used, such as during active labour, when accurate monitoring is especially important. This restricts the use of the AN24 to the antepartum period and/or first phase of labour.

Conclusion

The prevalence of obesity among women in the reproductive age is rising. Maternal obesity is associated with complications which may require frequent monitoring. Unfortunately, obesity impairs the quality of current recording methods using ultrasound technology. Our findings demonstrate that FHR monitoring using a fECG monitor can be considered an adequate alternative to Doppler CTG during a restful state in these high-risk pregnancies.

Acknowledgement

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Reference List

1. Galtier F, Raingeard I, Renard E, Boulot P, Bringer J. Optimizing the outcome of pregnancy in obese women: from pregestational to long-term management. Diabetes Metab 2008 February;34(1):19-25.
2. Yogev Y, Visser GHA. Obesity, gestational diabetes and pregnancy outcome. Semin Fetal Neonatal Med 2009;14: 77-84
3. Chu SY, Kim SY, Bish CL. Prepregnancy Obesity Prevalence in the United States, 2004-2005. Matern Child Health J 2009 September;13(5):614-20.
4. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006 April 5;295(13):1549-55.
5. Hendler I, Blackwell SC, Bujold E et al. The impact of maternal obesity on midtrimester sonographic visualization of fetal cardiac and craniospinal structures. Int J Obes Relat Metab Disord 2004 December;28(12):1607-11.
6. Graatsma EM, Jacod BC, van Egmond LA, Mulder EJH, Visser GHA. Fetal electrocardiography: feasibility of long-term fetal heart rate recordings. BJOG 2009 January;116(2):334-7.
7. Pieri JF, Crowe JA, Hayes-Gill BR, Spencer CJ, Bhogal K, James DK. Compact long-term recorder for the transabdominal foetal and maternal electrocardiogram. Med Biol Eng Comput 2001 January;39(1):118-25.
8. Peters M, Crowe J, Pieri JF et al. Monitoring the fetal heart non-invasively: a review of methods. J Perinat Med 2001;29(5):408-16.
9. Stinstra JG, Peters MJ. The influence of fetoabdominal tissues on fetal ECGs and MCGs. Arch Physiol Biochem 2002 July;110(3):165-76.
10. Dawes GS, Visser GHA, Goodman JD, Redman CW. Numerical analysis of the human fetal heart rate: the quality of ultrasound records. Am J Obstet Gynecol 1981 September 1;141(1):43-52.

Chapter 4

Average acceleration and deceleration capacity of fetal heart rate in normal pregnancy and in pregnancies complicated by intrauterine growth restriction

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Average acceleration and deceleration capacity of fetal heart rate in normal pregnancy and in pregnancies complicated by intrauterine growth restriction

Abstract

Background Although a variety of antenatal tests is available to monitor pregnancies complicated by intrauterine growth restriction (IUGR), decision making based on antenatal test results towards expectant management or (preterm) delivery remains difficult. Differentiation between contributions of the cardio-acceleratory and cardio-inhibitory components of the nervous system on fetal heart rate (FHR) regulation may offer a more specific assessment of the IUGR fetus.

Objective To study FHR, its short term variability (STV), average acceleration capacity (AAC) and average deceleration capacity (ADC) throughout uncomplicated gestation, and to perform a preliminary comparison of these FHR parameters between IUGR and control fetuses.

Study design Prospective observational study of FHR recordings as obtained with a fetal-ECG recorder in second half of uncomplicated (n=90) and IUGR (n=30) pregnancy. FHR and STV were calculated according to established analysis. True beat-to-beat FHR, recorded at 1ms accuracy, was used to calculate AAC and ADC using Phase Rectified Signal Averaging (PRSA). Mean values of the FHR, STV, AAC, and ADC from recordings in IUGR pregnancies were plotted in the reference curves as obtained from control recordings.

Results AAC and ADC remained relatively constant throughout gestation, whereas FHR decreased and STV increased with advancing gestation. 36% of AAC and ADC values were below the 2.5th percentile in IUGR pregnancies, compared to 8% of STV values ($p<0.05$; Fisher exact test). The degree of umbilical artery Doppler abnormalities did not contribute to the level of deviation of FHR parameters.

Conclusions Analysis of the AAC and ADC as recorded with a high resolution fECG recorder may differentiate better between normal and IUGR fetuses than STV. Whether this indicates that AAC or ADC represent a more sensitive parameter of fetal compromise compared to the currently used fetal parameter (STV) remains to be elucidated in future studies with longitudinal follow up of IUGR fetuses.

Introduction

There are a number of antenatal assessment techniques which are suitable for the diagnosis, classification and monitoring of pregnancies complicated by intra uterine growth restriction (IUGR): assessment of fundal height, kick-charts, ultrasound biometry, pulsatility index of the umbilical artery (PI UA) and fetal heart rate (FHR) testing. With progressive deterioration of the fetal condition a certain rank order can be determined in which test results become abnormal[1-5]. While it is relatively easy to recognize the severely IUGR fetus in poor condition, difficulties are encountered with the vast majority of IUGR fetuses that exhibit less severe degrees of compromise. Furthermore, the rank order of fetal assessment holds especially for the preterm period, as near term most Doppler indices are not particularly suitable[3,6,20].

Early studies of FHR monitoring in IUGR fetuses have demonstrated that the presence and amplitude of accelerations in IUGR fetuses after 30 weeks' gestation is comparable to those of healthy fetuses *before* 30 weeks' gestation[7]. This might indicate a delay in functional maturation of the beta-sympathetic (cardio-acceleratory) nervous system due to chronic nutritional deprivation and hypoxemia[5,7]. FHR decelerations appear after a gradual decrease in FHR variability and are considered a late sign of fetal impairment[8,9]. In case of mild hypoxemia the presence and duration of decelerations are comparable to those in healthy fetuses. It has therefore been suggested that the parasympathetic (cardio-inhibitory) system is probably not affected to the same extent as is the sympathetic tone[7].

Differentiation between contributions of the sympathetic and parasympathetic branches of the nervous system on FHR regulation may offer a more specific assessment of the (term) IUGR fetus. Such a differentiation is feasible using a signal processing technique called phase rectified signal averaging (PRSA). This technique provides separate characterizations of acceleration-related (sympathetic) and deceleration-related (parasympathetic) modulations in FHR, quantified by 'average acceleration capacity' (AAC) and 'average deceleration capacity' (ADC), respectively[10]. The PRSA methodology, proven to provide better prediction of survival in patients suffering myocardial infarction in adult cardiology, is currently gaining interest in fetal medicine[11,12]. Results from a pilot study indicated that the AAC, calculated from FHR recorded with Doppler cardiotocography (CTG), has the potential to provide better differentiation between normal and compromised fetuses compared to the calculation of short term variability (STV)[11,12]. Although this study demonstrated promising results, PRSA analysis of FHR recorded with CTG is not recommended, since conventional Doppler CTG devices have a low sample rate of 4 Hz and average FHR through a process of autocorrelation[13]. A preferable method for PSRA analysis of FHR is available using a high resolution fetal-ECG recorder, offering true beat-to-beat FHR with an accuracy of 1 ms due to a high sample rate of 1000 Hz. Since it is assumed that true beat-to-beat FHR provides a more accurate assessment of fetal cardiovascular (patho-) physiology compared to conventional Doppler FHR[14], PRSA analysis of true beat-to-beat FHR may offer an even better recognition of the compromised IUGR fetus.

Is was the objective of this investigation to study FHR, its short term variability, AAC and ADC throughout normal gestation as recorded with a high resolution fetal-ECG monitor, and to perform a preliminary comparison of these FHR parameters between IUGR and normal fetuses.

Methods

Study design and participants

A prospective observational study was performed from December 2006 until July 2008 at the University Medical Center Utrecht, The Netherlands. The study was approved by the local Institutional Review Board. Women with singleton pregnancies between 20 and 42 weeks gestation were considered eligible for participation. Exclusion criteria were multiple gestation and pregnancies complicated by congenital malformations and/or chromosomal abnormalities.

The control group consisted of 90 healthy women at 20-40 weeks' gestation at study entry. These pregnancies remained uncomplicated and no medication was administered. Thirty women with pregnancies complicated by intra uterine growth restriction were approached to participate in the study. For all participants, the pregnancies were reliably dated using the last menstrual period and/or by early ultrasound scan. After informed consent was obtained a single overnight FHR recording (17:00 – 08:00 h) was performed, either at home (controls) or in hospital (IUGR). Maternal co-morbidities and treatment, fetal characteristics (ultrasound measurements) and neonatal characteristics were noted from the women's medical charts.

Intra uterine growth restriction

IUGR was defined as estimated fetal weight ≤10th percentile, and birth weight ≤10 percentile corrected for gestational age (GA), sex and parity[15]. In some women IUGR was accompanied by hypertensive disorders. All women were admitted to the antenatal care unit and received daily computerized FHR monitoring, twice weekly Doppler measurements (pulsatility index of the umbilical artery; PI UA), and every two weeks ultrasound measurements of fetal biometry.

Subgroups of IUGR pregnancies were made to distinguish between the different degrees of fetal compromise based on PI UA. Both the results from the PI UA before and after study participation (if present) were retrieved from the women's chart. The first group was defined as IUGR fetuses with normal PI UA both before and after participation in this study. The second group had normal PI UA before participation, but showed progressive deterioration with abnormal PI UA later in gestation. Finally, the third group consisted of IUGR fetuses with abnormal PI UA (> 2SD, GA related) before and after participation.

FHR analysis and parameters

FHR recordings were performed with the AN24 fetal ECG monitor (Monica Healthcare, Nottingham, UK). The electrophysiological signal contains the maternal ECG (mECG), fetal ECG (fECG) and noise, and is recorded with a sample frequency of 1000 Hz using 5 disposable electrodes placed on the maternal abdomen in a standardized manner[14]. The methodology used for fECG signal extraction and analysis has been described in detail by Pieri et al[16]. Fetal ECG complexes were used to calculate true beat-to-beat (R-R) pulse intervals with an accuracy of approximately 1 millisecond. Short term variability (in milliseconds) was calculated from the derived FHR according to the analysis described by Dawes et al.[13].

For differentiation between the contributions of the parasympathetic and sympathetic branches, a signal processing technique called phase rectified signal averaging (PRSA) was used. PRSA provides separate characterizations of acceleration-related and deceleration-related modulations in FHR, quantified by average acceleration capacity (AAC) and average deceleration capacity (ADC), respectively[10]. The methodology has been described in detail by Bauer et al. and is summarized in Figure 1[10].

FHR recordings lasted for approximately 15 hours (17:00 – 08:00 h). For the present study we selected for analysis the time frame between 23:00 and 06:00h, since signal loss is known to be lowest during that period[14]. Cases with signal loss that exceeded 50% of time were excluded from analysis.

Statistics

SPSS for Windows (version 15.01, SPSS Inc., Chicago, Ill.) was used for statistical analysis. Results were summarized with the use of standard descriptives for parametric or non-parametric tests, where appropriate. For both uncomplicated and IUGR pregnancies the mean basal FHR, STV, ADC and AAC values were calculated over the selected time period (23:00-06:00).

A linear regression model was estimated using a FHR parameter (basal FHR, STV, AAC, ADC) and potential confounders (neonatal sex and gestational age; linear, quadratic and cubic functions were tested) to calculate reference percentiles. The reference ranges were compared to established normograms for FHR/STV as reported in literature[17,18]. Mean values of the FHR parameters from recordings in IUGR pregnancies were then plotted against the obtained reference curves.

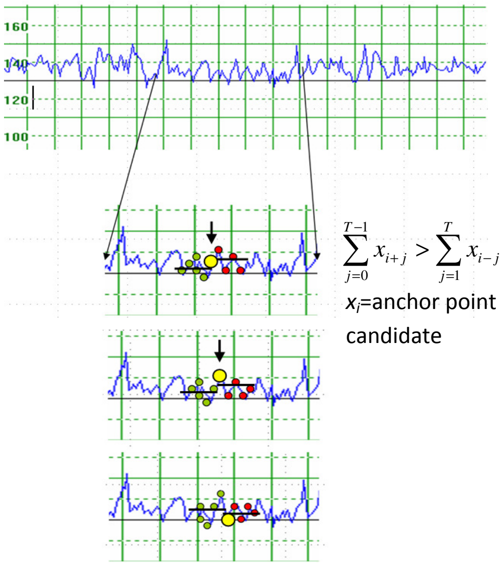
Results

The control group had a median gestational age at FHR recording of 34 weeks (range 21-40 weeks). All neonates were born after 36 weeks' gestation (median 39^{+2} weeks, range 36^{+1} – 41^{+6} weeks). Median birth weight was 3170 grams (range 2660-4650 grams). All neonates had a birth weight >10th percentile for GA according to customized growth charts[15]. Five FHR recordings were excluded from the analysis due to poor signal quality.

Reference curves of FHR, STV, AAC and ADC were constructed for this control group (n=85).
The IUGR fetuses eligible for the study had a median gestational age at participation of 31^{+6} weeks (range 27^{+0} - 36^{+2} weeks). Two out of 30 fetuses were excluded due to congenital malformations and/or chromosomal abnormalities diagnosed at delivery, and in 3/30 the derived FHR data was not suitable for analysis due to high signal loss. The characteristics of the remaining 25 IUGR pregnancies are displayed in Table 1.

Neonatal sex did not contribute significantly to the regression model and was therefore not included. Gestational age (either linear or with linear and cubic components) appeared to have a significant effect on FHR, STV, AAC, and ADC. The reference curves of FHR, STV, AAC and ADC are displayed in Figures 2 A-D, with the coefficients used to construct these figures displayed in Table 2. FHR decreased with advancing gestation, whereas short term variability increased in early gestation with stable values around term. The reference curve of FHR was comparable to those described previously in a large cross-sectional and a smaller longitudinal study, respectively[17,18]. Short term variability in our dataset was higher in early gestation as compared to the published normal curves[17,18]. Although gestational age (linear and cubic functions) showed significant contributions to the regression models of AAC and ADC, both parameters remained relatively constant throughout pregnancy (Figure 2 C-D).
In all IUGR fetuses, except one, mean FHR was within the boundaries of the reference curves. Short term variability was below the 2.5th percentile in 2/25 (8%) fetuses, while both the AAC and ADC values of IUGR fetuses were below the 2.5th percentile in 9/25 (36%), which was significantly more frequent compared with the STV values ($P < 0.05$; Fisher exact test). Inconsistent patterns were found when the PI UA was plotted against the various FHR parameters (Figure 2 A-D). It is noteworthy that 3/9 of the IUGR fetuses with AAC (and 3/9 with ADC -) values ≤ 2.5th percentile had received antenatal steroids ≤ 3 days prior to study participation.

Figure 1: Computation of acceleration capacity by PRSA in a fECG recording (steps for the calculation of deceleration capacity are similar, except for step 2 where intervals shorter than the preceding interval are identified as anchors). (Reproduced with kind permission. Lobmaier et al 2010[13])



$$\sum_{j=0}^{T-1} x_{i+j} > \sum_{j=1}^{T} x_{i-j}$$

x_i=anchor point candidate

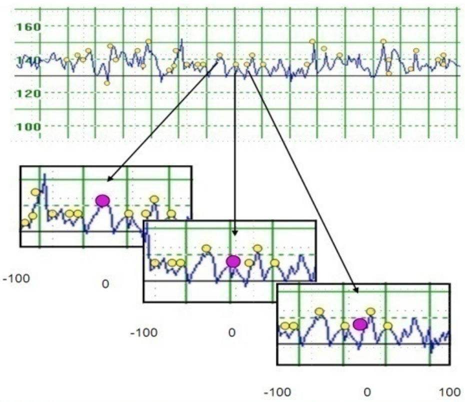
1. Filter application

Increases of T values for computation of acceleration capacity (AC). To suppress errors due to artifacts, accelerations more than 5% are excluded from the analysis.

2. Anchor point definition

Comparing averages of T values of a time interval before and after the anchor point candidate (indicated by black arrow). In this figure T=5. For computation of AC, heart rate intervals longer than the preceding interval are identified as anchors (black arrow in figure 1a, 1b). Time series of decelerations are excluded from the analysis (figure 1c)

Note that typically between one-third and one-half of all points of the time series will be anchor points. The parameter T sets an upper frequency limit for the periodicities that can be detected by PRSA (low-pass filter). The windows of interest are accelerations. The parts of decelerations are excluded.



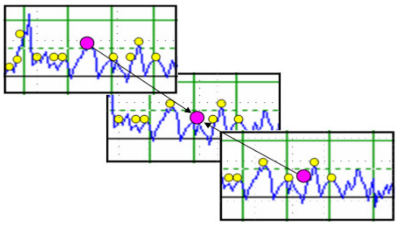
3. Definition of the surroundings (=tachograms)

$X_{i_v-L}, X_{i_v-L+1}, \ldots, X_{i_v}, \ldots, X_{i_v+L-2}, X_{i_v+L-1}$

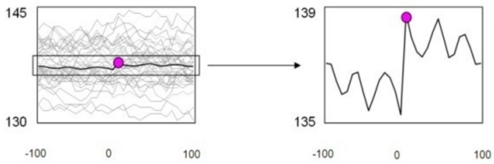
x_{i_v} anchor points with v = 1,…, M, (v = window number),

L = length of surroundings

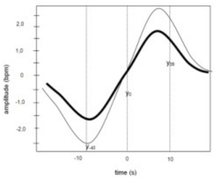
Windows of the length 2L (with L=100s) are defined around each anchor point (anchor point=grey circles). Note that many of these windows will overlap, since many anchor points are close to each other. The parameter L must be larger than the period of the slowest oscillation that one wants to detect.



4. Phase Rectification
Tachograms are aligned at the anchors (interlined circles). All the periodicities are superposed at the center. Averaging over all windows.



5. Signal averaging
The phase-rectified signal averaging is obtained by averaging over all windows aligned to each other with the anchor points (grey circle) at the center. Nonperiodic components that are not phase-synchronized with the anchor points cancel out. Only events that have a fixed phase relationship with the anchor points (all periodicities or quasi-periodicities) "survive" the procedure.



$$\sum_{i=0}^{X-1} \overline{y(i)} - \sum_{i=-X}^{-1} \overline{y(i)} = AAC$$

AAC: the difference of the mean of X values after the anchor point (i=0 until i=X-1) and the mean of X values

6. Quantification of Average Acceleration Capacity (AAC):
The central amplitude is a measure for the dynamic capacity of the whole system. It characterizes the average capacity of the heart to accelerate the cardiac rhythm from one beat to the next. FHR variation reflects complex non-linear dynamics, a loss of which is a sign of reduced reactivity and adaptability, indicating fetal distress.

Table 1: Characteristics of pregnancies complicated by IUGR.

No.	GA at recording (wks)	Hypertensive disorders	Nr.days antenatal steroids	PI UA before	PI UA after	PI UA category	GA at delivery (wks)	BW at delivery	BW percentile
1	27,0	-	35	normal	>2SD	2	35,1	1635	<p5
2	27,1	PE	8	normal	>3SD	2	29,9	840	<p10
3	27,7	-	2	normal	normal	1	34,0	1405	<p5
4	27,7	-	20	>2SD	-	3	33,2	1370	<p10
5	28,1	PE	1	normal	-	1	30,7	1000	<p10
6	29,0	-	1	normal	normal	1	34,8	1890	<p10
7	30,1	-	4	normal	>2SD	2	37,2	2075	<p5
8	30,4	PE	4	>3SD	>3SD	3	30,7	856	<p10
9	30,9	-	6	>3SD	>3SD	3	32,6	1075	<p5
10	31,0	PIH	22	normal	normal	1	34,0	1400	<p5
11	31,1	PE	4	>3SD	>3SD	3	31,4	1120	<p5
12	31,1	PIH	30	normal	normal	1	34,0	1405	<p5
13	31,7	-	-	normal	normal	1	40,1	2800	<p5
14	32,3	PE	2	normal	>2SD	2	33,3	1510	<p10
15	32,6	-	7	>2SD	>2SD	3	34,9	1505	<p5
16	32,9	PE	-	normal	>2SD	2	35,9	2130	<p10
17	33,3	-	-	normal	-	1	33,4	1330	<p5
18	34,0	-	-	normal	>2SD	2	38,2	2430	<p10
19	34,1	-	-	normal	>2SD	2	38,6	2300	<p5
20	35,0	-	-	normal	normal	1	41,0	3045	<p10
21	35,0	PIH	21	>2SD	>2SD	3	35,4	1590	<p5
22	35,1	PE	-	normal	normal	1	37,0	2090	<p5
23	36,0	PE	-	normal	normal	1	37,1	1995	<p5
24	36,3	-	-	normal	normal	1	40,0	2240	<p5
25	36,4	-	-	normal	normal	1	36,7	1985	<p10

Table legend: IUGR was defined as estimated fetal weight <p10. Abbreviations: GA: gestational age, PE: Preeclampsia, PIH: pregnancy induced hypertension, Nr.days between antenatal steroid administration and fECG recording. PI UA: pulsatility index of the umbilical artery. PIUA before and after fECG recording. PI UA categories: 1 = normal PI UA before and after FHR recording, 2 = normal PI UA before, abnormal PI UA after recording, 3 = Abnormal PI UA before and after recording, BW: birth weight.

Table 2: Coefficients used for the graphs of FHR, STV, AAC and ADC with gestational age in weeks (WGA)

y	b	a1	a2
FHR (bpm)	144,15	-0,67	-
STV (ms)	5,10	0,60	-0,001
AAC (bpm)	1,29	0,02	-5,00E-05
ADC (bpm)	-1,29	-0,02	-6,42E-05

Table legend: The equations must be read as y = b + a1(WGA-20) + a2(WGA-20)^3.

Figure 2: Reference curves for FHR (A), STV (B), AAC (C), and ADC (D). Coloured lines indicate reference percentiles calculated from control recordings.

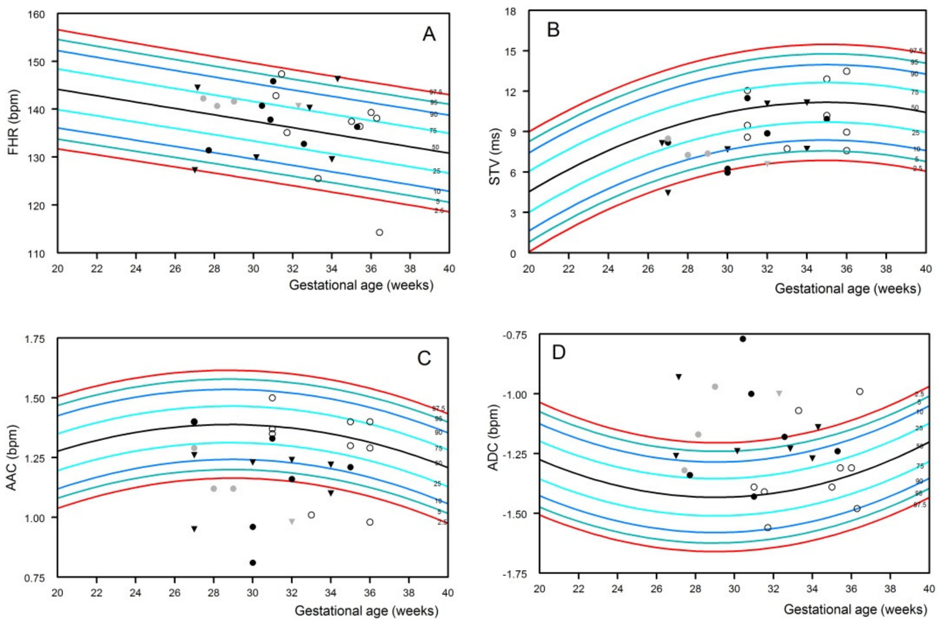


Figure legend: Categories of pulsatility index of the umbilical artery (PI UA); o = normal PI UA before and after FHR recording, ▼ = normal PI UA before, abnormal PI UA after recording, ● = Abnormal PI UA before and after recording. Grey symbols indicate steroid administration ≤ 3 days before study participation. Abbreviations: FHR, fetal heart rate; STV, short term variability; AAC, average acceleration capacity; ADC, average deceleration capacity.

Discussion

This study has provided reference values of a potential new FHR parameter for assessment of the fetal condition in pregnancies complicated by intra uterine growth restriction. Furthermore, our preliminary data showed that in IUGR fetuses both the acceleration capacity and the deceleration capacity reveal more prominent differences from the normograms than short term variability of FHR.

Recently, the advanced technique of phase rectified signal analysis (PRSA) has gained interest in fetal medicine[11,12]. PRSA enables differentiation of the FHR components of the parasympathetic and sympathetic nervous system. Since chronic oxygen and nutrient deprivation is suggested to lead to delayed maturation of the sympathetic nervous system[5,7], separate analysis of the sympathetic (or cardio-accelatory) and parasympathetic (or cardio-inhibitory) nervous system might offer a better recognition of compromise in IUGR fetuses .

Although FHR recordings as acquired with Doppler CTG are not ideal for PRSA analysis, previous research using this technique has similarly found significant differences between normal and IUGR fetuses, with the AAC showing a better differentiation between normal control fetuses than STV[11,12]. In those studies the average acceleration capacity (AAC), representing the sympathetic nervous system, showed better differentiation between normal and IUGR fetuses than the ADC, indicating that the role of the parasympathetic (or cardio-inhibitory) nervous system might not be affected to the same extent as the sympathetic tone. However, in our study we could not confirm superiority of the AAC over the ADC.

The reference values as calculated from our control group in the present study are comparable to those found in literature for FHR, but not for STV[17,18]. The latter is most likely due to diurnal differences in FHR variation, with highest values around midnight[19]. FHR recordings for the calculation of normograms as described in literature were performed in daytime, whereas our data were collected between 23:00-06:00h.

Since values of AAC and ADC as calculated with PRSA are dependent on the sample frequency of the (high resolution) FHR recorder, the reference curves for AAC and ADC as described in this study are only representative for FHR recordings with a sample frequency of 1000 Hz. It is remarkable that gestational age had only minimal effects on both AAC and ADC as indicated by the relative horizontal reference curve (Figure 2C-D).

Although the present study is limited by the small and rather heterogeneous character of the pregnancies complicated by IUGR (co-morbidities of hypertensive disorders with antihypertensive treatment, and administration of antenatal steroids) a large number of fetuses had AAC and ADC values below the 2.5th percentile. This is especially remarkable since only few (6/25) of the IUGR pregnancies showed abnormal velocity waveforms of the umbilical artery prior to study participation, and since it is known that abnormalities of UA Doppler usually precede a reduction in FHR variation before term age[3,6]. Interpretation of the presented data should, however, be performed with caution since environmental influences, such as administration of antenatal steroids and potentially other reasons not evident in the current dataset, could also cause deviations from normality.

The new technology of FHR assessment might especially be important at term to assess the condition of the small for gestational age fetus, since at that age Doppler waveform patterns do not discriminate between low and high risk small fetuses[6,20].

In conclusion, separate analysis of the cardio-acceleratory and cardio-inhibitory components of FHR as recorded with a high resolution fECG recorder seems to differentiate better between normal and IUGR fetuses than conventional methods of FHR variability. Whether this indicates that AAC or ADC represent a more sensitive parameter of fetal compromise compared to the currently used fetal parameter remains to be elucidated in future longitudinal studies in IUGR fetuses.

Reference List

1. Visser GH, Stigter RH, Bruinse HW. Management of the growth-retarded fetus. Eur.J.Obstet.Gynecol.Reprod.Biol. 1991 12;42 Suppl(0301-2115):S73-S78.
2. Bekedam DJ, Visser GH, van der Zee AG, Snijders RJ, Poelmann-Weesjes G. Abnormal velocity waveforms of the umbilical artery in growth retarded fetuses: relationship to antepartum late heart rate decelerations and outcome. Early Hum.Dev. 1990 10;24(0378-3782; 1):79-89.
3. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackeloer BJ, Kok HJ, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet.Gynecol. 2001 12;18(0960-7692; 6):564-570.
4. Bilardo CM, Wolf H, Stigter RH, Ville Y, Baez E, Visser GH, et al. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet.Gynecol. 2004 02;23(0960-7692; 2):119-125.
5. Baschat AA. Fetal responses to placental insufficiency: an update. BJOG 2004 Oct;111(10):1031-1041.
6. Visser G.H.A. Monitoring the growth-restricted fetus during the preterm period. In: Petraglia F., Gabbe S.G., Weiss G., Strauss J.F., editors. Preterm Birth: Mechanisms, Mediators, Prediction, Prevention and Interventions. first ed.: Informa Healthcare; 2007. p. 192.
7. Gagnon R, Hunse C, Bocking AD. Fetal heart rate patterns in the small-for-gestational-age human fetus. Am.J.Obstet.Gynecol. 1989 Sep;161(3):779-784.
8. Bekedam DJ, Visser GH, Mulder EJ, Poelmann-Weesjes G. Heart rate variation and movement incidence in growth-retarded fetuses: the significance of antenatal late heart rate decelerations. Am.J.Obstet.Gynecol. 1987 07;157(0002-9378; 1):126-133.
9. Snijders RJ, Ribbert LS, Visser GH, Mulder EJ. Numeric analysis of heart rate variation in intrauterine growth-retarded fetuses: a longitudinal study. Am.J.Obstet.Gynecol. 1992 01;166(0002-9378; 1):22-27.
10. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Makikallio T, Ulm K, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006 May 20;367(9523):1674-1681.
11. Huhn EA, et.al. Phasengleichgerichtete Signalmittelung der Kardiotokographie bei intrauteriner Wachstums-retardierung. Munchen, Germany: Frauenklinik der Technischen Universität München Klinikum rechts der Isar; 2007.
12. Lobmaier SM, Pildner von Steinburg S, Müller A, Schuster T, Huhn EA, Ortiz JU, Schneider KTM, Schmidt G. Phase rectified signal averaging as a new method for surveillance of growth restricted fetuses, a prospective observational study. Munchen, Germany: Frauenklinik, Abt. Perinatalmedizin, TU München.
13. Dawes GS. Computerised analysis of the fetal heart rate. Eur.J.Obstet.Gynecol.Reprod.Biol. 1991 Dec;42 Suppl:S5-8.

14. Graatsma EM, Jacod BC, van Egmond LA, Mulder EJ, Visser GH. Fetal electrocardiography: feasibility of long-term fetal heart rate recordings. BJOG 2009 Jan;116(2):334-7; discussion 337-8.
15. Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. New Dutch reference curves for birthweight by gestational age. Early Hum.Dev. 2009 Dec;85(12):737-744.
16. Pieri JF, Crowe JA, Hayes-Gill BR, Spencer CJ, Bhogal K, James DK. Compact long-term recorder for the transabdominal foetal and maternal electrocardiogram. Med.Biol.Eng.Comput. 2001 01;39(0140-0118; 1):118-125.
17. Serra V, Bellver J, Moulden M, Redman CW. Computerized analysis of normal fetal heart rate pattern throughout gestation. Ultrasound Obstet.Gynecol. 2009 Jul;34(1):74-79.
18. Nijhuis IJ, Ten Hof J, Mulder EJ, Nijhuis JG, Narayan H, Taylor DJ, et al. Fetal heart rate in relation to its variation in normal and growth retarded fetuses. Eur.J.Obstet.Gynecol.Reprod.Biol. 2000 03;89(0301-2115; 1):27-33.
19. Visser GHA, Goodman JDS, Levine DH, Dawes GS. Diurnal and other cyclic variations in human fetal heart rate near term. Obstet.Gynecol. 1982 03/01;142(0002-9378; 5):535-544.
20. Baschat AA. Fetal growth restriction - from observation to intervention. J.Perinat.Med. 2010 May;38(3):239-246.

Chapter 5

Glycaemic control throughout pregnancy in women with type 1 diabetes

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Submitted for publication

Glycaemic control throughout pregnancy in women with type 1 diabetes

Abstract

Objective In pregnant women with type 1 diabetes severe hypoglycaemia and accompanying large fluctuations in glucose values have been described in the first trimester of pregnancy. This study evaluated whether glycaemic control improves with advancing pregnancy.

Methods Prospective observational study of pregnant women with type 1 diabetes. In each trimester of pregnancy HbA1c-levels were assessed. Main outcome measures were the comparisons per trimester of median glucose values and measures of glucose variability calculated from 48-hour measurements with a continuous glucose monitoring system (CGM).

Results Twenty-six pregnant women with type 1 DM performed CGM in each trimester of pregnancy, resulting in 78 continuous glucose measurements. There were no differences between the trimesters for HbA1c-levels, median glucose values, glucose variability nor for the presence of hyper- and hypoglycaemia. Large variations for all parameters existed throughout pregnancy at both inter- and intra-individual level. The presence of mild or asymptomatic ((biochemical) hypoglycaemia was not restricted to early pregnancy. Extrapolation of the findings to the general pregnant diabetic population was confirmed by 46 cross-sectional CGM recordings.

Conclusions At individual level the degree of glycaemic variability during the first trimester does not predict variability in later pregnancy. Extrapolation of these results to the general diabetic population seems justified.

Introduction

The risk of adverse outcome in diabetic pregnancy is related to the degree of glycaemic control[1]. In order to reach optimal glycaemic control, insight has to be obtained in the evolution of glycaemic patterns in the course of pregnancy.

Continuous glucose monitoring (CGM) has gained interest as a method to acquire more in-depth insight into glycaemic control in diabetic patients and offers a variety of glucose parameters[2-4]. Self-measurement of glucose levels in capillary blood has the disadvantage that it only offers a snapshot image of the glucose profile and at least 10 measurements a day are needed to approach the degree of information on hyperglycaemia that CGM offers whereas at the same time hypoglycaemic episodes will still be missed[5]. Sequential determinations of glycosylated haemoglobin-levels (HbA1c) are of limited value since a physiologic decrease occurs during pregnancy[6]. Moreover, HbA1c is poorly related to macrosomia at birth, which is in contrast to data from 24 hour CGM recordings[7].

Currently, data on the patterns of mean glucose levels and parameters of glucose variability throughout the three trimesters of pregnancy in women with type 1 diabetes is limited. In an earlier study, we have found large day-to-day fluctuations during pregnancy in type 1 diabetes[4]. However, since most recordings were performed during the first trimester, it is unclear whether large day-to-day glucose variability persists at individual level in the second and third trimester of pregnancy.

It was the purpose of this study to evaluate the evolution of glucose patterns and (day-to-day) glucose variability with advancing gestation in type 1 diabetes.

Methods

Study design and patients

A prospective observational study was conducted from December 2003 until July 2008 at the University Medical Center Utrecht, The Netherlands. The study was approved by the local Institutional Review Board. Women with type 1 diabetes mellitus with singleton pregnancies were eligible for participation. All women gave their written informed consent.

Parameters of glycaemic control

Glycaemic control during the three trimesters of pregnancy was assessed using HbA1c-levels, median glucose levels and parameters of (day-to-day) glucose variability calculated from measurements with CGM. HbA1c-levels were assessed every four weeks of pregnancy and retrieved from the medical records. In each trimester of pregnancy the HbA1c level, matched +/- two weeks within the date of CGM measurement, was used for analysis.

The study participants were asked to use CGM (Medtronic MiniMed, Northridge, CA, USA). in each trimester of pregnancy irrespective of the glycaemic control at first antenatal visit during the first trimester. Glucose values were stored off-line and blinded during CGM. After completing the measurement, the clinician discussed the results with the participants and, when necessary, insulin therapy was adjusted. The CGM-system stores values within a range of 2.2 – 22.2 mmol/l (40 – 400 mg/dl) every 5 minutes providing 288 readings in 24 hours. The methodology and criteria for optimal accuracy of CGM have been described in detail previously[8].

Median glucose levels and the standard deviation (mmol/l) were calculated for each 24 hours of CGM. As a representative of ‘day-to-day variability’ the mean absolute difference (MAD; mmol/l) was selected (mean absolute difference between glucose values obtained at the same time of day on two consecutive days). A previous study defined high day-to-day variability when MAD values exceed 2.35 mmol/l[4]. Finally, the extent of glucose control was studied using the percentage of time spent in hyperglycaemia

(hyperglycaemia ≥ 7.8 mmol/l; severe hyperglycaemia ≥ 10.0 mmol/l), and time spent in hypoglycaemia (hypoglycaemia ≤ 3.9 mmol/l; severe hypoglycaemia ≤ 2.8 mmol/l).
In order to test whether data from longitudinal measurements (in each trimester of pregnancy) could be extrapolated to the general pre-gestational diabetic population, cross-sectional data from women using CGM in only one or two trimesters was used for comparison. Women in the cross-sectional study-group, equal to women in the longitudinal study-group, were asked to use CGM irrespective of their current glycaemic control.

Statistics
SPSS for Windows (version 15.01; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Results were summarised with the use of standard descriptives, where appropriate, for parametric or non-parametric tests.
Parameters of median glucose and glucose variability were compared between the three trimesters of pregnancy using longitudinal mixed linear models. Comparison between longitudinal – and cross-sectional data was performed using independent samples t-test, with significance defined as a p value <0.05.

Results

Twenty-six women contributed to the longitudinal dataset by using CGM in each trimester of pregnancy. Median age was 34 years (interquartile range (IQR) 31-37 years), median duration of diabetes was 13 years (IQR 7 - 21 years). Median gestational age at CGM was 12^{+1} weeks in the first trimester, 25^{+0} weeks in the second trimester and 34^{+5} weeks in the third trimester of pregnancy. All women received intensive insulin treatment with half of them using continuous subcutaneous insulin infusion, and half of them using multiple injection treatment.
Multilevel analysis demonstrated that, when duration of diabetes was included in the model, no effect of gestational age on mean HbA1c levels, median glucose values, standard deviation and day-to-day variability (MAD) could be found (Figure 1). The mean MADs were 2.6, 2.5 and 2.1 mmol/l in 1st, 2nd, and 3rd trimester of pregnancy, respectively (non-significant). MAD values were found to be ≥ 2.35 mmol/l in 39/78 (50%) recordings. Analysis of the incidence and duration of (severe) hypoglycaemia and (severe) hyperglycaemia showed no differences between the trimesters of pregnancy (Figure 2A-B). Results were comparable between women using multiple injection therapy and continuous insulin infusion systems.
All glucose parameters showed wide distributions (Figures 1 and 2) due to large inter-individual differences. Moreover, when analysing the data at intra-individual level, first trimester glucose values did not predict the values found in advancing pregnancy (Figure 3).

Cross-sectional data from 34 women with pre-gestational diabetes was analysed to test comparability to the longitudinal results. 12 women used CGM in two trimesters of pregnancy and 22 women performed a single CGM recording, resulting in 46 cross-sectional recordings in total. No significant differences for all glucose parameters were found when comparing cross-sectional and longitudinal data, with in the former MAD values ≥ 2.35 mmol/l in 20/46 (43%) recordings.

Figure 1: Median HbA1c, median glucose, standard deviation (SD) and mean absolute difference (MAD) per trimester of pregnancy displayed in box plots with medians and interquartile ranges (IQR).

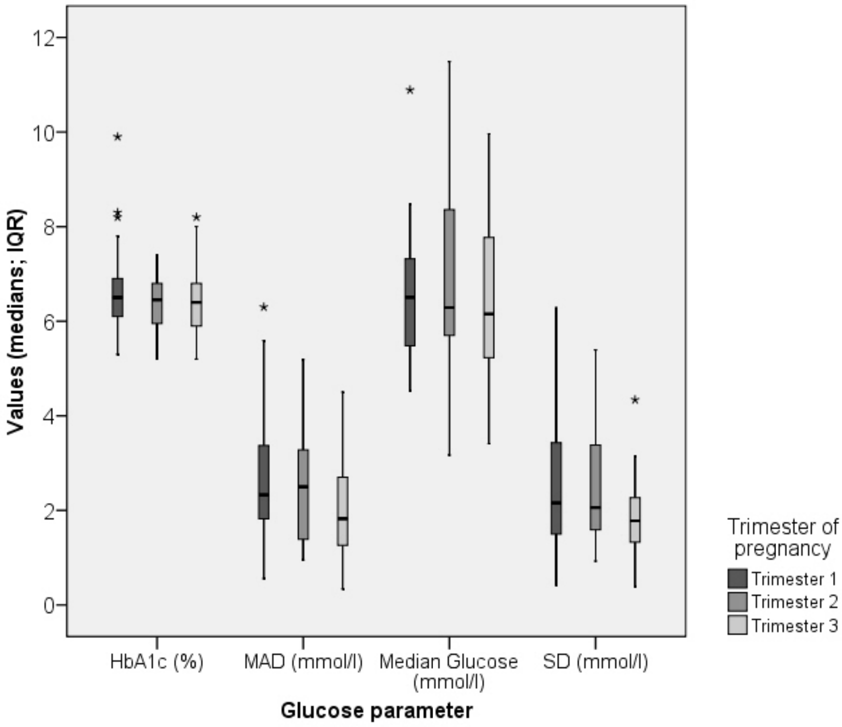

Figure legend: Outliers are indicated by an asterisk. Median HbA1c, median glucose, MAD and SD were comparable between trimesters of pregnancy.

Figure 2: Percentages of time of the 48 hour CGM spent in mild - or severe hypoglycaemia (A) and hyperglycaemia (B) per trimester of pregnancy (box plots with medians and interquartile ranges (IQR)).

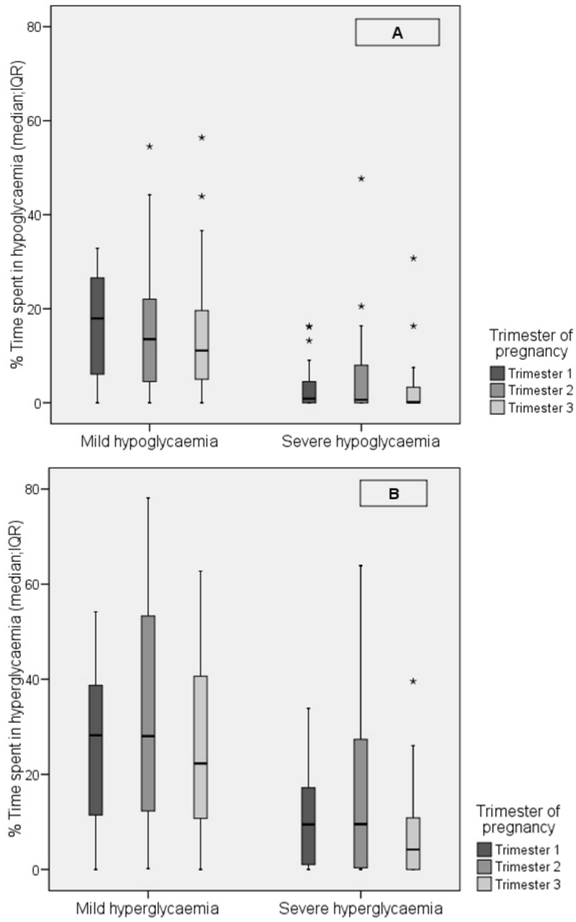

Figure legend: Mild hypoglycaemia <3.9 mmol/l, severe hypoglycaemia <2.8 mmol/l, mild hyperglycaemia >7.8 mmol/l, severe hyperglycaemia >10.0 mmol/l. Outliers are indicated by an asterisk. Comparison between trimesters showed no significant differences in time spent in hypo- or hyperglycaemia.

Figure 3: Estimates of median glucose values for women with type 1 diabetes obtained from applying generalised linear mixed models to the median glucose values acquired with CGM in each trimester of pregnancy.

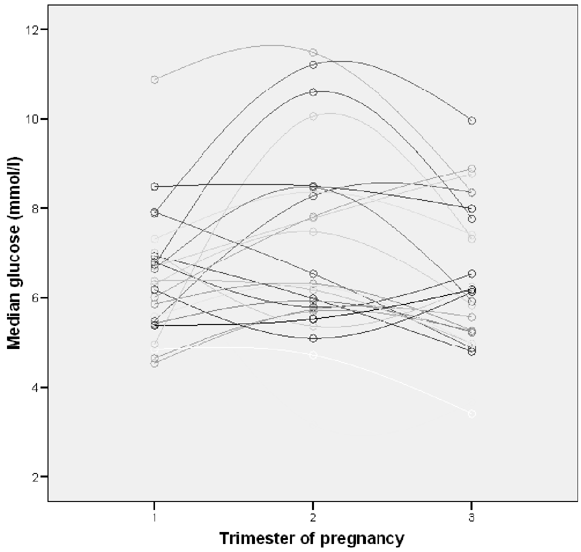

Figure legend: Each line represents changes in median glucose values for individual subjects. Note how for most individuals the glucose values in first trimester do not predict values in second and third trimester.

Discussion

This study emphasises the difficulties encountered in glucose control in type 1 diabetic pregnancy reflected by the large inter- and intra-individual differences that were found for all glucose parameters throughout the three trimesters of pregnancy.

This is the first study on glycaemic variability longitudinally throughout the three trimesters of pregnancy exclusively in women with type 1 diabetes. Murphy et al. described a decrease in hyperglycaemic episodes, mean blood glucose and HbA1c with advancing pregnancy in a mixed group of women with either type 1 or type 2 diabetes. However, it seems that their described effect might mainly be explained by the contribution of women with type 2 diabetes[9].

Comparison of our longitudinal data to cross-sectional results from a single or two CGM recordings per pregnancy showed no significant differences indicating that our results can be extrapolated to the general pre-gestational diabetic population.

Classically, severe clinical hypoglycaemia, defined as requiring help from another person to actively administer carbohydrates or injections of glucagon or glucose, is most frequent during the first trimester[10,11]. Unfortunately our study does not provide data on clinical hypoglycaemic events in our study population. However, in accordance with other studies, our data show that mild or asymptomatic (biochemical) hypoglycaemic episodes occur at least as frequent in advanced pregnancy[9,10]. An explanation for the decrease in incidence of severe clinical hypoglycaemia in the second half of gestation with persisting presence of mild or asymptomatic (biochemical) hypoglycaemia remains to be elucidated.

Our previous study defined a cut-off value of 2.35 mmol/l for MAD to distinguish between high and low day-to-day glucose variability, based on CGM, and predominantly in first trimester of pregnancy[4]. The current study demonstrates that approximately half of the women in each trimester of pregnancy show high day-to-day glucose variability, with MAD values above the cut-off in both the longitudinal as the cross-sectional dataset.

A recent randomised study using repetitive offline CGM during pregnancy has shown the potential of CGM to reduce macrosomia with improved glycaemic control[12]. Although offline use of CGM gives both clinicians and diabetic women insight into the daily fluctuations of glucose patterns in retrospect, insulin adjustment is hampered in women with high glucose variability[4]. In the non-pregnant diabetic population frequent use of real time CGM measurements with instantaneous feedback has proven to result in improvement of glycaemic control since insulin schemes can be adjusted according to real time glucose levels[13]. Whether real time CGM in pregnancy results in improved glycaemic control and further reduction of macrosomia remains to be established.

In conclusion this study shows the difficulties encountered in optimising glycaemic control in pregnancy. Large variations for all parameters of glycaemic control including day-to-day variations hamper treatment in all three trimesters of pregnancy.

Reference List

1. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004 04/17;328(1468-5833; 7445):915.
2. Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. Obstet.Gynecol. 2003 Apr;101(4):633-638.
3. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. Diabetes Technol.Ther. 2009 Jun;11 Suppl 1:S55-67.
4. Kerssen A, de Valk HW, Visser GH. Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. BJOG 2004 09;111(1470-0328; 9):919-924.
5. Kerssen A, de Valk HW, Visser GH. Do HbA1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus? Diabetologia 2006 01;49(0012-186; 1):25-28.
6. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, et al. HbA1c levels are significantly lower in early and late pregnancy. Diabetes Care 2004 May;27(5):1200-1201.
7. Kerssen A, de Valk HW, Visser GH. Increased second trimester maternal glucose levels are related to extremely large-for-gestational-age infants in women with type 1 diabetes. Diabetes Care 2007 May;30(5):1069-1074.
8. Kerssen A, de Valk HW, Visser GH. The Continuous Glucose Monitoring System during pregnancy of women with type 1 diabetes mellitus: accuracy assessment. Diabetes Technol.Ther. 2004 10;6(1520-9156; 5):645-651.
9. Murphy HR, Rayman G, Duffield K, Lewis KS, Kelly S, Johal B, et al. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. Diabetes Care 2007 Nov;30(11):2785-2791.
10. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen ER. Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. Diabetes Care 2008 Jan;31(1):9-14.
11. Kimmerle R, Heinemann L, Delecki A, Berger M. Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. Diabetes Care 1992 Aug;15(8):1034-1037.
12. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ 2008 Sep 25;337:a1680.
13. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N.Engl.J.Med. 2008 Oct 2;359(14):1464-1476.

Chapter 6

Continuous simultaneous monitoring of maternal glucose and fetal heart rate in diabetic pregnancy

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Submitted for publication

Continuous simultaneous monitoring of maternal glucose and fetal heart rate in diabetic pregnancy

Abstract

Background Diabetic pregnancy is associated with an increased risk of intrauterine fetal death. Difficulties are encountered in the recognition of the fetus at risk, since routine fetal heart rate (FHR) monitoring during euglycaemia can falsely reassure clinicians. FHR monitoring during prolonged excursions in glucose levels might offer insight into the fetal compensatory mechanisms.

Objectives To assess the effect of spontaneous occurring excursions of maternal glucose measured with continuous glucose monitoring (CGM) on fetal heart rate (FHR) parameters.

Study Design Prospective observational study in twenty-two women with (pre)gestational diabetes. Simultaneous recording of FHR by abdominal ECG-electrodes and CGM was performed continuously for 15 hours. Main outcome measure was FHR and its short term variability (STV) in relation to excursions of glucose into the hypo- and hyperglycaemic range (≤3.9 and ≥7.8 mmol/l, respectively).

Results Maternal glucose levels ranged between 2.2 mmol/l (lowest detectable value) and 18.1 mmol/l. FHR and STV were within limits of normality during all episodes of hyperglycaemia (n=28 events) and hypoglycaemia (n=18 events). Multilevel analysis of the hyperglycaemic events showed a significant effect of glucose on FHR, but not on STV. During hypoglycaemia no significant effect of glucose on FHR or STV could be established.

Conclusions This study confirms an effect of maternal glucose on FHR during hyperglycaemia. This effect probably represents an expression of physiology rather than pathology. Whether simultaneous recording of FHR and CGM offers additional value in high risk cases (macrosomia and poor glucose control) needs to be consolidated.

Introduction

Despite improvements in fetal monitoring diabetic pregnancy is still associated with a ten-fold increased risk for sudden unexplained intrauterine deaths in the third trimester of pregnancy[1-4]. Poor maternal glycaemic control is implicated to play a role in this high incidence, since maternal hyperglycaemia has been demonstrated to coincidence with fetal hyperglycaemia, hyperinsulinaemia, acidaemia and (chronic) hypoxia[5,6].

Various monitoring techniques are available for antenatal assessment of fetal wellbeing in diabetic pregnancy; ultrasound assessment of fetal biometry, Doppler velocimetry and fetal heart rate (FHR) monitoring. There exists no consensus towards the optimal method and frequency of antenatal monitoring[7-9] and the question remains how to recognize the fetus at increased risk of deterioration.

Several studies have used FHR monitoring to assess fetal compensatory behaviour following induced or natural occurring changes in maternal glucose values, however the findings are inconsistent. Some authors described significant changes of FHR following hyperglycaemia[10,11], whereas others failed to establish a relationship between FHR and maternal glucose levels[8,12-14]. Although in diabetic pregnancy spontaneous excursions of maternal glucose have been described lasting for many hours and sometimes reaching extreme values[15], fetal compensatory behaviour during prolonged and/or extreme hypo- and hyperglycaemia has not been studied. Recently, an improved technique for continuous FHR monitoring using abdominal ECG-electrodes has been validated[16], allowing combined assessment of continuous FHR monitoring and continuous glucose monitoring. The objective of this study was to assess the relationship between computerized fetal heart rate parameters and spontaneous glucose excursions present during the second half of gestation in women with (pre)gestational diabetes.

Materials and methods

Study design and patients

A prospective observational study was conducted at University Medical Center Utrecht, The Netherlands. The study was approved by the local medical ethical committee. Women with (pre)gestational diabetes with singleton pregnancies were eligible for participation. Exclusion criteria were multiple gestation, congenital malformations, and hypertensive disorders. Twenty-two diabetic women, irrespective of their current glycaemic control, were approached to participate in a simultaneous FHR and maternal glucose recording to be performed either at home or in the obstetric ward. After informed consent was obtained, patients were asked to simultaneously wear a Continuous Glucose Monitoring System (CGMS, MiniMed, etc) and a fetal-ECG monitor (AN24, Monica Healthcare, Nottingham, UK) for a combined continuous measurement of FHR and maternal glucose.

The control group consisted of 90 healthy non-diabetic women at 21-40 weeks' gestation at study entry. These pregnancies remained uncomplicated and no medication was administered. Control women participated in the fetal ECG part of the study only; recordings were made at home[16].

For all participants, the pregnancies were reliably dated using the last menstrual period and by early ultrasound scan. Recordings started around 17:00 hours lasting for approximately 15 consecutive hours. Demographic and clinical characteristics were collected from the patients' medical charts.

Fetal heart rate monitoring and analysis

The FHR signal was recorded with a portable fetal ECG monitor using five disposable electrodes placed on the maternal abdomen. The placement of electrodes and methodology for signal extraction have been described previously[16]. All recordings were performed overnight, during sleep, to minimize maternal abdominal muscle activity that can distort the fECG signal. Data was downloaded offline. Basal FHR (in bpm) and its short term variability (STV; in ms) were calculated from consecutive R-R intervals according to established definitions for computerized FHR analysis[17-19]. The FHR data was averaged over 30-minute periods; time periods with FHR data loss of ≥50% were considered inappropriate for analysis. For each recording, we also calculated night time (23:00 to 06:00 h) FHR parameters as the mean basal FHR and STV values over twelve 30-min periods. This way, cross-sectional reference curves over gestation were constructed for FHR data from the control patients. The night time FHR parameters similarly obtained from diabetic patients were plotted against the reference curves for comparison.

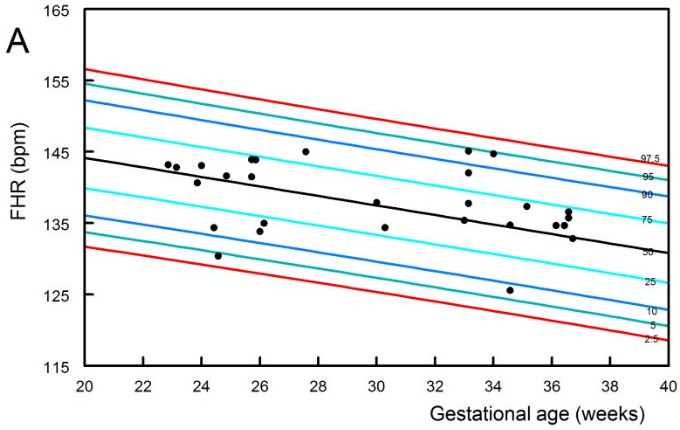
Continuous Glucose Monitoring

The CGMS measures glucose levels (values blinded to patient and clinician) in the extracellular fluid of the abdominal subcutaneous tissue, and stores values within a range of 2.2 – 22.2 mmol/l (40 – 400 mg/dl) every 5 minutes providing 288 readings in 24 hours. Glucose recordings were considered valid if the criteria for optimal accuracy were met as defined in previous studies[20,21].

Simultaneous recording of FHR parameters and maternal glucose

Glucose levels of the diabetic women were averaged over 30-minute periods and coupled to the simultaneously recorded FHR data. In case multiple recordings were performed in a single participant, a maximum of two recordings were considered appropriate for the overall analysis only if the recordings were made at least three weeks apart. The dataset was searched for the occurrence of hyper- and hypoglycaemic events to study the effect of spontaneous maternal glucose excursions on FHR parameters. Hyperglycaemia was defined as glucose levels equal to or above 7.8 mmol/l, whereas hypoglycaemia was defined as glucose levels equal to or below 3.9 mmol/l during at least one hour (two successive periods of 30 minutes). FHR parameters were examined for two hours prior to and during the hyper- or hypoglycaemic events.

Figure 1: FHR (A) and STV (B) from women with (pre-)gestational DM plotted against reference values of FHR as obtained from uncomplicated pregnancies.



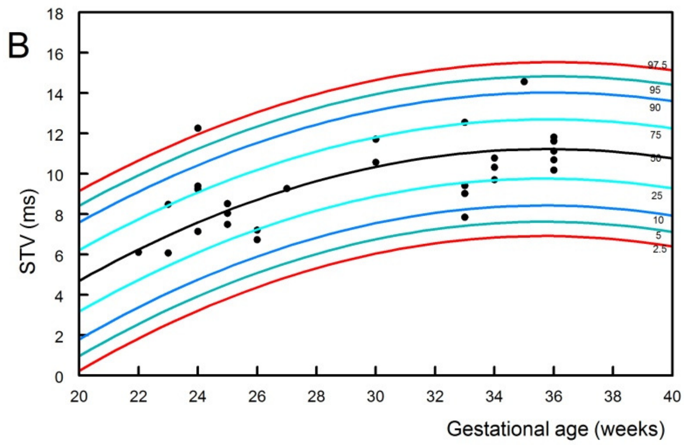


Table 1: Patient characteristics of pregnant women with (pre)gestational diabetes (N=22).

Maternal descriptions	**Median**	**Range**
Maternal age (years)	34	24-40
BMI (kg/m2)	30.0	20-45.5
Duration of diabetes (years)	15	1 – 30
Type diabetes (1 / 2 / GDM)	15 / 4 / 3	
White class (A2 / B / C / D / D4)	3 / 4 / 9 / 5 / 1	
Insulin treatment (MIS / CSII)	9 / 13	
HbA1c level at conception (%)	7,0	5.5 - 9.2
HbA1c level at recording (%)	6,1	4.6 - 8.4
Pregnancy characteristics	**Median**	**Range**
Gestational age at recording (weeks)	30+0	22+6 - 36+5
Gestational age at delivery (weeks)	38+1	27+0 - 39+6
Parity (0 / 1 / 2)	9 / 8 / 5	
Mode of delivery (vaginal / caesarean section)	10 / 12	
Neonatal descriptions	**Median**	**Range**
Birth weight (kg)	3,6	1.0 - 5.6
Neonates with birthweight percentile > 90 (%)	42%	

Abbreviations: GDM: gestational diabetes; MIS: multiple injection scheme; CSII continuous subcutaneous insulin injections

Table 2: Results for multilevel analysis of basal fetal heart rate (FHR) and short term variability (STV) before and during hyper- and hypoglycaemic events (repeated measurements for 5 successive 30-min periods; Time). Model estimates are presented as beta (β) and standard error (SE) or as F-statistic with their level of significance. A single event per participant was selected for analysis.

	Hyperglycaemia (n = 15)		Hypoglycaemia (n = 13)	
	FHR (bpm)	STV (ms)	FHR (bpm)	STV (ms)
Intercept (β; SE) #	135.0 (3.6) *	8.3 (1.3) *	139.5 (3.4) *	9.6 (1.6) *
Glucose (β; SE)	0.83 (0.32) &	-0.09 (0.12) n.s.	-0.21 (0.56) n.s.	0.03 (0.21) n.s.
GA at recording (β; SE)	-0.40 (0.16) &	0.21 (0.06) $	-0.40 (0.27) n.s.	0.11 (0.14) n.s.
Time (F-statistic; df=4)	0.57 n.s.	0.44 n.s.	1.01 n.s.	1.37 n.s.
Time x Glucose (F-statistic; df=4)	1.14 n.s.	1.10 n.s.	0.89 n.s.	0.41 n.s.

*Table legend: # intercept for gestational age at recording centered at 20 weeks; * p<0.0001; & p<0.05; $ p<0.005. GA: gestational age.*

Statistics

SPSS for Windows (version 15, SPSS Inc., Chicago III.) was used for data management and statistical analysis. Variables were summarized with the use of standard descriptive statistics. Reference curves for the FHR parameters in the control group were constructed using linear regression analysis with linear and cubic components of gestational age. Relationships between maternal glucose and FHR parameters before and during hyper- and hypoglycaemic events (five successive 30-min periods) were studied by multilevel analysis. Duration of maternal diabetes, and HbA1c level and gestational age at recording were considered as potential confounders. With all tests, significance was assumed at the level of $\alpha = 0.05$ (two sided tests).

Results

Twenty-eight simultaneous recordings (total recording time 424 hours) of maternal glucose and FHR parameters were performed in 22 women with (pre)gestational diabetes. Six women were monitored on two occasions ≥ 3 weeks apart. Fifteen women (68%) had type 1 diabetes. Patient baseline characteristics are summarized in Table 1.

In the control group, single FHR recordings were obtained from 90 women at 20-40 weeks' gestation (median 34 weeks). Five FHR recordings were excluded due to poor overall signal quality. All fetuses were born after 36 weeks' gestation (median 39^{+2}, range 36^{+1} – 41^{+6}), weighed between 2660 and 4650 g (median weight 3170 g), and all had a birth weight <90th percentile for gestation according to customized growth charts[22].

Fetal heart rate monitoring

The median percentage of data loss among the FHR recordings from women with (pre-) gestational diabetes was 22% (IQR 3–53%) whereas for the control group median data loss was 10% (IQR 0–52%) for the total duration of recording. Night time FHR parameters of the diabetic group are presented in Figure 1 plotted against the reference curves. Both FHR and STV values obtained from the diabetic group were well within the limits of normality throughout gestation, with one exception.

Continuous Glucose Monitoring

All continuous glucose recordings were considered valid according to predefined criteria[20]. Only two women (2 recordings) remained euglycaemic (glucose values 3.9 - 7.8 mmol/l) during the total duration of recording. For the total study group, the median percentage of time women spent in euglycaemia was 58% (interquartile range; IQR 43-79%), in hypoglycaemia 5% (IQR 0 - 19%) and in hyperglycaemia 26% (IQR 4 - 41%). The occurrence of hyperglycaemia was equally distributed over the recording period, whereas hypoglycaemic events were mostly present in the early morning.

FHR parameters and maternal glucose excursions

A total of 28 hyperglycaemic and 18 hypoglycaemic events were identified among 15 and 13 CGM recordings, respectively. With a single hyper- and/or hypoglycaemic event selected per patient, there remained 15 hyperglycaemic and 13 hypoglycaemic events for further analysis.

For hyperglycaemia, the individual lines in Figure 2A-C show the courses of maternal glucose, basal FHR, and STV, respectively, before (2 hr) and during the distinct hyperglycaemic events (minimum duration 60 min). Glucose values during the hyperglycaemic events ranged up till 18.1 mmol/l. FHR and STV remained within limits of normality during all periods of hyperglycaemia (FHR 110-160 bpm[19], and STV above 4.0 ms[18,19](Figure 2B-C). Multilevel analysis of the hyperglycaemic events was confined to five successive 30-min periods (from -60 to +90 min; 'Time'; Figure 2A-C). Analysis showed a significant 'Glucose main effect' on basal FHR, but not on STV, after correction for gestational age at recording (Table 2). There was no significant 'Time main effect' or 'Time x Glucose interaction effect' on FHR or STV (Table 2; Figure 2). With a similar analysis, hypoglycaemia was not associated with any significant changes in FHR or STV (Table 2; Figure 3A-C).

Neither for hyperglycaemic nor hypoglycaemic events, the duration of maternal diabetes or HbA1c content at recording had a significant contribution to the model.

Figure 2: The courses of maternal glucose (A), basal FHR (B), and STV (C), before, during, and following hyperglycaemic events. The black box indicates the first 30-min period of hyperglycaemia.

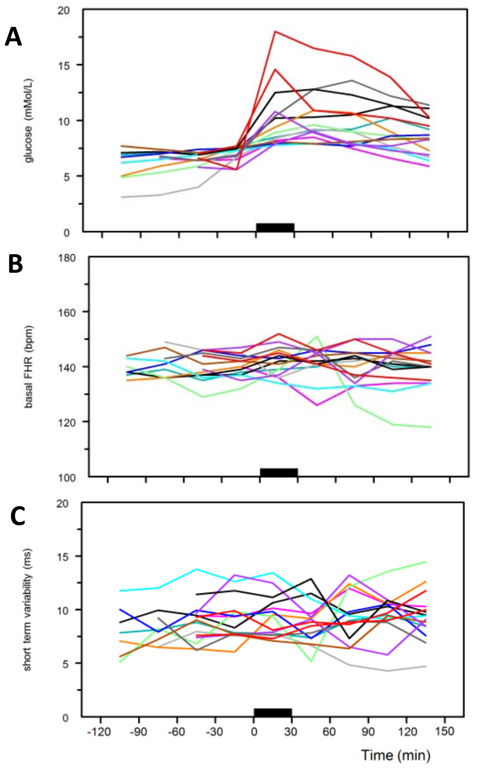
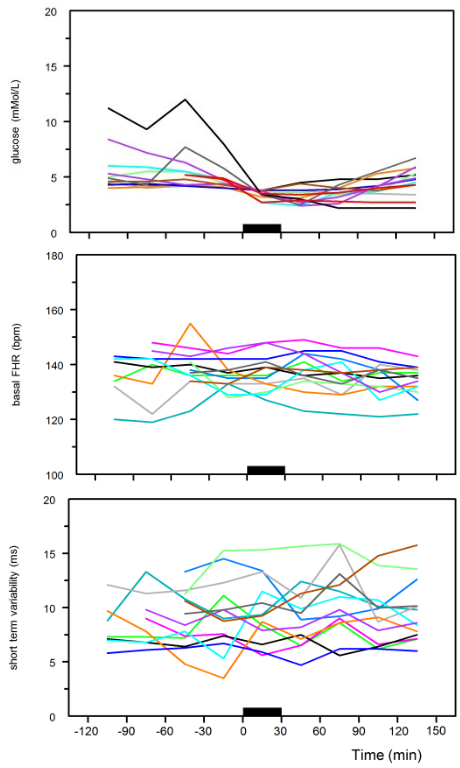


Figure 3: The courses of maternal glucose (A), basal FHR (B), and STV (C), before, during, and following hypoglycaemic events. The black box indicates the first 30-min period of hypoglycaemia.



Discussion

The results of the present study demonstrate an effect of glucose on FHR, but not on STV, during episodes of hyperglycaemia. Maternal hypoglycaemia, in some studies described to increase fetal activity[23,24], did not have any effect on FHR parameters.

FHR remained within the ranges of normality during hyperglycaemia[18,19], demonstrating that hyperglycaemic excursions were well tolerated by the fetuses in our study population. This finding is comparable to results found in previous studies assessing the effect of prandial or spontaneous glycaemic changes on FHR parameters with the use of two or three capillary glucose measurements during 1 hour FHR monitoring[11,14]. In studies failing to demonstrate any changes the primary objective was not to study the effect of maternal glycaemia on FHR parameters, but to investigate deviations from normality of FHR parameters regardless of maternal glucose level[8,12]. Finally, poor fetal toleration with tachycardia and late decelerations has been described during extreme hyperglycaemia with maternal ketoacidosis, but was not found in our study group[25,26].

This is the first study presenting data derived from simultaneous and continuous maternal glucose and FHR monitoring. Previous studies have shown that in pregnant women with diabetes glucose values vary largely over the day with hyper- or hypoglycaemia occurring during prolonged periods and/or reaching extreme values[15]. Therefore, combining FHR and glucose monitoring techniques enables clinicians to assess fetal compensatory behaviour during such spontaneous glucose excursions. Although the median percentage of time spent in euglycaemia was only 58%, the number of extreme fluctuations into the hypo- or hyperglycaemic range was limited in this study. Therefore, the interpretation of our results remains restricted to the effect of mild glycaemic excursions on FHR.

This study was initiated because of the spontaneous remark of some women with type-1 diabetes to one of us (G.H.A.V.) over the years, that they did not feel the baby moving anymore in case of high glucose values. This seems plausible given the relationship between increased fetal glucose and low pH as has been found at cordocentesis[5]. High glucose values and placental immaturity with increased distance between maternal intervillous space and placental capillaries, as has been found in case of maternal diabetes[27,28] may hamper oxygen diffusion and result in lactate accumulation/acidosis. 'Sudden' fetal death in case of type-1 diabetes occurs in 1-2 percent of cases[1-4], so our study may have lacked the power to identify cases at risk. However, it seems a good habit to ask women about fetal movements in relation to their glucose values.

In conclusion, this study confirms a relationship between maternal glucose and FHR as present during hyperglycaemia. Since FHR values during hyperglycaemia remain within levels of normality, these findings are probably a physiological response rather than pathological. Further studies, assessing fetal behaviour during extreme hyperglycaemia, need to consolidate whether simultaneous and continuous monitoring of glucose and FHR can help in the recognition of the fetus increased risk of deterioration.

Reference List

1. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004 04/17;328(1468-5833; 7445):915.
2. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006 Jul 22;333(7560):177.
3. Penney GC, Mair G, Pearson DW, Scottish Diabetes in Pregnancy Group. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. BJOG 2003 Mar;110(3):315-318.
4. Jensen DM, Damm P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004 Dec;27(12):2819-2823.
5. Salvesen DR, Freeman J, Brudenell JM, Nicolaides KH. Prediction of fetal acidaemia in pregnancies complicated by maternal diabetes mellitus by biophysical profile scoring and fetal heart rate monitoring. Br.J.Obstet.Gynaecol. 1993 Mar;100(3):227-233.
6. Lauenborg J, Mathiesen E, Ovesen P, Westergaard JG, Ekbom P, Molsted-Pedersen L, et al. Audit on stillbirths in women with pregestational type 1 diabetes. Diabetes Care 2003 May;26(5):1385-1389.
7. Landon MB, Gabbe SG. Fetal surveillance and timing of delivery in pregnancy complicated by diabetes mellitus. Obstet.Gynecol.Clin.North Am. 1996 Mar;23(1):109-123.
8. Tincello D, White S, Walkinshaw S. Computerised analysis of fetal heart rate recordings in maternal type I diabetes mellitus. BJOG 2001 Aug;108(8):853-857.
9. Kontopoulos EV, Vintzileos AM. Condition-specific antepartum fetal testing. Am.J.Obstet.Gynecol. 2004 Nov;191(5):1546-1551.
10. Kariniemi V, Forss M, Siegberg R, Ammala P. Reduced short-term variability of fetal heart rate in association with maternal hyperglycemia during pregnancy in insulin-dependent diabetic women. Am.J.Obstet.Gynecol. 1983 Dec 1;147(7):793-794.
11. Costa VN, Nomura RM, Reynolds KS, Miyadahira S, Zugaib M. Effects of maternal glycemia on fetal heart rate in pregnancies complicated by pregestational diabetes mellitus. Eur.J.Obstet.Gynecol.Reprod.Biol. 2009 Mar;143(1):14-17.
12. Devoe LD, Youssef AA, Castillo RA, Croom CS. Fetal biophysical activities in third-trimester pregnancies complicated by diabetes mellitus. Am.J.Obstet.Gynecol. 1994 Aug;171(2):298-303; discussion 303-5.
13. Reece EA, Hagay Z, Roberts AB, DeGennaro N, Homko CJ, Connolly-Diamond M, et al. Fetal Doppler and behavioral responses during hypoglycemia induced with the insulin clamp technique in pregnant diabetic women. Am.J.Obstet.Gynecol. 1995 Jan;172(1 Pt 1):151-155.

14. Serra-Serra V, Camara R, Sarrion P, Jareno M, Cervera J, Bellver J, et al. Effects of prandial glycemic changes on objective fetal heart rate parameters. Acta Obstet.Gynecol.Scand. 2000 Nov;79(11):953-957.
15. Kerssen A, de Valk HW, Visser GH. Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. BJOG 2004 09;111(1470-0328; 9):919-924.
16. Graatsma EM, Jacod B, van Egmond L, Mulder E, Visser G. Fetal electrocardiography: feasibility of long-term fetal heart rate recordings. BJOG 2008 05/18;2008(1471-0528).
17. Dawes GS. Computerised analysis of the fetal heart rate. Eur.J.Obstet.Gynecol.Reprod.Biol. 1991 Dec;42 Suppl:S5-8.
18. Nijhuis IJ, Ten Hof J, Mulder EJ, Nijhuis JG, Narayan H, Taylor DJ, et al. Fetal heart rate in relation to its variation in normal and growth retarded fetuses. Eur.J.Obstet.Gynecol.Reprod.Biol. 2000 03;89(0301-2115; 1):27-33.
19. Serra V, Bellver J, Moulden M, Redman CW. Computerized analysis of normal fetal heart rate pattern throughout gestation. Ultrasound Obstet.Gynecol. 2009 Jul;34(1):74-79.
20. Kerssen A, de Valk HW, Visser GH. The Continuous Glucose Monitoring System during pregnancy of women with type 1 diabetes mellitus: accuracy assessment. Diabetes Technol.Ther. 2004 10;6(1520-9156; 5):645-651.
21. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). J.Pediatr.Endocrinol.Metab. 1999;12 Suppl 3:751-758.
22. Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. New Dutch reference curves for birthweight by gestational age. Early Hum.Dev. 2009 Dec;85(12):737-744.
23. Holden KP, Jovanovic L, Druzin ML, Peterson CM. Increased fetal activity with low maternal blood glucose levels in pregnancies complicated by diabetes. Am.J.Perinatol. 1984 Jan;1(2):161-164.
24. Persson B, Hanson U. Insulin dependent diabetes in pregnancy: impact of maternal blood glucose control on the offspring. J.Paediatr.Child Health 1993 Feb;29(1):20-23.
25. Hughes AB. Fetal heart rate changes during diabetic ketosis. Acta Obstet.Gynecol.Scand. 1987;66(1):71-73.
26. LoBue C, Goodlin RC. Treatment of fetal distress during diabetic keto-acidosis. J.Reprod.Med. 1978 Feb;20(2):101-104.
27. Evers IM, Nikkels PG, Sikkema JM, Visser GH. Placental pathology in women with type 1 diabetes and in a control group with normal and large-for-gestational-age infants. Placenta 2003 09;24(0143-4004; 8-9):819-825.
28. Laurini RN, Visser GH, van Ballegooie E. Morphological fetoplacental abnormalities despite well-controlled diabetic pregnancy. Lancet 1984 04/07;1(0140-6736; 8380):800.

Chapter 7

A validation of electrohysterography for uterine activity monitoring during labour

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A validation of electrohysterography for uterine activity monitoring during labour

Abstract

Objectives Validation of electrohysterography (EHG) as a method for uterine activity monitoring during labour by comparing with intra-uterine pressure catheter (IUPC) recordings.

Study design Thirty two women in labour participated in a prospective observational study and performed simultaneous recordings of uterine activity with EHG and IUPC for at least 30 minutes.

Main outcome measures Number of uterine contractions detected by both EHG and IUPC (sensitivity). Number of contractions detected by EHG only (positive predictive value (PPV)). Correlation between contraction amplitude and duration measured by EHG and IUPC.

Results EHG detects uterine contractions accurately: sensitivity=94.5% (95%CI: 87.5–100), PPV=88.3% (95%CI: 76.2–100). The correlation of contractions' duration and amplitude between both methods is r=0.31 (95%CI: 0.23–0.39) and r=0.45 (95%CI: 0.38–0.52), respectively.

Conclusions EHG detects uterine contractions accurately during labour but the contraction's characteristics it measures are not directly comparable with that of IUPC.

Introduction

Recording uterine activity is a standard component of obstetric care during labour. It informs on the adequacy of uterine activity and is therefore essential to assess progress of labour. It also gives information on fetal condition when combined with fetal heart rate recording. The two methods currently used, external tocodynamometry or internal monitoring using intra-uterine pressure catheters (IUPC) have disadvantages. Tocodynamometry is non-invasive and easy to use but its recording quality depends on correct positioning of the sensor on the maternal abdomen and is influenced by maternal movements and BMI[1-3]. Intra-uterine pressure catheters are invasive and have been associated in rare cases with intra-uterine infection, uterus perforation and placental abruption[1,4]. The search for an alternative has led to the investigation of methods measuring the uterus' electrical activity. This approach, denoted either uterine electromyography (uterine EMG) or electrohysterography (EHG) has been known for more than fifty years[5-7]. It is experiencing a renewed surge of interest recently thanks to technical improvements and because of indications that it could be able to discriminate between efficient and inefficient contractions. This distinction is particularly relevant in the context of threatened preterm labour[8-13].

Although promising results have been obtained on this issue, EHG is a method that is still under development. Studies focusing on signal analysis have shown that the EHG signal could be made to agree with IUPC measurements using algorithms of varying complexity[14-18]. Only few studies, however, have compared the performance of EHG to other methods of uterine activity monitoring under conditions representative of clinical practice[9,19]. The objective of the current study is to further consolidate the validation of EHG by comparing it with the method of reference, IUPC, in clinical practice.

Methods

Population

Thirty two women at term (gestational age ≥37 weeks and <42weeks) admitted to the labour ward of the University Medical Centre, Utrecht, the Netherlands, for whom use of an IUPC was considered necessary following the local obstetrical protocol (induction of labour or labour augmentation). The study was approved by the institutional medical ethical committee.

Uterine activity registration

Once informed consent had been obtained, the five electrodes of the EHG apparatus (AN24 Maternal Heart rate/Fetal Heart Rate/EHG recorder, Monica Healthcare, Nottingham, UK) were positioned on the abdomen: two electrodes along the midline (at the side of the uterine fundus and above the symphysis), one on each side of the uterus and the ground electrode on the left flank. Skin impedance was reduced before placing the electrodes using abrading paper at the electrode placement site. Skin impedance was below 5 kΩ in all recordings. Data were analysed off line after computer download. The aim was to register EHG and IUPC simultaneously for at least 30 minutes, although participants were free to stop prematurely or prolong the EHG registration.

Processing EHG signal

The original raw electrophysiological signal from one pair of electrodes was processed to extract the EHG signal contained in one low frequency band (0.1 – 0.9 Hz) and subsequently filtered using a low-pass filter (0.01Hz) to provide an envelope of the signal comparable with the IUPC recording. This process is illustrated in Figure 1.

Contraction detection

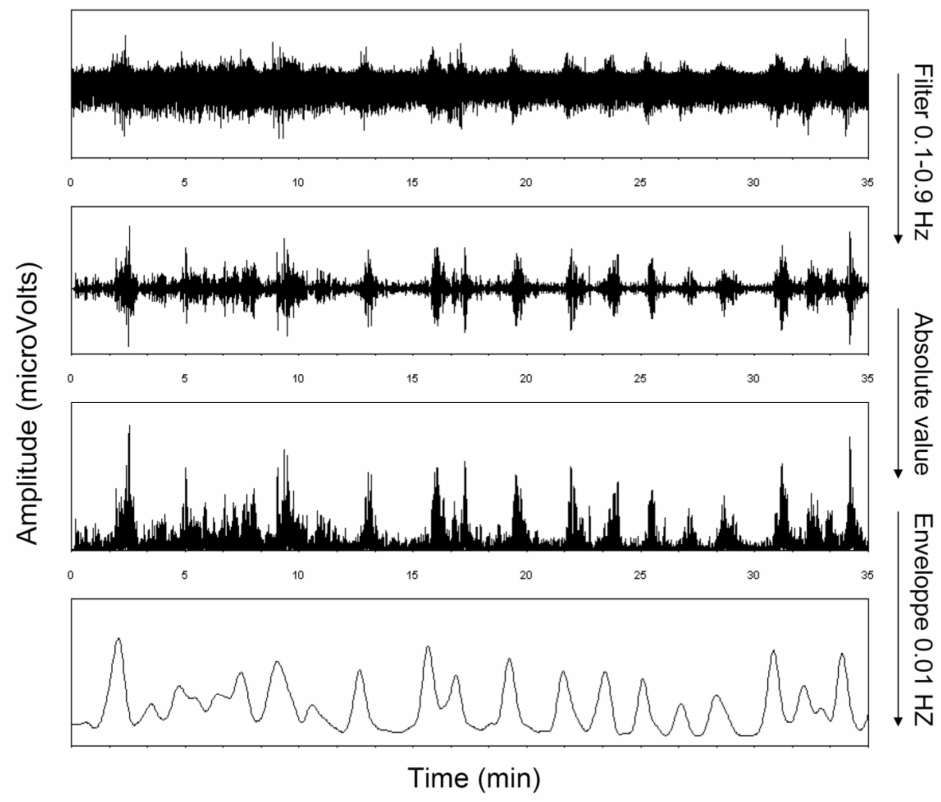
Contractions were identified from both IUPC and EHG signals automatically using a simple algorithm. The algorithm identifies all maxima in the signal as potentially representing the top of a contraction. It discards maxima with an amplitude smaller than 5 mmHg (IUPC) or 10 microvolts (EHG) and those maxima much lower than others in the vicinity. The exact criteria being that a maximum should be higher than 3/4th of the standard deviation in the variation of amplitude of 7 consecutive maxima. The remaining maxima represent uterine contractions. Their amplitude is given by the value of the maximum and their duration by 3/4th of the time between the two minima flanking the contraction peak. Contractions measured with EHG were considered to be matching those measured by IUPC if the peak of the EHG contraction was found within the duration of the IUPC contraction.

Statistics
Statistical analyses were performed using SPSS 15.0 and OpenEpi 2.2. Correlation coefficients are calculated using Spearman's two tailed test. Confidence intervals on means are calculated using a two-tailed t-test. Confidence intervals on medians are calculated by normal approximation method of large sample size theory.

Results
Characteristics of the 32 women participating in the study and of the uterine activity recordings are shown in Table 1. The median recording time was 66.5 minutes (inter-quartile range (IQR) 51.6-78) with a median of 23 contractions per recording (IQR 18-30). Slightly more than half of the recordings, 53%, were performed during the latent phase of the first stage of labour defined as a cervical dilation ≤4cm during the recording.

Contraction detection
Figure 2 shows the number of contractions measured by both methods in each recording. Overall, EHG shows a tendency to overestimate the number of contractions compared to IUPC. The proportion of contractions that are detected by both methods (sensitivity: number of contractions detected by both methods divided by the number of contractions detected by IUPC) and the proportion of contractions that are detected by EHG alone (positive predictive value (PPV): number of contractions detected by both methods divided by the number of contractions detected by EHG) are shown in Figure 3. In most recordings, a high value of both sensitivity and PPV was found, sensitivity being usually higher than PPV. Both values were correlated ($r=0.51$, $p<0.01$). The median of the sensitivity and PPV, calculated by pooling the means obtained for each recording using equal weight, irrespective of recording duration or number of contractions, were 94.5% (95%CI: 87.5–100) and 88.3% (95%CI: 76.2–100), respectively.

Figure 1: Illustration of the different step of signal processing applied to the raw electrophysiological signal. Top: raw signal. Second from top: signal after filtering (0.1 -0.9 Hz) to extract uterine activity information. Third from top: absolute values of filtered signal. Bottom: Filtering with low-pass 0.01Hz filter to obtain the envelope for comparison with IUPC signal.



Contraction amplitude and duration

The amplitude and duration of the contractions detected by both EHG and IUPC were compared. Note that the amplitude of the contractions can not be compared directly as one measures pressure (mmHg) with IUPC compared to electrical activity (µV) with EHG. A correlation coefficient was calculated in each recording by comparing the amplitude obtained by both methods in paired contractions. The results are plotted in Figure 4 as a function of the sensitivity obtained in each recording. The value of the correlation coefficient varied widely, from below 0.1 to 0.8. It is correlated to the sensitivity ($r=0.46$, $p<0.01$). Overall, the mean correlation coefficient for amplitude obtained by pooling the results obtained for each recording was 0.45 (95%CI: 0.38–0.52).

A similar approach was used to calculate the correlation coefficient for contraction duration between both methods (Figure 5). There also, the values of the correlation

coefficient varied widely and were correlated to the sensitivity, albeit, less strongly ($r=0.38$, $p<0.05$). The mean correlation coefficient for duration was 0.31 (95%CI: 0.23–0.39). In addition, the agreement between both methods was evaluated by calculating the mean difference in contraction duration for each recording and comparing it to the mean duration of contractions for that recording. The mean difference is calculated by taking the mean of the absolute values of the difference in duration in each pair of contractions in the recording. This data is shown in Figure 6. The agreement between both methods was best for contractions of short duration but became poorer when contractions lasted longer. Overall the mean difference in contraction duration represented 27.3% (95%CI: 22.6-32.1) of the mean contraction duration.
All results are summarized in Table 2. We performed statistical analyses to identify factors influencing the agreement between EHG and IUPC. Age and BMI of the patients were not correlated to sensitivity, PPV, or correlation coefficients for amplitude or duration of contractions. Furthermore, we did not find significant differences in the proportion of recordings with a sensitivity or PPV above 90% or correlation coefficients above 0.5 between nullipara and multipara, between induction and augmentation of labour and between recordings performed before or after 5cm of cervical dilation. We could not identify, based on this limited set of data, the conditions for which agreement between EHG and IUPC can be expected to be poor. On the other hand, the fact that the agreement between IUPC and EHG does not seem to depend on BMI is an important finding given the rise of obesity in western countries and confirms previous reports[19].

Table 1: Characteristics of the study population and of the uterine activity recordings.

Study population, N=32	
Age (mean (SD))	31.2 (5.4)
BMI (kg/m^2) (mean (SD))	27.2 (6.0)
Nullipara (%)	46.9
Indication for IUPC (%)	
Induction of labour	13 (40.6)
Augmentation of labour	17 (53.1)
Epidural anaesthesia	2 (6.3)
Cervical dilation ≤4cm during the recording (%)	53.1
Duration of recordings (min) [median (IQR)]	66.5 (51.6 – 78.0)
Nbr of contractions per recording [median (IQR)]	23 (18 – 30)

Abbreviation: IQR, inter quartile range

Table 2: Results.

	Median* or mean (95% CI)	IQR or SD
Sensitivity (%)	94.5* (87.5 - 100)	86.8-100
Positive predictive value (%)	88.3* (76.2 - 100)	75.9 - 100
Correlation coefficient for the contractions' amplitude, r(a)	0.45 (0.38 - 0.52)	0.2
Correlation coefficient for the contractions' duration, r(d)	0.31 (0.23 - 0.39)	0.21
Normalized mean difference in contration duration (%)	27.3 (22.6 - 32.1)	13.1

Figure 2: Number of contractions measured by EHG and IUPC for each recording. Grey circles indicate two recordings with an identical number of contractions.

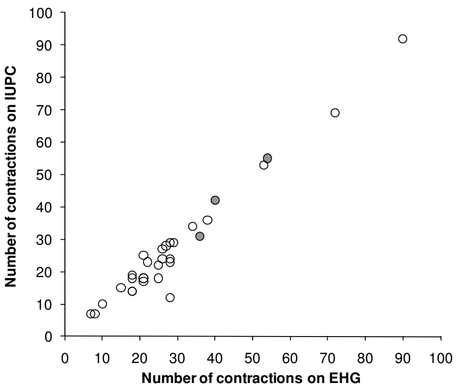


Figure 3: Sensitivity and positive predictive value obtained for each recording. Grey and black circle indicates two and five recordings with identical values, respectively.

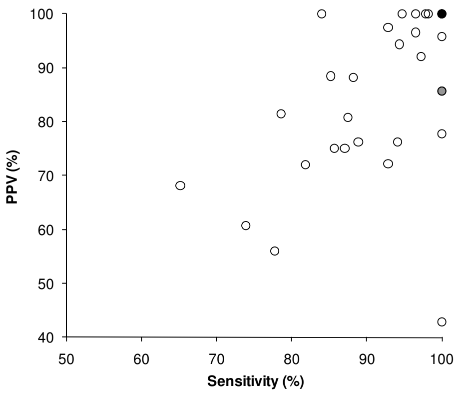


Figure 4: Correlation coefficient of the contractions' amplitude between EHG and IUPC for each recording plotted as a function of the sensitivity obtained in that recording. The grey circle indicates 2 recordings with the same values.

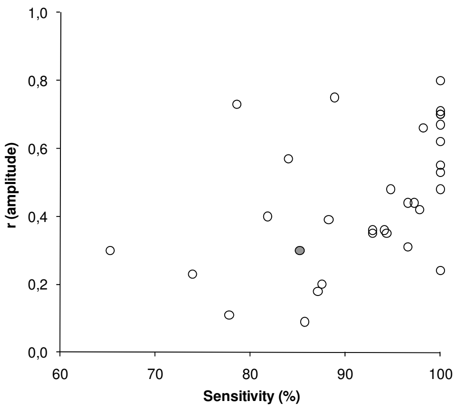


Figure 5: Correlation coefficient of the contractions' duration between EHG and IUPC for each recording plotted as a function of the sensitivity obtained in that recording. The grey circle indicates 2 recordings with the same values.

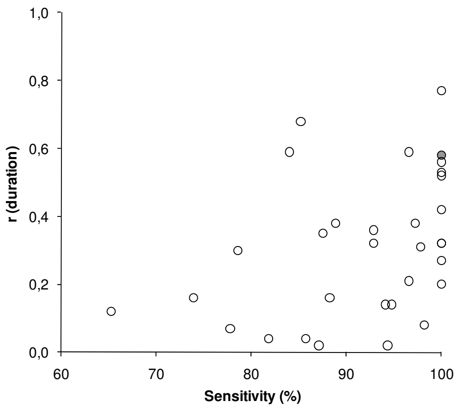
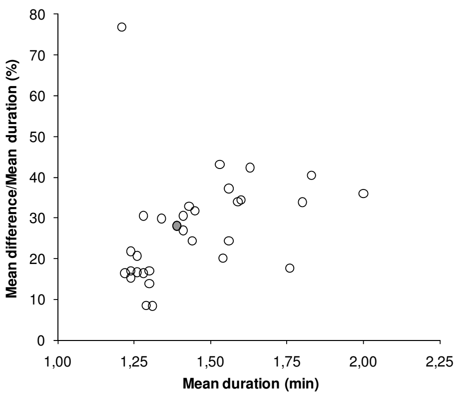


Figure 6: Agreement between EHG and IUPC in terms of contraction duration. The mean difference between contraction duration normalized on the mean duration of the contractions is plotted for each recording as a function of the mean duration of the contractions in this recording. The grey circle indicates 2 recordings with the same values.



Discussion

Our study shows that EHG detects uterine contractions accurately during labour but that the correlation between the two methods regarding contraction's characteristics (amplitude and duration) is moderate.

The high rate of concordance between EHG and IUPC concerning the occurrence of uterine contractions found in the current study confirms results published previously in a smaller study[19]. The sensitivity and PPV values found in that study were 97.2% and 90.6%, respectively. This is slightly higher than the findings in our cohort. However, the values in that study were calculated by pooling the contractions of all registrations together. This means that a long registration with very good agreement could influence the overall results. Our study shows that EHG can detect most of the contractions that an IUPC would detect and "adds" a small number of bursts of uterine electrical activity that do not seem to lead to an increase in intra-uterine pressure. This is due either to the existence of bursts of electrical activity in the uterus that are not coordinated enough to give rise to a contraction, or to noise from, for instance, abdominal muscles being mistaken for a uterine contraction. The latter hypothesis seems more likely given the fact that sensitivity and PPV are correlated. In other words, there are relatively few extra contractions in those recordings of good quality where a large proportion of the IUPC contractions are detected by EHG. Overall, EHG shows the tendency to detect a slightly higher number of contractions than IUPC.

The comparison of contractions' amplitude measured by both methods is difficult because of the different nature of the signal measured. Electrohysterography monitors the process by which contractions are formed while intra-uterine pressure catheters measure the end result of that process. Intra-uterine pressure, for instance, depends strongly on the synchronisation of myometrial activity. Only synchronized contractions will lead to high intrauterine pressures. On the other hand, even unsynchronized contractions from myometrial cells can be associated with a high total electrical energy and therefore high readings with EHG. Moreover, the absolute value of the electrical signal does not have to be linearly related to intra-uterine pressure but may contain a non-linear component. One study has reported a good correlation between the total energy of a burst and intra-uterine pressure (r=0.762, p=0.002)[9]. This is not confirmed by our study although we only considered the maximum amplitude and not the total energy. However, an additional analysis using the product of the maximum amplitude and contraction duration as a surrogate for the total energy did not improve the correlation coefficient.

Similarly, there is no compelling reason to consider that the duration of the depolarization phase in the uterus should directly be related to the duration of its effect in terms of intra-uterine pressure. Uterine activity might start or end with a period of unsynchronized depolarisation which would not lead to a rise in intra-uterine pressure but be recorded by EHG. Long IUPC contractions are likely to represent merging double contractions. The electrical activity of the uterus might not show the same sustained character. The increasing lack of agreement between IUPC and EHG with increasing contraction's duration found in the current study supports this view. Our findings do not agree with that of Euliano et al.[19] who reported that "contraction lengths closely approximated those calculated from the intra-uterine pressure catheter signal". It is, however, difficult to compare their analysis with ours given the fact that they pooled the results of all contractions while we considered each recording separately.

Overall, the correlation found between EHG and IUPC is nevertheless comparable or slightly better than that found between IUPC and external tocodynamometry. Miles et al.[2] reported a correlation coefficient of only 0.26 for the contraction amplitude and 0.27 for the contraction duration while there the physiological basis of the measurement methods are more similar.

Electrohysterography has been studied for more than 50 years but there is still no uniform way of acquiring and processing the electrical signal coming from the uterus. This lack of uniformity and the varying definitions for uterine contractions form a limitation of any study aiming to validate the method, the present one included. We have tried to limit the influence of having had to define our own set of criteria by applying them consistently to EHG as well as to IUPC recordings. In addition, the method has been tested under conditions representative of common clinical practice with prolonged recording time at each stage of labour. Bearing these limitations in mind, the agreement between the detection rate found in the current study and the only other study comparable in design, is noteworthy[19].

The method now seems accurate enough for one to be confident that the EHG signal represents uterine activity. One should bear in mind, though, that signals of different nature are measured compared to the usual uterine monitoring techniques and that EHG is not a direct alternative. The access it provides to the basis of uterine activity, instead of being a limitation of the method, could, however, be one of its main advantages. The recent studies published on the characterization of preterm contractions are an example thereof [8-11,13,20,21]: they have shown that information contained in the power spectrum of contractions could indicate a difference in the quality of contractions leading to early delivery compared to those that do not. Additionally, EHG also opens the possibility to follow the build-up of contractions spatially[22,23]. The current study contributes to establish the validity of this promising method and forms a basis from which more studies along the directions outlined above can be performed.

Aknowledgements

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Reference List

1. Vanner T, Gardosi J. Intrapartum assessment of uterine activity. Baillieres Clin Obstet Gynaecol 1996; Jun;10(2):243-57.
2. Miles AM, Monga M, Richeson KS. Correlation of external and internal monitoring of uterine activity in a cohort of term patients. Am J Perinatol 2001; May;18(3):137-40.
3. Bakker PC, Zikkenheimer M, van Geijn HP. The quality of intrapartum uterine activity monitoring. J Perinat Med 2008;36(3):197-201.
4. Bakker PC, van Geijn HP. Uterine activity: implications for the condition of the fetus. J Perinat Med 2008;36(1):30-7.
5. Steer CM, Hertsch GJ. Electrical activity of the human uterus in labor; the electrohysterograph. Am J Obstet Gynecol 1950; Jan;59(1):25-40.
6. Wolfs GM, van Leeuwen M. Electromyographic observations on the human uterus during labour. Acta Obstet Gynecol Scand Suppl 1979;90:1-61.
7. Devedeux D, Marque C, Mansour S, Germain G, Duchene J. Uterine electromyography: a critical review. Am J Obstet Gynecol 1993; Dec;169(6):1636-53.
8. Maner WL, Garfield RE. Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. Ann Biomed Eng 2007; Mar;35(3):465-73.
9. Maul H, Maner WL, Olson G, Saade GR, Garfield RE. Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery. J Matern Fetal Neonatal Med 2004; May;15(5):297-301.
10. Garfield RE, Maner WL. Physiology and electrical activity of uterine contractions. Semin Cell Dev Biol 2007; Jun;18(3):289-95.
11. Garfield RE, Maner WL, MacKay LB, Schlembach D, Saade GR. Comparing uterine electromyography activity of antepartum patients versus term labor patients. Am J Obstet Gynecol 2005; Jul;193(1):23-9.
12. Garfield RE, Maner WL, Maul H, Saade GR. Use of uterine EMG and cervical LIF in monitoring pregnant patients. BJOG 2005; Mar;112 Suppl 1:103-8.
13. Maner WL, Garfield RE, Maul H, Olson G, Saade G. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet Gynecol 2003; Jun;101(6):1254-60.
14. Maner WL, MacKay LB, Saade GR, Garfield RE. Characterization of abdominally acquired uterine electrical signals in humans, using a non-linear analytic method. Med Biol Eng Comput 2006; Mar;44(1-2):117-23.

15. Jezewski J, Horoba K, Matonia A, Wrobel J. Quantitative analysis of contraction patterns in electrical activity signal of pregnant uterus as an alternative to mechanical approach. Physiol Meas 2005; Oct;26(5):753-67.
16. Skowronski MD, Harris JG, Marossero DE, Edwards RK, Euliano TY. Prediction of intrauterine pressure from electrohysterography using optimal linear filtering. IEEE Trans Biomed Eng 2006; Oct;53(10):1983-9.
17. Euliano T, Skowronski M, Marossero D, Shuster J, Edwards R. Prediction of intrauterine pressure waveform from transabdominal electrohysterography. J Matern Fetal Neonatal Med 2006; Dec;19(12):811-6.
18. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW. Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. Physiol Meas 2008; Jul;29(7):829-41.
19. Euliano TY, Nguyen MT, Marossero D, Edwards RK. Monitoring contractions in obese parturients: electrohysterography compared with traditional monitoring. Obstet Gynecol 2007; May;109(5):1136-40.
20. Verdenik I, Pajntar M, Leskosek B. Uterine electrical activity as predictor of preterm birth in women with preterm contractions. Eur J Obstet Gynecol Reprod Biol 2001; Apr;95(2):149-53.
21. Marque CK, Terrien J, Rihana S, Germain G. Preterm labour detection by use of a biophysical marker: the uterine electrical activity. BMC Pregnancy Childbirth 2007; Jun 1;7 Suppl 1:S5.
22. Rabotti C, Mischi M, van Laar J, Oei G, Bergmans J. Electrohysterographic analysis of uterine contraction propagation with labor progression: a preliminary study. Conf Proc IEEE Eng Med Biol Soc 2007;2007:4135-8.
23. Jiang W, Li G, Lin L. Uterine electromyogram topography to represent synchronization of uterine contractions. Int J Gynaecol Obstet 2007; May;97(2):120-4.

Chapter 8

Towards the understanding of labour arrest using non-invasive electrohysterography

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Preliminary report

Towards the understanding of labour arrest using non-invasive electrohysterography

Abstract

Background Approximately 50% of caesarean sections (CS) in nulliparous women at term are performed because of arrest of labour despite augmentation and continuous monitoring of uterine activity.

Objectives To study uterine activity in the course of normal dilation using abdominal electrohysterography (EHG) and to investigate if this technique may help to understand the aetiology of labour arrest in nulliparous women.

Methods Prospective multi-centre observational study. Uterine activity during (induced or spontaneous) labour was measured using EHG in nulliparous women with singleton pregnancies in cephalic position at term (≥ 37 weeks). Progress of labour was monitored using standard cervical examination from admission to delivery. Electrical activity of the myometrium during contractions was characterized by its power density spectrum (PDS). Peak frequencies (PF) of the PDS observed in women undergoing CS for failure to progress were compared with PF in women reaching full cervical dilation using a matched case-control analysis.

Results A total of 95 EHG-recordings were made, of which 50 were performed during spontaneous labour and 45 in induced labour. In both groups the peak frequency increased significantly with increasing cervical dilation. CS was performed in 19 women because of arrest of labour (10 in spontaneous and 9 in induced labour). The peak frequency was higher (borderline significant) in women with CS for first stage labour arrest compared to women reaching full cervical dilation (OR 1.75; 95%CI [0.97 – 3.16]). This effect was present in spontaneous labour but not in induced labour.

Conclusions Labour arrest showed a trend towards an association with abnormal myometrial depolarization patterns in spontaneous term labour. In induced labour this effect was not observed.

Introduction

The rate of caesarean sections (CS) has increased significantly in all western countries over the past 20 years[1-4]. Low risk nulliparous women, i.e. women with a term singleton fetus in cephalic presentation, account for a large part to this rise[5], with labour arrest as the leading indication for intervention[6]. Causes of the rise in CS rate are diverse including an increase in induced labours, rising maternal age and prepregnancy weight and changing attitudes towards obstetric risk management and liability[3,7,8]. Ultimately, in CS performed for first stage labour arrest these risk factors often result in dysfunctional uterine contractility. Understanding of the biological or pathological pathways leading to dysfunctional contractility is still mostly lacking. There have been several relatively small studies coupling in-vitro analysis of myometrium contractility to either maternal age or myometrial pH levels[7,9]. These studies provide interesting insights in what might cause dysfunctional contractions. They are, however, limited by the difficulty to translate specific laboratory conditions into conditions during labour, and more importantly the impossibility to consider the uterus as a whole. Nevertheless, they do show that an understanding of uterine dysfunctionality might be achieved by focusing on its contractility. Non-invasive electromyography of the uterus' activity, i.e. electrohysterography (EHG) provides the possibility of an in-vivo analysis[10-13]. Seemingly chaotic electrical activity caused by myocyte depolarisations can be analysed by several methods. Most commonly used until now is the power density spectrum (PDS) which enables to identify the frequency at which most of the myocytes depolarize[14]. In preterm labour there are indications that PDS analysis of the EHG may help in the recognition of true labour[15]. In term labour it is not the recognition of the onset of labour, but the differentiation between progression of labour and labour arrest that is essential to improve pregnancy outcome and reduce obstetric interventions.

It was the aim of this study to investigate whether non-invasive monitoring of uterine activity using electrohysterography may help to differentiate between dysfunctional labour and normal labour in nulliparous women.

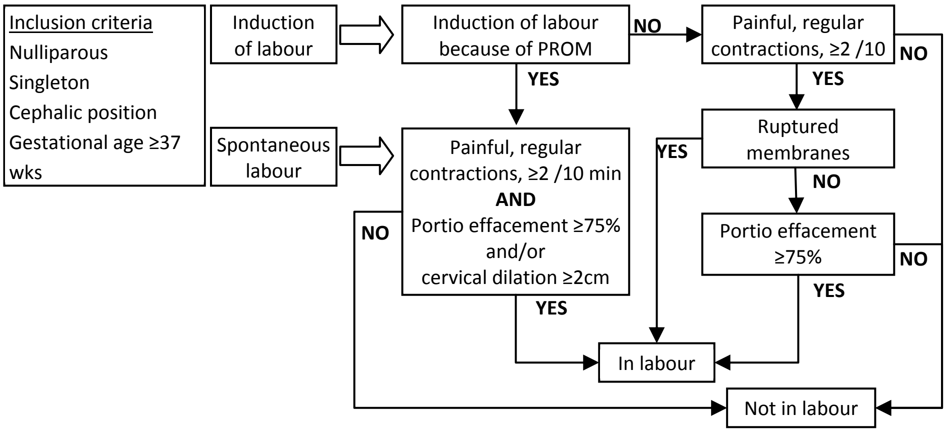
Methods

Study design and population

A prospective multi-center observational study was conducted in The Netherlands from December 2009 to May 2010. The study was approved by the institutional medical ethical committees of the participating hospitals.

Inclusion criteria involved nulliparous women with singleton term fetus in cephalic position (gestational age ≥ 37 weeks) admitted to the labour ward for spontaneous or induced labour (Figure 1). Exclusion criteria were suspected congenital or chromosomal abnormalities. After informed consent was obtained, measurements of uterine activity were performed using the electrohysterogram (EHG) as recorded non-invasively from the maternal abdominal surface. EHG-recordings started from the onset of labour or during the first stage of labour upon arrival at the labour ward, until delivery. Progress of labour was monitored by digital cervical examinations. According to clinical protocol regulations, cervical examination was performed at least every two hours or more frequently when indicated. Maternal characteristics, labour characteristics, and neonatal characteristics were collected from the patients' charts.

Figure 1: Flowchart for the diagnosis of (spontaneous or induced) labour.



Monitoring of uterine activity

Uterine activity was monitored using the portable AN24 Maternal Heart Rate/Fetal Heart Rate/EHG recorder (AN24, Monica Healthcare Ltd. Nottingham, UK) through five disposable electrodes that were positioned on the maternal abdomen in a standardized manner[13]. The raw abdominal electromyogram was recorded at 300 Hz and filtered in the 0.1 – 1 Hz bandwidth to obtain the EHG. The algorithm for the identification of contractions and validation of the method has been described previously in detail[13]. Power density spectral (PDS) analysis was performed to calculate the peak frequency for each contraction using Scilab and Visual C++. The signal processing steps are illustrated in Figure 2.

Figure 2: EHG signal processing steps

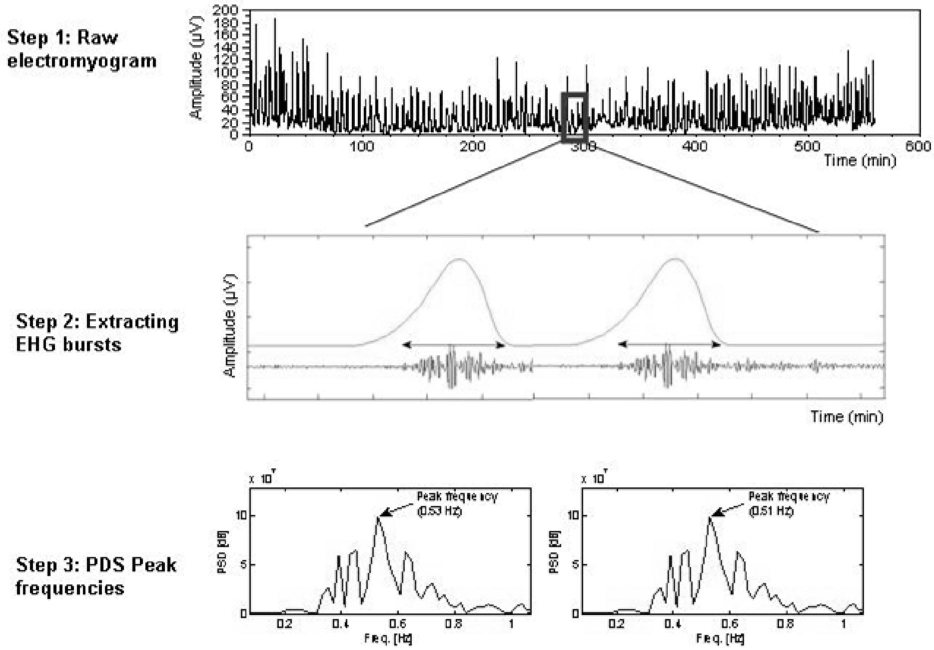


Figure legend: Step 1: Raw electromyogram from onset of labour until delivery as recorded from the maternal abdomen during labour. Step 2: EHG extraction; Upper line indicates uterine activity; Lower line represents an electrical burst/contraction. Step 3: For each burst/contraction the peak frequency is calculated with PDS analysis.

Statistical analysis

A matched case-control analysis was performed separately for spontaneous and induced labour. Cases were defined as women with a caesarean section for first stage labour arrest, whereas controls were women who had reached full cervical dilation Their mode of delivery was either vaginal, instrumental (vacuum - or forcipal extraction), or CS for second stage labour arrest. Two physicians (M.G., B.V.) independently reviewed each woman's chart to ensure that for cases CS was performed only for first stage labour arrest and not for other confounding reasons such as fetal distress. Each case was matched with 4 controls within +/- 1 cm of the maximal achieved cervical dilation prior to CS. Intravenous oxytocin was administered following local protocol for labour induction; some women in the spontaneous subgroup also received oxytocin for labour augmentation.

The main explanatory outcome was the peak frequency (PF) as calculated from PDS analysis of the EHG. The PF of each contraction was coupled to labour progression as determined by cervical examination performed by midwives and obstetricians. For example, if a CS for first stage labour arrest was performed at approximately 5-6 cm cervical dilation, the peak frequencies of all contractions between the maximal reached cervical dilation minus 1 (5 - 1 = 4 cm) until the CS were assessed and compared to the peak frequency of controls between -1cm and +1cm cervical dilation (for this example the PF's of contractions of the control recording from 4-7 cm cervical dilation).

Baseline characteristics of the matched study population were calculated with the use of standard descriptive statistics; medians and ranges (minimum and maximum), unless reported otherwise. The optimal measure of peak frequency (mean-PF, PF-standard deviation, median-PF, and PF-percentiles) was chosen using Receiver Operating Characteristics (ROC) curves. Median PF values and interquartile ranges for five stages of cervical dilation were calculated from all contractions in controls. Median PF per 'stage' of cervical dilation were compared using one way ANOVA with Bonferroni post hoc testing.

A conditional logistic regression model was estimated using the optimal measure of peak frequency and potential confounders (gestational age, maternal age and BMI) to calculate odds ratios (OR) for the occurrence of CS for first stage labour arrest. Potential confounders were added to the model using forward stepwise selection; as a final step the optimal measure of peak frequency was added. Neonatal birth weight was not included as a potential confounder since antenatal birth weight estimations (by ultrasound or manual) have been found to exhibit large variations compared to true birth weight. ORs for the measures of peak frequency are presented for an increase of 0.05 Hz, and ORs for gestational age for an increase of 1 week.

In order to investigate the potential effect of oxytocin within the spontaneous labour subgroup, a separate model was estimated.

Results

A total of nineteen cases with a CS during the first stage, were randomly matched with seventy-six controls (ratio 1:4). Baseline characteristics for matched cases and controls are described in Table 1. In the induced labour subgroup, all cases and nearly all controls received intravenous oxytocin administration, whereas in the spontaneous subgroup 65% of controls received oxytocin and 100% of cases. The indications for induction of labour and/or referral for medically assisted delivery are summarized in Table 2. The mode of delivery in controls and cervical dilation (cm) at CS for labour arrest in cases are displayed in Table 3.

Table 1: Study characteristics of the matched cases and controls. All values displayed as medians, ranges (min-max) or numbers and percentages.

	Spontaneous labour (N = 50)		Labour induction (N = 45)	
	Controls (N = 40)	Cases (N=10)	Controls (N = 36)	Cases (N = 9)
Maternal characteristics				
Maternal age	31 (20-42)	32 (26-37)	32 (23-45)	33 (27-42)
Body Mass Index	27.0 (18.8-32.2)	27.0 (17.7-42,0)	27.9 (19.7-47.5)	31.1 (23.6-37.6)
Gestational age (weeks)	39+6 (37+6 - 41+6)	41+0 (39+3 - 42+2)	39+1 (37+0 - 42+0)	40+5 (38+0 - 42+0)
Labour characteristics				
Labour induction (prostaglandines)	-	-	13/36 (36%)	3/9 (33%)
Labour augmentation (oxytocin)	26/40 (65%)	10/10 (100%)	34/36 (94%)	9/9 (100%)
Epidural analgesia	21/40 (53%)	8/10 (80%)	22/36 (61%)	7/9 (78%)
Neonatal characteristics				
Birth weight (grams)	3500 (2330-4290)	3863 (3400-4460)	3200 (2320-4800)	3820 (2650-4960)

Table 2: Most frequent indication for induction and complications of pregnancy of delivery.

	%	N
Spontaneous labour		
Meconium stained amniotic fluid	10%	5/50
First stage labour arrest	30%	15/50
Epidural analgesia	32%	16/50
Induction of labour		
Meconium stained amniotic fluid	7%	3/45
(Pre)gestational diabetes	11%	5/45
Post term pregnancy	16%	7/45
Hypertensive disorders in pregnancy	27%	12/45

Table 3: Mode of delivery in matched population and cervical dilation at labour arrest in cases.

Mode of delivery in matched population	**Spontaneous N (%)**	**Induction N (%)**
Vaginal	31/50 (62%)	24/45 (54%)
Instrumental	4/50 (8%)	6/45 (13%)
CS second stage arrest	5/50 (10%)	6/45 (13%)
CS first stage arrest	10/50 (20%)	9/45 (20%)

Cervical dilation (cm) at caesarean section in CASES	**Spontaneous N (%)**	**Induction N (%)**
0-2 cm	-	-
2-4 cm	2/10 (20%)	1/9 (11%)
4-6 cm	5/10 (50%)	2/9 (22%)
6-8 cm	2/10 (20%)	3/9 (33%)
8-10 cm	1/10 (10%)	3/9 (33%)

The median peak frequency (median-PF) was selected as optimal value on the basis of the ROC analyses (data not shown). Median and interquartile ranges of the median-PF in spontaneous labour were 0.49 (IQR 0.46-0.53) in controls and 0.55 (IQR 0.47-0.60) in cases, and in induced labour 0.53 (IQR 0.49-0.57) in controls and 0.49 (IQR 0.47-0.57) in cases. The number of contractions, median peak frequency (PF) and interquartile range (IQR) per centimeter cervical dilation as calculated from both spontaneous - and induced labour are displayed in table 4 (uterine characteristics from women receiving CS for arrest of labour were excluded). Compared to spontaneous labour the median PF was generally higher in induced labour. The median PF increased significantly with increasing cervical dilation (spontaneous labour $F(4, 6695) = 18.24$, p-value < 0.001, induced labour $F(4,13019) = 36.6$, p-value <0.001).

Maternal age and BMI did not contribute significantly to the conditional logistic regression models, and were therefore not included. Gestational age was a significant predictor of CS in both the spontaneous (OR=1.12, 95% CI: [1.02 – 1.22]) and induced labour groups (OR=1.09, 95% CI: [1.01 – 1.17]). In spontaneous labour the median-PF was borderline significant (OR=1.75, 95% CI [0.97 – 3.16]), whereas for induction of labour the median-PF was not a significant predictor of CS (OR=0.63, 95% CI [0.32 – 1.24]), see Table 5.

A separate model within the spontaneous subgroup of cases and controls with oxytocin administration for labour augmentation showed inconclusive results due to a small number of cases and controls (data not shown).

Table 4: Number of contractions, median peak frequency (PF, in Hz) and interquartile range (IQR) per centimeter cervical dilation as calculated from uncomplicated spontaneous - and induced labour.

Spontaneous labour				Induction of labour			
Cervial dilation	Number of contractions	Median PF (Hz)	IQR	Cervial dilation	Number of contractions	Median PF (Hz)	IQR
0-2 cm	101	0.45	0.39-0.50	0-2 cm	1126	0.51	0.45-0.57
2-4 cm	924	0.49	0.41-0.59	2-4 cm	3419	0.53	0.45-0.61
4-6 cm	1350	0.49	0.41-0.57	4-6 cm	2548	0.53	0.45-0.59
6-8 cm	1693	0.51	0.43-0.59	6-8 cm	2736	0.53	0.45-0.61
8-10 cm	2632	0.51	0.45-0.59	8-10 cm	3195	0.55	0.47-0.63

Table legend: PF values (in Hz) from all contractions from controls were included in the table. Comparison of the median PF with One way ANOVA demonstrated a significant rise in median PF with increasing cervical dilation in both spontaneous and induced labour ((F4,6695) = 18.24, p <0.001 and (F(4:13019) = 36.6, p <0.001, respectively). Abbreviations:PF, peak frequency; IQR,inter quartile range

Table 5: Results of conditional logistic regression analysis for the prediction of caesarean section.

		OR	95% CI
Spontaneous labour	Gestational age	1.12	(1.02-1.22)
	Median PF	1.75	(0.97-3.16)
Induced labour	Gestational age	1.09	(1.01-1.17)
	Median PF	0.63	(0.32-1.24)

Table legend: Odds ratios for the measures of peak frequency (median PF) are presented for an increase of 0.05 Hz, and OR for gestational age for an increase of 1 week. Abbreviations: OR: odds ratio, PF: peak frequency

Discussion

This article reports preliminary data of the first large scale prospective study using power density spectral analysis of non-invasive EHG to differentiate between normal progression of term labour and first stage labour arrest leading to caesarean section. Our data demonstrate that EHG peak frequencies show a trend towards significance in predicting CS for labour arrest in spontaneous labour, but not in induced labour. This is a novel finding that has not been reported earlier. The fact that the peak frequency of the power spectrum density increases with increasing cervical dilation is in agreement with studies on preterm labour. These studies have shown that a higher PF was predictive of a short recording-delivery interval[14,15]. Similarly, it has been shown that the PF decreases after the administration of tocolytic drugs[16].

Power spectrum analysis of EHG has proven to be particularly useful in quantifying uterine EMG[13,14] and has been demonstrated to differentiate between true and false labour in women with (pre)term contractions[10,14]. We hypothesized that this effect in preterm labour could be translated into a difference between efficient and inefficient contractions in term labour. First stage labour arrest is easy to diagnose with advancing time and regular cervical examinations. Therefore, the added value of EHG does not lie in the diagnosis of the condition but in its potential for understanding its pathophysiological background. It is of interest that none of the current techniques of contraction monitoring have an impact on reducing CS rates[17]. Faced with labour arrest, the obstetrician has limited options. Until now, no augmentation protocol has been proven to be superior. Likewise, active management of labour, a concept including several aspects, from one-to-one nursing to strict definition of labour, has not been shown to decrease the rate of CS significantly[18], apart from the presence of a doula[19].

It is time for a more thorough understanding of the pathophysiology of labour arrest. EHG might help to target different types of intervention in appropriate groups of women in labour. Some women might show good response to early, high dosage oxytocin schemes while others might benefit more from expectant management. In this context it is particularly interesting that a recent study by Quenby discussed that oxytocin, instead of increasing the contraction efficiency, might degrade uterine efficiency by increasing the degree of lactic acidosis present in myometrial cells[9]. Furthermore, similar to our study results, the study by Quenby could only describe significant differences in myometrial pH in spontaneous labour and not in induced labour[9]. This finding suggests that the mechanisms underlying normal or dysfunctional induced labour might be different in case of spontaneous labour onset as compared to induced labour .

One of the strengths of the present study is the homogeneous study population; solely nulliparous women, cervical assessment at set times (every 2 hours, or more when indicated) and standard augmentation protocol was followed. Furthermore diagnosis of labour arrest was confirmed by independent obstetricians to prevent selection bias. There are, however, also several limitations to this study. Due to the small number of cases, we could not match cases on a number of potential confounders (BMI, maternal age, and gestational age) instead these potential confounders were added to logistic regression models according to a stepwise procedure. Furthermore, although several authors performed EHG recordings to study (pre)term labour there is no consensus on the technique to be used for EHG analysis. For identification of the optimal technique for EHG analysis, our data should be reassessed with other available analysis techniques.

The results presented are preliminary data from an ongoing study. Improvement of both the EHG analysis technique and larger numbers of cases might further consolidate the value of EHG monitoring for the identification of labour arrest.

Conclusion

Labour arrest showed a trend towards an association with abnormal myometrial depolarization patterns in spontaneous term labour. In induced labour this effect was absent.

Reference List

1. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: final data for 2005. Natl.Vital Stat.Rep. 2007 Dec 5;56(6):1-103.
2. RCOG. Caesarean sectio. 2008.
3. Kwee A, Elferink-Stinkens PM, Reuwer PJ, Bruinse HW. Trends in obstetric interventions in the Dutch obstetrical care system in the period 1993-2002. Eur.J.Obstet.Gynecol.Reprod.Biol. 2007 May;132(1):70-75.
4. Odlind V, Haglund B, Pakkanen M, Otterblad Olausson P. Deliveries, mothers and newborn infants in Sweden, 1973-2000. Trends in obstetrics as reported to the Swedish Medical Birth Register. Acta Obstet.Gynecol.Scand. 2003 Jun;82(6):516-528.
5. Menacker F. Trends in cesarean rates for first births and repeat cesarean rates for low-risk women: United States, 1990-2003. Natl.Vital Stat.Rep. 2005 Sep 22;54(4):1-8.
6. Gifford DS, Morton SC, Fiske M, Keesey J, Keeler E, Kahn KL. Lack of progress in labor as a reason for cesarean. Obstet.Gynecol. 2000 Apr;95(4):589-595.
7. Smith GC, Cordeaux Y, White IR, Pasupathy D, Missfelder-Lobos H, Pell JP, et al. The effect of delaying childbirth on primary cesarean section rates. PLoS Med. 2008 Jul 1;5(7):e144.
8. Bergholt T, Lim LK, Jorgensen JS, Robson MS. Maternal body mass index in the first trimester and risk of cesarean delivery in nulliparous women in spontaneous labor. Am.J.Obstet.Gynecol. 2007 Feb;196(2):163.e1-163.e5.
9. Quenby S, Pierce SJ, Brigham S, Wray S. Dysfunctional labor and myometrial lactic acidosis. Obstet.Gynecol. 2004 Apr;103(4):718-723.
10. Garfield RE, Chwalisz K, Shi L, Olson G, Saade GR. Instrumentation for the diagnosis of term and preterm labour. J.Perinat.Med. 1998;26(6):413-436.
11. Euliano TY, Nguyen MT, Marossero D, Edwards RK. Monitoring contractions in obese parturients: electrohysterography compared with traditional monitoring. Obstet.Gynecol. 2007 May;109(5):1136-1140.
12. Marque CK, Terrien J, Rihana S, Germain G. Preterm labour detection by use of a biophysical marker: the uterine electrical activity. BMC Pregnancy Childbirth 2007 Jun 1;7 Suppl 1:S5.
13. Jacod BC, Graatsma EM, Van Hagen E, Visser GH. A validation of electrohysterography for uterine activity monitoring during labour. J.Matern.Fetal.Neonatal Med. 2010 Jan;23(1):17-22.
14. Maner WL, Garfield RE, Maul H, Olson G, Saade G. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet.Gynecol. 2003 Jun;101(6):1254-1260.
15. Garfield RE, Maner WL, MacKay LB, Schlembach D, Saade GR. Comparing uterine electromyography activity of antepartum patients versus term labor patients. Am.J.Obstet.Gynecol. 2005 Jul;193(1):23-29.

16. Vinken MP, Rabotti C, Mischi M, van Laar JO, Oei SG. Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice. Obstet.Gynecol.Int. 2010;2010:325635.
17. Bakker JJ, Verhoeven CJ, Janssen PF, van Lith JM, van Oudgaarden ED, Bloemenkamp KW, et al. Outcomes after internal versus external tocodynamometry for monitoring labor. N.Engl.J.Med. 2010 Jan 28;362(4):306-313.
18. Brown HC, Paranjothy S, Dowswell T, Thomas J. Package of care for active management in labour for reducing caesarean section rates in low-risk women. Cochrane Database Syst.Rev. 2008 Oct 8;(4)(4):CD004907.
19. Zhang J, Bernasko JW, Leybovich E, Fahs M, Hatch MC. Continuous labor support from labor attendant for primiparous women: a meta-analysis. Obstet.Gynecol. 1996 Oct;88(4 Pt 2):739-744.

Chapter 9

Summary & general discussion

Summary & general discussion

In this thesis a renewed monitoring technique for fetal heart rate (FHR) and uterine activity has been investigated. Through non-invasive measurements of electrical signals as recorded from the maternal abdomen, both the fetal electrocardiogram (fECG) and uterine electrohysterogram (EHG) can be filtered for calculation of FHR and uterine contractions, respectively. This monitoring technique has been known for over 100 years, however due to technical difficulties clinical implementation has not yet been feasible[1,2]. Recently, thanks to technical improvements, both fECG - and EHG monitoring have experienced a renewed surge of interest. Moreover, the use of fECG - and EHG signals yield more information compared to FHR and uterine activity as acquired with conventional monitoring techniques. For example, the high resolution characteristics of current fECG monitors offers true beat-to-beat FHR, enabling more specific assessment of the fetal condition in complicated pregnancies[3-6]. EHG monitoring holds the promise that it might discriminate between efficient and inefficient contractions, by using power density spectral analysis[7-9].

Therefore the aims of part I of this thesis were to validate FHR monitoring using the fetal ECG signal and to study the fetal condition in pregnancies complicated by intra uterine growth restriction (IUGR) and (pre)gestational diabetes by using this technique.

The aims of part II of this thesis were to validate monitoring of uterine contractions using EHG during labour by comparing it to the method of reference, intrauterine pressure recording (IUP), and to study whether non-invasive monitoring of uterine activity using EHG may help to differentiate between normal and dysfunctional term labour in nulliparous women.

PART I

Monitoring of the fetal condition using fetal electrocardiography

In chapter 2 the accuracy and quality of FHR monitoring using the fECG signal were studied. First the accuracy of transabdominal fECG recordings was confirmed by comparison to scalp electrode measurements in 22 women during early labour. Furthermore, the results of antepartum fECG recordings showed optimal recording quality overnight (23:00-07:00h) during maternal sleep. A slight decrease in recording quality was found between 26 and 34 weeks of gestation, which is in line with previous studies[10-12]. This transient decrease in recording quality is most probably due to the formation of a vernix caseosa which interferes with electrical conductivity[10], but does not hamper adequate recording in over 90 percent of women[3].

Since the obesity epidemic challenges traditional antenatal FHR monitoring technologies, we also studied the association between maternal Body Mass Index (BMI) and fECG recording quality (Chapter 3). It was remarkable that the quality of fECG-monitoring was not influenced by maternal obesity. This finding indicates that fECG monitoring can be regarded as an alternative in cases where Doppler ultrasound FHR monitoring is hampered by maternal obesity.

After validation of fECG monitoring in terms of accuracy and recording quality, it was the next step to study the potential benefits of fECG monitoring for assessment of fetal wellbeing as compared to conventional FHR monitoring with Doppler ultrasound.

In pregnancies complicated by intra uterine growth restriction monitoring of fetal biometry, FHR, its variability (STV) and Doppler measurements (pulsatility index of the uterine artery) is recommended for assessment of the fetal condition[13]. However, decision making as to when to deliver the growth restricted fetus based remains difficult. With high resolution fECG recorders, true beat-to-beat FHR can be recorded for the calculation of the average acceleration - and deceleration capacity of FHR (AAC and ADC, respectively). These parameters, reflecting the sympathetic and parasympathetic components of the nervous system, have proven to provide better prediction of survival in adults suffering myocardial infarction, however are new in fetal medicine. Previous studies have indicated that chronic nutritional deprivation may lead to a delay or disturbance in functional maturation of the sympathetic nervous system[13-15]. Therefore we hypothesized that separate analysis of the sympathetic and parasympathetic components of FHR might lead to a better recognition of fetal compromise as compared to conventional FHR parameters (rate and variability).

In chapter 4 mean values of FHR, STV, AAC and ADC from recordings in twenty-five IUGR pregnancies were plotted in the reference curves as obtained from ninety control recordings. It was a remarkable finding that 36% (9/25) of AAC and ADC values in IUGR fetuses were below the 2.5th percentile as compared to only 8% (2/25) when using conventional measures of FHR variation (STV values; $p<0.05$). The degree of Doppler abnormalities did not contribute to the level of deviation of the FHR parameters. These findings suggest that AAC and ADC may well differentiate better between normal and IUGR fetuses. Whether this indicates that AAC and ADC represent a more sensitive parameter of fetal compromise remains to be elucidated in future studies with longitudinal follow up of IUGR fetuses. This might especially be important near term, since discrimination between low risk small for gestational age fetuses and truly growth restricted fetuses is difficult, given the absence of Doppler anomalies at that age[16,17].

Similar to fetuses suffering intrauterine growth restriction, fetuses of mothers with pre-gestational diabetes are also at high risk for fetal deterioration. Unfortunately, the etiology for this increased risk is only partly understood. It is most likely associated to maternal hyperglycaemia, and a (sub)acute development of fetal lactic acidosis (due to the combination of high glucose values and a relative hypoxemia)[18,19]. Occasionally, some of these women indeed indicate that fetal movements decrease in case of hyperglycaemia. Therefore, we first studied the occurrence of hyperglycaemia in the three trimesters of pregnancy (chapter 5). In addition, the relationship between maternal glucose and fetal heart rate parameters was evaluated by combining continuous subcutaneous glucose monitoring with continuous fECG monitoring (chapter 6).

We hypothesized that glycaemic control would improve with advancing gestation, since severe hypoglycaemia has especially been associated with the first trimester of pregnancy[20]. We were surprised to find that overall glycaemic control, and the occurrence of both hyper and hypoglycaemia remained relatively stable throughout gestation. However, between individuals large differences were found per trimester of pregnancy, whereas within individuals large variation existed in the course of pregnancy. This indicates that glycaemic control in women with pre-gestational diabetes is highly unpredictable, thereby not only increasing maternal risks associated with poor glycaemic control, but also increasing fetal risks such as macrosomia, and sudden intrauterine death.

Difficulties are encountered in the recognition of the fetus at increased risk of deterioration, since routine FHR monitoring can falsely reassure clinicians and since Doppler blood flow measurement in the umbilical artery have failed to identify these fetuses[21]. We hypothesized that FHR monitoring during prolonged excursions of maternal glucose levels might offer insight into the fetal compensatory mechanisms, especially in case of maternal hyperglycaemia. Simultaneous measurements of continuous glucose monitoring and fECG monitoring were performed in 22 women with (pre)gestational diabetes in second half of pregnancy. In this study-group neither hyperglycaemia nor hypoglycaemia had a significant effect on FHR and its short-term variability (STV). However, fetuses showing a hyperglycaemic period had a somewhat higher basal FHR not only during hyperglycaemia but also during the hour prior to the onset of hyperglycaemia when glucose levels were still in the normal range. In other words, most fetuses of women with diabetes tolerate hyperglycaemia well. Whether simultaneous recording of FHR and CGM offers additional value in high risk cases (macrosomia and poor glucose control) needs to be investigated in a larger study population.

In conclusion, our studies using fECG have shown that: True beat-to-beat recordings can be obtained throughout pregnancy, also in obese women. Long recordings are feasible during night time when women are asleep. And some promising observations have been made in IUGR fetuses. This indicates that there will be place for this innovative technique. This will hold especially for monitoring of the IUGR fetus and fetuses of women with diabetes, although this has to be substantiated in larger series. Moreover, this technique may be used in home monitoring of pregnancies at risk and for indications warranting prolonged recordings, such as in the assessment of the effects of medication given to treat fetal tachycardia. In this respect it should also be emphasized, that when the electrode position is adequate, prolonged recordings can be made without adjustment, with is in contrast to the conventional Doppler recording of FHR. Moreover, fECG monitoring is truly non-invasive, again in contrast to Doppler recording.

PART II

Monitoring uterine contractions using electrohysterography

The objective of chapter 7 was to validate electrohysterography (EHG) as a method for uterine activity monitoring during labour by comparing with the reference test, intra uterine pressure (IUP) recordings. Following thirty-two simultaneous recordings of EHG and IUP in labour we concluded that EHG detects uterine contractions accurately, but the contractions characteristics as measured with IUP (amplitude and duration) were not directly comparable. The latter was possibly due to the different nature of the signals measured (electrical activity versus pressure).

As outlined in the introduction of this thesis, EHG offers more than recognition of the presence of uterine contractions. When EHG is analyzed using a power density spectrum, it can be utilized to study (dys-)functional uterine activity. Given the relatively high proportion of low risk nulliparous women undergoing a Caesarean section (CS) because of arrest of labour (despite augmentation and continuous monitoring of uterine activity)[22,23], additional information regarding the characteristics of uterine activity might well lead to an earlier recognition and treatment of dysfunctional uterine activity.

In chapter 8 we described the preliminary results of our study using non-invasive registrations of uterine activity using EHG to differentiate between normal term labour and arrest of labour. Uterine activity during (induced or spontaneous) labour was measured using EHG in nulliparous women with singleton pregnancies in cephalic position at term (≥ 37 weeks). Progress of labour was monitored using standard cervical examination from admission to delivery. Electrical activity of the myometrium during contractions was characterized by its power density spectrum (PDS). Peak frequencies (PF) of the PDS observed in women undergoing CS for failure to progress were compared to those of women reaching full cervical dilation using a matched case-control analysis. A total of 95 EHG-recordings were analyzed, of which 50 were performed during spontaneous and 45 during induced labour. CS was performed in 19 women because of arrest of labour (10 in spontaneous -, 9 in induced labour). In both groups the peak frequency increased significantly with increasing cervical dilatation, which is in agreement with studies on preterm labour[7,8]. PDS was higher (borderline significant) in women with CS for first stage labour arrest compared to women reaching full cervical dilation (OR 1.75; 95%CI [0.97 – 3.16]). This effect was present in case of spontaneous labour but not in induced labour. In conclusion, labour arrest showed a trend towards an association with abnormal myometrial depolarisation patterns (i.e. higher peak frequencies) in spontaneous term labour.

In part II of this thesis we presented our first results on a renewed EHG technique for monitoring of uterine activity. Limitations of conventional techniques have enhanced the search for a true non-invasive technique, which preferably would also correlate to relevant clinical outcomes such as progress of labour, or identification of true preterm labour.
Our validation study on EHG has shown that uterine activity can be monitored accurately in term labour[24]. This is in line with findings from other research groups who reported similar data while using different devices and signal analysis techniques[25-27]. Work still needs to be undertaken to reach uniformity in the acquisition and processing of the uterine electrical signal.

The preliminary results from this thesis on differences in peak frequency of efficient and inefficient contractions during labour (chapter 8) together with the findings of other groups on propagation patterns seem to indicate that EHG may give access to additional and clinical relevant information not provided by either tocodynamometry or IUPC[28-30]. Obviously, these results need to be confirmed by large scale studies and coupled to interventions to evaluate their clinical relevance during labour. Encouraged by those findings one can, however, already think of other fields of application of EHG. It can potentially be complementary in the assessment of women with induced labour or threatened preterm labour. Currently the mode of induction of labour, using local hormonal therapy (prostaglandins), or oxytocin infusion, is based on digital assessment of cervical ripening (Bishop score). Unfortunately, the process (and progress) of labour following cervical ripening with prostaglandins or augmentation with oxytocin is highly unpredictable. Potentially EHG analysis of the uterus could give additional information on the stage of uterine ripening, thereby facilitating the choice and/or dosage of treatment. Furthermore, the role of labour augmentation needs to be studied more in detail since recent research implies that arrest of labour due to uterine exhaustion might not benefit from extra uterine stimulation through administration of oxytocin[31].
Preterm labour is another area of great interest. For women with threatened preterm labour the recognition of 'true' preterm labour would dramatically reduce the number of unnecessary treatments since approximately 70% of women admitted to hospital with threatened preterm labour eventually deliver at term[32]. Several research groups have already published interesting results on the capacity of EHG to distinguish between preterm contractions leading to short term delivery or not[8,25]. A recent article considering EHG characteristics of contractions before and after tocolysis in threatened preterm labour is of great interest in this context[30]. It shows that clinically successful tocolysis is reflected by a decrease of the peak frequency of contractions registered by EHG. This is in line with other studies showing that the higher the peak frequency, the higher the risk of an imminent preterm delivery[7,8].

Concluding, EHG while still having to be standardized, is now established as an accurate technique to measure the incidence of contractions during labour. Moreover, there is converging evidence towards a possible role in the diagnosis of preterm labour and encouraging preliminary results from our group and others over a potentially clinically relevant role in the understanding of dysfunctional labour.

Main conclusions of this thesis

- Fetal ECG recording is a valid and accurate and truly non-invasive method for FHR monitoring in the (obese) pregnant population during the second half of gestation.
- Reference ranges of FHR and its short term variation as recorded with fECG monitoring are comparable to those recorded with conventional cardiotocography.
- FHR monitoring using high resolution fECG devices offers true beat-to-beat FHR with an accuracy of 1 ms, potentially offering more accurate assessment of fetal cardiovascular (patho-)physiology.
- Differentiation between contributions of the sympathetic and parasympathetic branches of the nervous system on FHR regulation may offer a more specific assessment of the condition of the IUGR fetus.
- Continuous and simultaneous recording of maternal glucose and fetal heart rate in women with type 1 diabetes, enables to study their interaction.
- In women with type 1 diabetes large variations in glucose values are present in all trimesters of pregnancy.
- In these women the fetus generally tolerates both hypo and hyperglycaemia well, but is remains uncertain if this will hold for the total population
- With electrohysterography (EHG) uterine contractions can be adequately identified during labour. Power density spectral analysis of EHG offers additional information on the efficiency of uterine activity.
- Interpretation of EHG-validation studies is complicated by the lack of uniformity in EHG signal acquisition and processing.
- Labour arrest may be associated with abnormal myometrial depolarization patterns in spontaneous term labour.

Reference List

1. Steer CM, Hertsch GJ. Electrical activity of the human uterus in labor; the electrohysterograph. Am.J.Obstet.Gynecol. 1950 Jan;59(1):25-40.
2. Roche JB, HON EH. The fetal electrocardiogram. V. comparison of lead systems. Obstet.Gynecol. 1965 08/15;92(0002-9378):1149-1159.
3. Graatsma EM, Jacod BC, van Egmond LA, Mulder EJ, Visser GHA. Fetal electrocardiography: feasibility of long-term fetal heart rate recordings. BJOG 2009 Jan;116(2):334-7; discussion 337-8.
4. Taylor MJ, Thomas MJ, Smith MJ, Oseku-Afful S, Fisk NM, Green AR, et al. Non-invasive intrapartum fetal ECG: preliminary report. BJOG 2005 08;112(1470-0328; 8):1016-1021.
5. Cleal JK, Thomas M, Hanson MA, Paterson-Brown S, Gardiner HM, Green LR. Noninvasive fetal electrocardiography following intermittent umbilical cord occlusion in the preterm ovine fetus. BJOG 2010 Mar;117(4):438-444.
6. van Laar JO, Peters CH, Vullings R, Houterman S, Bergmans JW, Oei SG. Fetal autonomic response to severe acidaemia during labour. BJOG 2010 Mar;117(4):429-437.
7. Garfield RE, Maner WL, MacKay LB, Schlembach D, Saade GR. Comparing uterine electromyography activity of antepartum patients versus term labor patients. Am.J.Obstet.Gynecol. 2005 Jul;193(1):23-29.
8. Maner WL, Garfield RE, Maul H, Olson G, Saade G. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet.Gynecol. 2003 Jun;101(6):1254-1260.
9. Marque CK, Terrien J, Rihana S, Germain G. Preterm labour detection by use of a biophysical marker: the uterine electrical activity. BMC Pregnancy Childbirth 2007 Jun 1;7 Suppl 1:S5.
10. Oldenburg JT, Macklin M. Changes in the conduction of the fetal electrocardiogram to the maternal abdominal surface during gestation. Obstet.Gynecol. 1977 10/15;129(0002-9378; 4):425-433.
11. Crowe JA, Woolfson MS, Hayes-Gill BR, Peasgood W, Mohd-Ali MA, Huang Y, et al. Antenatal assessment using the FECG obtained via abdominal electrodes. J.Perinat.Med. 1996;24(0300-5577; 1):43-53.
12. Pieri JF, Crowe JA, Hayes-Gill BR, Spencer CJ, Bhogal K, James DK. Compact long-term recorder for the transabdominal foetal and maternal electrocardiogram. Med.Biol.Eng.Comput. 2001 01;39(0140-0118; 1):118-125.
13. Visser G.H.A. Monitoring the growth-restricted fetus during the preterm period. In: Petraglia F., Gabbe S.G., Weiss G., Strauss J.F., editors. Preterm Birth: Mechanisms, Mediators, Prediction, Prevention and Interventions. first ed.: Informa Healthcare; 2007. p. 192.

14. Gagnon R, Hunse C, Bocking AD. Fetal heart rate patterns in the small-for-gestational-age human fetus. Am.J.Obstet.Gynecol. 1989 Sep;161(3):779-784.
15. Baschat AA. Fetal responses to placental insufficiency: an update. BJOG 2004 Oct;111(10):1031-1041.
16. Baschat AA. Fetal growth restriction - from observation to intervention. J.Perinat.Med. 2010 May;38(3):239-246.
17. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackeloer BJ, Kok HJ, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet.Gynecol. 2001 12;18(0960-7692; 6):564-570.
18. Salvesen DR, Freeman J, Brudenell JM, Nicolaides KH. Prediction of fetal acidaemia in pregnancies complicated by maternal diabetes mellitus by biophysical profile scoring and fetal heart rate monitoring. Br.J.Obstet.Gynaecol. 1993 Mar;100(3):227-233.
19. Lauenborg J, Mathiesen E, Ovesen P, Westergaard JG, Ekbom P, Molsted-Pedersen L, et al. Audit on stillbirths in women with pregestational type 1 diabetes. Diabetes Care 2003 May;26(5):1385-1389.
20. Kerssen A, de Valk HW, Visser GHA. Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. BJOG 2004 09;111(1470-0328; 9):919-924.
21. Salvesen DR, Higueras MT, Mansur CA, Freeman J, Brudenell JM, Nicolaides KH. Placental and fetal Doppler velocimetry in pregnancies complicated by maternal diabetes mellitus. Am.J.Obstet.Gynecol. 1993 Feb;168(2):645-652.
22. Gifford DS, Morton SC, Fiske M, Keesey J, Keeler E, Kahn KL. Lack of progress in labor as a reason for cesarean. Obstet.Gynecol. 2000 Apr;95(4):589-595.
23. Menacker F. Trends in cesarean rates for first births and repeat cesarean rates for low-risk women: United States, 1990-2003. Natl.Vital Stat.Rep. 2005 Sep 22;54(4):1-8.
24. Jacod BC, Graatsma EM, Van Hagen E, Visser GHA. A validation of electrohysterography for uterine activity monitoring during labour. J.Matern.Fetal.Neonatal Med. 2010 Jan;23(1):17-22.
25. Maul H, Maner WL, Olson G, Saade GR, Garfield RE. Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery. J.Matern.Fetal.Neonatal Med. 2004 May;15(5):297-301.
26. Euliano T, Skowronski M, Marossero D, Shuster J, Edwards R. Prediction of intrauterine pressure waveform from transabdominal electrohysterography. J.Matern.Fetal.Neonatal Med. 2006 Dec;19(12):811-816.
27. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW. Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. Physiol.Meas. 2008 Jul;29(7):829-841.

28. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK. Spatiotemporal electrohysterography patterns in normal and arrested labor. Am.J.Obstet.Gynecol. 2009 Jan;200(1):54.e1-54.e7.
29. Rabotti C, Mischi M, Oei G, Bergmans J. Noninvasive estimation of the electrohysterographic action-potential conduction velocity. IEEE Trans.Biomed.Eng. 2010 May 10.
30. Vinken MP, Rabotti C, Mischi M, van Laar JO, Oei SG. Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice. Obstet.Gynecol.Int. 2010;2010:325635.
31. Quenby S, Pierce SJ, Brigham S, Wray S. Dysfunctional labor and myometrial lactic acidosis. Obstet.Gynecol. 2004 Apr;103(4):718-723.
32. Tsoi E, Akmal S, Geerts L, Jeffery B, Nicolaides KH. Sonographic measurement of cervical length and fetal fibronectin testing in threatened preterm labor. Ultrasound Obstet.Gynecol. 2006 Apr;27(4):368-372.

Addendum

Nederlandse samenvatting

Nederlandse samenvatting

In dit proefschrift worden nieuwe methoden beschreven voor het meten van de hartfrequentie van het ongeboren kind (de foetus) tijdens de zwangerschap (Deel I) en voor het meten van baarmoedercontracties (weeën) tijdens de bevalling (Deel II).

Deel I

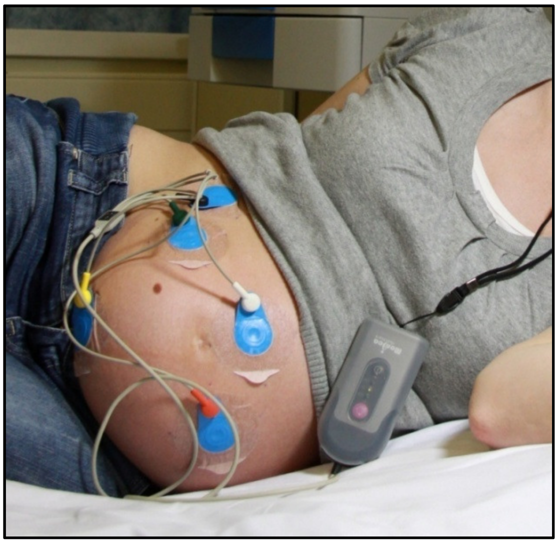
Foetale bewaking met het foetale elektrocardiogram

Voor een goede afloop van de zwangerschap en bevalling is het van belang om inzicht te verkrijgen in de conditie van de foetus. Wanneer er sprake is van moederlijke ziekte (bijvoorbeeld bij diabetes mellitus, hypertensie, medicatie gebruik, etc.) of achterblijven van de groei van de foetus, dan is frequente bepaling van de foetale conditie noodzakelijk. In het tweede deel van de zwangerschap kan de conditie van de foetus worden beoordeeld met ultrageluidsmetingen van foetale hartfrequentie (cardiotocografie; CTG). Deze methode heeft echter een aantal nadelen; een hoog signaalverlies bij bewegingen van de foetus buiten het gebied van de ultrageluidstransducer, slechte signaalkwaliteit bij vrouwen met veel abdominaal vetweefsel en het 'invasieve' karakter van ultrageluidsbelasting bij langdurige en frequente hartfrequentie metingen[1]. Daarnaast ervaren de zwangeren een meting vaak als niet prettig vanwege een beperkte bewegingsvrijheid en omdat de elastische banden die de transducer op zijn plaats houden vaak strak zijn aangetrokken[1].

Een alternatieve methode is het meten van de foetale hartfrequentie met het foetale elektrocardiogram (fECG). Het ECG is voornamelijk bekend vanuit de volwassen geneeskunde. In de verloskunde wordt het fECG momenteel alleen gebruikt voor hartfrequentiemetingen tijdens de bevalling. Na het breken van de vliezen kan via een schedelelektrode het fECG signaal worden opvangen. Gedurende de zwangerschap kan het foetale ECG ook worden geregistreerd op de moederlijke buikwand, hoewel tot nu toe alleen in wetenschappelijke setting. Het foetaal ECG wordt opgevangen via (non-invasieve) plakelektrodes op de zwangere buik (transabdominaal), om zo met het fECG signaal een foetale hartfrequentie te berekenen (figuur 1). Voorheen werd deze transabdominale registratie van het fECG bemoeilijkt door 'elektrische ruis' van onder andere het moederlijke ECG, moederlijke en foetale beweging of spieractiviteit. Na verbetering van de 'filter-techniek' van het foetale ECG lijkt dit probleem grotendeels opgelost te zijn[1,2].

De beperkingen van hartfrequentiemetingen met ultrageluid, zoals hierboven vermeld vormen geen probleem bij de fECG techniek; het fECG signaal kan ongeacht de foetale ligging worden opgevangen, het non-invasieve karakter (er wordt geen signaal de buik ingestuurd, slechts opgevangen) maakt langdurig meten ongevaarlijk. Tenslotte biedt deze methode behoud van mobiliteit, wat door zwangere vrouwen als comfortabel wordt beschouwd. Daarnaast bieden foetale hartfrequentiemetingen met fECG als voordeel dat de precieze slag-tot-slag ('beat-to-beat') variabiliteit van de foetale hartfrequentie kan worden berekend. Men veronderstelt dat het berekenen van 'beat-to-beat' variabiliteit meer informatie oplevert over de conditie van de foetus dan foetale hartfrequentie alleen[3-6].

Figuur 1: AN24 - foetale ECG (en weeën) monitor (Monica Healthcare Ltd., Nottingham, UK).



Validatie van de foetale ECG techniek

Voordat een (nieuwe) medische techniek in de patiëntenzorg gebruikt kan worden moet deze gevalideerd worden ten opzichte van bestaande technieken. Daarom wordt in hoofdstuk 2 de kwaliteit van langdurige fECG hartfrequentie metingen in het tweede deel van de zwangerschap beschreven. Tevens wordt de nauwkeurigheid van de transabdominale fECG methode gevalideerd ten opzichte van de gouden standaard die bestaat uit foetale ECG metingen tijdens de bevalling, zoals gemeten met een schedelelektrode. In totaal is bij 150 zwangeren (zwangerschapsduur tussen 20 en 41 weken) gedurende gemiddeld 15 uur een eenmalige fECG meting verricht. Daarnaast is bij 22 vrouwen tijdens de bevalling een gelijktijdige meting gedaan van abdominaal fECG met plakelektroden en fECG zoals gemeten met de schedelelektrode. Uit de resultaten van het onderzoek blijkt dat fECG metingen kwalitatief goed zijn, met name gedurende de nacht wanneer de zwangere slaapt en het foetale ECG signaal niet wordt verstoord door elektrische (spier)activiteit. Eerder onderzoek suggereerde dat het ontstaan van de vernix (de 'smeerlaag' rondom de foetus) tussen 28 en 34 weken zwangerschap de fECG signaalgeleiding bemoeilijkt en daardoor een verminderde fECG kwaliteit oplevert in deze zwangerschapsperiode[1,2,7]. Gezien de geringe (maar significante daling) in fECG signaalkwaliteit in onze studie kunnen wij deze bevinding bevestigen. Verder wordt in hoofdstuk 3 beschreven dat de kwaliteit van fECG hartfrequentiemetingen (in tegenstelling tot het CTG) niet wordt beïnvloed door de body mass index (BMI) van de moeder. Bovenstaande bevindingen bevestigen dat de fECG techniek een nauwkeurige en kwalitatief goede methode is voor het meten van de foetale hartfrequentie bij zwangere vrouwen in het tweede deel van de zwangerschap.

Toepassingen van de foetale ECG techniek
Een aantal parameters van de foetale hartfrequentie zijn van belang wanneer hartfrequentiemetingen worden verricht bij gecompliceerde zwangerschappen; de basis hartfrequentie, de mate van hartfrequentie variabiliteit (korte termijn variabiliteit) en de aan- of afwezigheid van acceleraties en deceleraties (d.w.z. kortdurende toename- en afname van de hartfrequentie). Bij zwangerschappen gecompliceerd door intra uteriene groeirestrictie (IUGR) wordt voornamelijk gekeken naar de mate van korte termijn variabiliteit en de aanwezigheid van deceleraties: verminderde variabiliteit en de aanwezigheid van deceleraties voorspellen een verminderde conditie van de foetus. Naast beoordeling van de verschillende hartfrequentie parameters is bij IUGR foetussen ook de doorstroming van de foetale bloedvaten van belang, zoals gemeten met Doppler-ultrageluid.
Hoewel op basis van korte termijn variabiliteit in combinatie met Doppler-metingen geen eenduidig (klinisch) beleid kan worden afgestemd, zijn dit momenteel de enige beschikbare foetale parameters. Afhankelijk van de resultaten moet een keuze worden gemaakt voor het voortzetten van de zwangerschap, met het risico van plotselinge verslechtering van de foetale conditie, of voor het nastreven van de bevalling, waarbij de risico's van een vroeggeboorte aanwezig zijn. In hoofdstuk 4 wordt een nieuwe parameter van de foetale hartfrequentie beschreven die mogelijk bijdraagt aan hetvroegtijdig herkennen van een verminderde of een verslechterende conditie van de IUGR foetus.
Recent onderzoek heeft een nieuwe foetale hartfrequentie parameter opgeleverd die mogelijk een betere voorspeller is voor de conditie van de IUGR foetus vergeleken met de korte termijn variabiliteit[4,5]. Deze nieuwe parameter maakt onderscheid tussen de sympathische - en parasympathische invloed op de foetale hartfrequentie. Aangezien de nieuwe sympathische - (AAC; average acceleration capacity) en parasympathische (ADC; average deceleration capacity) parameters nog niet eerder zijn beschreven in gezonde zwangerschappen zijn in hoofdstuk 4 allereerst de AAC en ADC waarden bestudeerd bij ongecompliceerde zwangerenschappen in het verloop van de tweede helft van de zwangerschap. Ter vergelijking worden ook de basis hartfrequentie en korte termijn variabiliteit zoals gemeten met de fECG techniek vanaf 20 weken zwangerschapsduur vermeld. Vervolgens is een voorlopige analyse verricht van 25 zwangerschappen gecompliceerd door IUGR waarbij de waarden van de basis hartfrequentie, korte termijn variatie, AAC en ADC zijn vergeleken met de normaalwaarden zoals verkregen vanuit negentig ongecompliceerde zwangerschappen. In dit hoofdstuk wordt aangetoond dat

een significant groter percentage van de AAC en ADC waarden van zwangerschappen gecompliceerd door foetale IUGR (36%; 9/25) onder de 2.5de percentiel van de normaalwaarden wordt gemeten in vergelijking met de korte termijn variabiliteit (8%; 2/25). Daarnaast valt op dat abnormale waarden van foetale bloedvatdoorstroming (Doppler) niet geassocieerd zijn met afwijkende AAC en ADC waarden.
Deze bevindingen suggereren dat AAC en ADC beter onderscheid kunnen maken tussen normale en IUGR foetussen. Of AAC en ADC ook een betere voorspellende waarde hebben voor het herkennen van het verslechteren van de foetale conditie van IUGR foetussen moet worden bestudeerd in toekomstig onderzoek met longitudinale follow up van de IUGR foetussen. Een dergelijk onderzoek is voornamelijk van belang bij groeirestrictie rondom de a terme datum, aangezien Doppler ultrageluid metingen van de foetale bloedvaten rondom de a terme datum niet tot nauwelijks voorspellend zijn voor het herkennen van een verslechtering van de foetale conditie[8].

Net als bij zwangerschappen gecompliceerd door IUGR, hebben foetussen van moeders met diabetes mellitus eveneens een verhoogde kans op een verslechterde foetale conditie[26]. Helaas wordt de achtergrond van dit verhoogde risico maar deels begrepen. Hoogstwaarschijnlijk is er een associatie met hoge bloedsuiker waarden van de zwangere (maternale hyperglycaemie) en een (sub)acute ontwikkeling van foetale verzuring (lactaat acidose), door een combinatie van hoge bloedglucosewaarden en relatief zuurstofgebrek (hypoxie)[9,10]. Tijdens poliklinische bezoeken van zwangeren met diabetes valt op dat sommige vrouwen verminderde foetale bewegingen opmerken ten tijde van verhoogde bloedglucose waarden. Deze bevinding gaf aanleiding om allereerst inzicht te krijgen in het voorkomen van hyperglycaemieën in de drie trimesters van de zwangerschap bij vrouwen met type 1 diabetes mellitus (hoofdstuk 5). Vervolgens wordt in hoofdstuk 6 beschreven of de foetus reageert op schommelingen van moederlijke bloedsuiker-waarden.
In hoofdstuk 5 wordt onderzoek beschreven waarbij bij 26 vrouwen met type 1 diabetes in elk trimester van de zwangerschap gedurende 48 uur een continue subcutane glucose meting is verricht. Voor aanvang van het onderzoek werd de hypothese geformuleerd dat met het vorderen van de zwangerschap een betere glucose regulatie zou optreden (met minder hyperglycaemieën). Deze hypothese was gebaseerd op het feit dat hypoglycaemieën (lage bloedsuikers), en daarbij frequent optredende reactieve hyperglycaemieën, voornamelijk beschreven zijn in het eerste trimester van de zwangerschap[11]. Als uitkomstmaten van het onderzoek worden het voorkomen van hyper- en hypoglycaemieën, de gemiddelde glucose waarde, de standaard deviatie en de variabiliteit in glucosewaarden van de een op de andere dag (glucose dag-na-dag variabiliteit) beschreven.
Uit de resultaten van hoofdstuk 5 blijkt dat de mate van glucose regulatie en het voorkomen van hypo- en hyperglycaemieën relatief onveranderd blijven gedurende de

zwangerschap. Echter, op individueel niveau zijn de verschillen voor de verschillende maten van glucose regulatie erg groot en is het individuele verloop van glucose regulatie volstrekt onvoorspelbaar. Hierdoor bestaat niet alleen een hoog risico voor de (slecht gereguleerde) zwangere met diabetes, maar ook voor de foetus. De belangrijkste risico's voor de foetus zijn overgewicht (geboortegewicht ≥ 90ste percentiel) en plotseling intra-uterien overlijden.
Bij zwangerschappen gecompliceerd door maternale diabetes mellitus kan het van betekenis zijn om te weten hoe de foetus reageert op schommelingen van de moederlijke glucose waarden. Immers, de aanwezigheid van hyperglycaemie bij een bovengemiddeld gegroeide foetus in combinatie met een onrijp placentabed kan lactaat vorming (dan wel lactaat stapeling) veroorzaken, met uiteindelijk intra-uterien overlijden als gevolg[9,10]. Helaas is in deze context het routinematig verrichten van foetale hartfrequentie metingen weinig zinvol omdat de meeste vrouwen ten tijde van het polikliniek bezoek een normale glucose waarde zullen hebben. Daarnaast is het induceren van hyperglycaemie ethisch onverantwoord. Een alternatief voor het meten van de foetale reactie op hoge en lage bloedglucose waarden is het observeren van de spontaan optredende schommelingen in bloedglucose waarden. Dit is mogelijk door simultane metingen van de foetale hartfrequentie (zoals gemeten met de fECG monitor) en maternale glucose waarden (zoals gemeten met continue subcutane glucose metingen) te verrichten. In hoofdstuk 6 wordt het onderzoek beschreven waarbij 28 simultane hartfrequentie en glucose metingen zijn verricht bij vrouwen met (zwangerschaps-) diabetes. De resultaten tonen geen significant effect van hypo- of hyperglycaemie op de foetale hartfrequentie en korte termijn variabiliteit van de hartfrequentie. Echter, voorafgaand aan en ten tijde van hyperglycaemie is de foetale hartfrequentie licht verhoogd. Uit de resultaten van deze studie kan worden geconcludeerd dat het voorkomen van hoge bloedglucose waarden door de meeste foetussen redelijk tot goed wordt verdragen. Dit geldt ook voor lage bloedglucose waarden. Vervolgonderzoek moet aantonen of het simultaan verrichten van foetale hartfrequentie metingen en continue glucose metingen een bijdrage levert in de zorg voor zwangeren met diabetes mellitus met een hoog risico op complicaties.

Samenvattend, wordt in deel I van dit proefschrift beschreven dat (beat-to-beat) fECG metingen gedurende de tweede helft van de zwangerschap kunnen worden verricht, ook bij zwangeren met obesitas (BMI ≥ 30 kg/m2). Langdurige metingen zijn voornamelijk zinvol gedurende de nacht wanneer de zwangere slaapt. Deze metingen zijn veilig voor de foetus dankzij het niet-invasieve karakter van de techniek. Herpositioneren van de plakelektroden is niet nodig (de laatste twee aspecten zijn in tegenstelling tot ultrageluid CTG). Het feit dat langdurig meten mogelijk is maakt dat deze techniek ook geschikt voor het bestuderen van effecten van medicatie op de foetus, zoals bij de behandeling van foetale tachycardie. Ten slotte zijn de resultaten zoals beschreven bij zwangerschappen gecompliceerd door IUGR veelbelovend en bevestigen dat verder onderzoek met deze techniek goed mogelijk is.

Deel II

Weeënregistratie met behulp van elektrohysterografie

Men spreekt van 'de bevalling' wanneer regelmatige, pijnlijke weeën leiden tot veranderingen van de baarmoedermond (verstrijken en ontsluiting). Om inzicht te krijgen in het karakter van weeën worden de frequentie en duur van weeën gemeten. Hoewel weeënregistratie op verschillende manieren kan worden verricht, zijn de meest gebruikelijke methoden gebaseerd op het meten van drukverschillen. Dit kan zowel uitwendig door middel van tocodynamometrie als ook inwendig met behulp van een (met vocht gevulde) intra-uteriene druk katheter. Uitwendige tocodynamometrie is veilig gezien het non-invasieve aspect en is gemakkelijk in het gebruik. Echter, de kwaliteit van weeënregistratie is met deze methode niet alleen afhankelijk van de juiste plaatsing van de sensor op de zwangere buik, maar wordt tevens negatief beïnvloed door (moederlijke en foetale) bewegingen en een hoge BMI[12]. Weeënregistratie met intra-uteriene druk katheters (ook wel druklijnen genoemd) wordt sinds kort ontraden. Deze veranderde instelling ten aanzien van het gebruik is niet alleen tot stand gekomen door de zeldzame associatie met baarmoederperforatie of placenta losraking, maar ook omdat recent onderzoek heeft aangetoond dat zowel het gebruik van druklijnen als ook het gebruik van uitwendige tocodynamometrie in het algemeen geen gezondheidswinst opleveren[13]. Deze bevinding is niet geheel onverwacht aangezien beide methoden slechts de frequentie en duur van weeën kunnen meten, en geen inzicht geven in de efficiëntie van weeën. Een nieuwe methode van weeënregistratie kan wellicht meer inzicht geven in de efficiëntie van weeën. Deze methode heet elektrohysterografie (hyster = baarmoeder) en is gebaseerd op het meten van de elektrische activiteit van de baarmoeder tijdens een wee. De elektrische activiteit wordt opgevangen door middel van plakelektrodes, die (net als bij het foetale ECG) worden geplakt op de buik van de zwangere (zie Figuur 1). Elektrohysterografie (EHG) is al 50 jaar bekend, maar is pas sinds kort in de belangstelling komen te staan, mede door technische verbeteringen. Daarnaast geeft EHG de mogelijkheid om de opbouw van weeën vanuit de contracties van baarmoedercellen (myometrium cellen) in detail te bestuderen. Dit is mogelijk door het analyseren van de elektrische activiteit die tijdens een wee gegenereerd wordt door de verschillende myometrium cellen. Hoewel meerdere technieken beschikbaar zijn voor het analyseren van elektrische (myometrium) activiteit, is tot nu toe de meeste ervaring opgedaan met het 'power density spectrum' (PDS)[14-19]. Deze techniek maakt het mogelijk om tussen de ogenschijnlijke chaos van depolarisaties van de verschillende myometrium cellen de frequentie te identificeren waarmee de meeste cellen contraheren. Deze frequentie wordt de peak frequency genoemd. Met behulp van het power density spectrum hebben verschillende onderzoeksgroepen al aannemelijk gemaakt dat er wél onderscheid kan worden gemaakt tussen efficiënte en inefficiënte weeën)[20-22].

Validatie van EHG weeënregistratie

Zoals eerder in deze samenvatting beschreven voor de ECG-techniek, geldt ook voor weeënregistratie met behulp van EHG, dat alvorens gebruik in wetenschappelijke of klinische setting gerechtvaardigd is, deze methode gevalideerd moet worden ten opzichte van de gouden standaard. In hoofdstuk 7 wordt de validatie van de EHG techniek ten opzichte van de intra-uteriene druklijn beschreven. Hierbij moet vermeld worden dat het gebruik van intra-uteriene druklijnen ten tijde van de uitvoering van dit onderzoek nog als gangbaar werd beschouwd. In het onderzoek beschreven in hoofdstuk 7 werden bij 32 vrouwen tijdens de bevalling gelijktijdige weeënregistraties verricht met zowel de intra-uteriene druklijn als met de EHG methode. De technieken werden vergeleken op basis van de frequentie, de duur en de amplitude van de weeën. Uit het onderzoek blijkt dat de EHG methode het aantal weeën (de frequentie) adequaat kan meten, maar dat de duur en amplitude van de weeën niet goed overeen komt met de duur en amplitude zoals gemeten met de druklijn. Deze laatste bevinding is niet geheel onverwacht gezien de verschillende aard van de registratiemethodes (druk versus elektrische activiteit).

Toepassingen van EHG weeënregistratie

Zoals eerder vermeld kan de EHG methode, na analyse van het power density spectrum, méér dan alleen de frequentie van weeën meten. Weeënregistratie met behulp van EHG wordt verondersteld onderscheid te kunnen maken tussen efficiënte weeën (leidend tot ontsluiting) en inefficiënte weeën (niet vorderende ontsluiting)[14]. Bij a terme zwangerschappen kan het tijdig herkennen van inefficiënte weeën gezondheidswinst opleveren gezien het relatief hoge aantal laag-risico nulliparae (vrouwen die voor het eerst gaan bevallen) die een keizersnede krijgen in verband met de diagnose 'niet vorderende ontsluiting'. Als inefficiënte weeën in een eerder stadium worden herkend, dan kan de weeënactiviteit bijvoorbeeld tijdig worden gestimuleerd met weeënopwekkende medicatie (oxytocine).

In hoofdstuk 8 worden de voorlopige resultaten beschreven van een lopend onderzoek naar EHG registraties tijdens de (a terme) bevalling om onderscheid te maken tussen efficiënte en inefficiënte weeënactiviteit. Bij niet vorderen van de ontsluiting (NVO) en een daarop volgende keizersnede , werd aangenomen dat inefficiënte weeën daar (grotendeels) aan ten grondslag lagen . In deze studie onderzoeken wij of de karakteristieken van weeën bij vrouwen die een keizersnede krijgen in verband met NVO verschillen van die bij vrouwen met een normaal ontsluitingspatroon.

Zwangeren met een eenling in hoofdligging en een zwangerschapsduur van meer dan 37 weken werden gevraagd deel te nemen aan het onderzoek. Onderscheid wordt gemaakt tussen zwangeren met een spontaan begin van de bevalling en vrouwen waarbij de bevalling wordt ingeleid. Bij deelname worden de weeën tot aan de geboorte van het kind met de EHG methode geregistreerd en de voortgang van de ontsluiting bepaald met behulp van vaginale touchers (standaard elke 2 uur of wanneer anderzijds geïndiceerd). De EHG karakteristieken (peak frequentie; PF) van weeën van zwangeren die een keizersnede kregen in verband met NVO zijn vergeleken met die van vrouwen die een spontane bevalling ondergingen (matched case-control analyse). In totaal kregen 9/45 zwangere vrouwen een keizersnede in verband met NVO nadat de bevalling was ingeleid en 10/50 zwangere vrouwen kregen een keizersnede na een spontaan begin van de bevalling. De voorlopige resultaten van dit lopende onderzoek tonen allereerst dat de peak frequentie van weeën stijgt met vorderende baring. Daarnaast is de peak frequentie hoger bij zwangeren die een keizersnede krijgen in verband met NVO, vergeleken met zwangeren die volledige ontsluiting bereiken. Dit effect werd alleen gezien bij vrouwen met een spontaan begin van de bevalling, en niet wanneer de bevalling wordt ingeleid. Deze voorlopige resultaten suggereren dat een niet vorderende baring geassocieerd is met abnormale elektrische (myometrium) activiteit van de baarmoeder.

In deel II van dit proefschrift is een nieuwe methode voor het registreren van weeënactiviteit beschreven. Niet alleen de beperkte waarde van huidige beschikbare methoden, maar ook het feit dat weeënregistratie met EHG mogelijk inzicht kan geven in relevante klinische uitkomsten, zoals het vorderen van de baring, of het herkennen van voortijdige weeënactiviteit, heeft aangezet tot de ontwikkeling dan wel verbetering van EHG registraties.

De validatie studie in hoofdstuk 7 heeft aangetoond dat (a terme) weeënregistratie met EHG nauwkeurig is. Ondanks het gebruik van verschillende apparatuur en analyse technieken komen de resultaten zoals beschreven in hoofdstuk 7 overeen met bevindingen van andere onderzoeken [15,17,23,24]. Het verdient aanbeveling om in de toekomst te werken naar en meer eenduidige wijze van analyseren van de EHG data om zo studieresultaten beter te kunnen vergelijken of interpreteren.

De voorlopige resultaten van hoofdstuk 8 ten aanzien van verschillen in peak frequentie bij efficiënte en inefficiënte weeën, vormen samen met bevindingen van eerder onderzoek naar het verloop van de richting van weeën een indicatie dat EHG méér potentie heeft voor het herkennen van pathologie in het verloop van de ontsluiting dan de huidige weeënregistratie methoden (IUD en externe tocodynamometrie)[20-22,24]. Naast het afronden van de lopende studie (hoofdstuk 8) zullen bij toekomstig onderzoek de EHG resultaten moeten worden gekoppeld aan interventies (bijstimuleren van de bevalling, keizersnede) om de klinische relevantie van deze techniek te kunnen evalueren. Naast het huidige beschreven onderzoek zijn er nog meer indicaties waarbij het belang van EHG registraties kan worden onderzocht, zoals bij het beoordelen van de wijze van inleiden van de bevalling en ook bij zwangeren met een dreigende vroeggeboorte.

Momenteel wordt de wijze van inleiden van de bevalling bepaald aan de hand van de Bishop score, waarbij de mate van rijping van de baarmoedermond doorslaggevend is voor enerzijds het toedienen van locale hormonale behandeling (primen met prostagladines) of anderzijds intraveneuze toediening van weeën stimulerende middelen (oxytocine). Helaas is het verloop van de bevalling, hetzij na priming van de baarmoedermond, hetzij bij intraveneuze behandeling, erg onvoorspelbaar. Wellicht dat hier een rol is weggelegd voor EHG weeënregistratie. Mogelijk kan met behulp van EHG metingen inzicht worden verkregen in de mate van rijping van de baarmoeder (in tegenstelling tot rijping van de baarmoedermond), zodat hiermee de dosering en timing van behandeling beter kunnen worden afgesteld. Daarnaast kan bijstimulatie van de baring met intraveneuze toediening van oxytocine meer in detail worden bestudeerd met EHG metingen. Dit is met name interessant gezien de resultaten van recent onderzoek waarbij is aangetoond dat bijstimulatie bij zwangeren met NVO niet effectief lijkt omdat de baarmoeder mogelijk al dusdanig is uitgeput dat bijstimulatie geen effect meer kan bewerkstelligen[25].

Eerdere onderzoeken hebben aangetoond dat slechts 30% van de zwangeren bij wie dreigende vroeggeboorte wordt gediagnosticeerd daadwerkelijk voortijdig gaan bevallen. Hieruit kan worden geconcludeerd dat met de huidige technieken ‘echte’ vroeggeboorte moeilijk te herkennen is. Verschillende onderzoeken hebben gesuggereerd dat met EHG dreigende vroeggeboorte mogelijk beter herkend kan worden[16,21]. Daarnaast is recent een artikel verschenen dat het karakter van premature weeën voor en na toediening van weeënremmende medicatie (tocolyse) heeft bestudeerd. Hierbij is klinisch effectieve weeenremming geassocieerd met een afname van de peak frequentie van weeën[20]. Deze bevinding komt overeen met eerdere bevindingen dat er bij een hogere peak frequentie een hoger risico bestaat op vroeggeboorte[14,16].

Samenvattend is EHG een gevalideerde methode voor weeënregistratie, hoewel eenduidige analyse van de signalen moet worden gerealiseerd. In toenemende mate zijn er aanwijzingen dat EHG een rol kan spelen bij herkenning van zowel dreigende vroeggeboorte, als ook bij het herkennen van het niet vorderen van de a terme baring.

Referenties

1. Peters M, Crowe J, Pieri JF, Quartero H, Hayes-Gill B, James D, et al. Monitoring the fetal heart non-invasively: a review of methods. J.Perinat.Med. 2001;29(0300-5577; 5):408-416.
2. Pieri JF, Crowe JA, Hayes-Gill BR, Spencer CJ, Bhogal K, James DK. Compact long-term recorder for the transabdominal foetal and maternal electrocardiogram. Med.Biol.Eng.Comput. 2001 01;39(0140-0118; 1):118-125.
3. Graatsma EM, Jacod BC, van Egmond LA, Mulder EJ, Visser GH. Fetal electrocardiography: feasibility of long-term fetal heart rate recordings. BJOG 2009 Jan;116(2):334-7; discussion 337-8.
4. Huhn EA, Phasengleichgerichtete Signalmittelung der Kardiotokographie bei intrauteriner Wachstumsretardierung. Munchen, Germany: Frauenklinik der Technischen Universität München Klinikum rechts der Isar; 2007.
5. Lobmaier SM, Pildner von Steinburg S, Müller A, Schuster T, Huhn EA, Ortiz JU, Schneider KTM, Schmidt G. Phase rectified signal averaging as a new method for surveillance of growth restricted fetuses, a prospective observational study. Munchen, Germany: Frauenklinik, Abt. Perinatalmedizin, TU München.
6. Kariniemi V, Hukkinen K, Katila T, Laine H. Quantification of fetal heart rate variability by abdominal electrocardiography. J.Perinat.Med. 1979;7(1):27-32.
7. Stinstra JG, Peters MJ. The influence of fetoabdominal tissues on fetal ECGs and MCGs. Arch.Physiol.Biochem. 2002 07;110(1381-3455; 3):165-176.
8. Baschat AA. Fetal growth restriction - from observation to intervention. J.Perinat.Med. 2010 May;38(3):239-246.
9. Salvesen DR, Freeman J, Brudenell JM, Nicolaides KH. Prediction of fetal acidaemia in pregnancies complicated by maternal diabetes mellitus by biophysical profile scoring and fetal heart rate monitoring. Br.J.Obstet.Gynaecol. 1993 Mar;100(3):227-233.
10. Lauenborg J, Mathiesen E, Ovesen P, Westergaard JG, Ekbom P, Molsted-Pedersen L, et al. Audit on stillbirths in women with pregestational type 1 diabetes. Diabetes Care 2003 May;26(5):1385-1389.
11. Kerssen A, de Valk HW, Visser GH. Day-to-day glucose variability during pregnancy in women with Type 1 diabetes mellitus: glucose profiles measured with the Continuous Glucose Monitoring System. BJOG 2004 09;111(1470-0328; 9):919-924.
12. Bakker PC, Zikkenheimer M, van Geijn HP. The quality of intrapartum uterine activity monitoring. J.Perinat.Med. 2008;36(3):197-201.
13. Bakker JJ, Verhoeven CJ, Janssen PF, van Lith JM, van Oudgaarden ED, Bloemenkamp KW, et al. Outcomes after internal versus external tocodynamometry for monitoring labor. N.Engl.J.Med. 2010 Jan 28;362(4):306-313.
14. Garfield RE, Maner WL, MacKay LB, Schlembach D, Saade GR. Comparing uterine electromyography activity of antepartum patients versus term labor patients. Am.J.Obstet.Gynecol. 2005 Jul;193(1):23-29.

15. Maul H, Maner WL, Olson G, Saade GR, Garfield RE. Non-invasive transabdominal uterine electromyography correlates with the strength of intrauterine pressure and is predictive of labor and delivery. J.Matern.Fetal.Neonatal Med. 2004 May;15(5):297-301.
16. Maner WL, Garfield RE, Maul H, Olson G, Saade G. Predicting term and preterm delivery with transabdominal uterine electromyography. Obstet.Gynecol. 2003 Jun;101(6):1254-1260.
17. Euliano T, Skowronski M, Marossero D, Shuster J, Edwards R. Prediction of intrauterine pressure waveform from transabdominal electrohysterography. J.Matern.Fetal.Neonatal Med. 2006 Dec;19(12):811-816.
18. Marque CK, Terrien J, Rihana S, Germain G. Preterm labour detection by use of a biophysical marker: the uterine electrical activity. BMC Pregnancy Childbirth 2007 Jun 1;7 Suppl 1:S5.
19. Rabotti C, Mischi M, Oei G, Bergmans J. Noninvasive estimation of the electrohysterographic action-potential conduction velocity. IEEE Trans.Biomed.Eng. 2010 May 10.
20. Vinken MP, Rabotti C, Mischi M, van Laar JO, Oei SG. Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice. Obstet.Gynecol.Int. 2010;2010:325635.
21. Schlembach D, Maner WL, Garfield RE, Maul H. Monitoring the progress of pregnancy and labor using electromyography. Eur.J.Obstet.Gynecol.Reprod.Biol. 2009 May;144 Suppl 1:S33-9.
22. Euliano TY, Marossero D, Nguyen MT, Euliano NR, Principe J, Edwards RK. Spatiotemporal electrohysterography patterns in normal and arrested labor. Am.J.Obstet.Gynecol. 2009 Jan;200(1):54.e1-54.e7.
23. Rabotti C, Mischi M, van Laar JO, Oei GS, Bergmans JW. Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. Physiol.Meas. 2008 Jul;29(7):829-841.
24. Rabotti C, Mischi M, van Laar J, Oei G, Bergmans J. Electrohysterographic analysis of uterine contraction propagation with labor progression: a preliminary study. Conf.Proc.IEEE Eng.Med.Biol.Soc. 2007;2007:4135-4138.
25. Quenby S, Pierce SJ, Brigham S, Wray S. Dysfunctional labor and myometrial lactic acidosis. Obstet.Gynecol. 2004 Apr;103(4):718-723.
26. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004 04/17;328(1468-5833; 7445):915.

Addendum

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List of publications

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Fetal electrocardiography: feasibility of long-term fetal heart rate recordings.
Graatsma EM, Jacod BC, van Egmond LA, Mulder EJ, Visser GH.
BJOG. 2009 Jan;116(2):334-7; discussion 337-8.

Maternal body mass index does not affect performance of fetal electrocardiography.
Graatsma EM, Miller J, Mulder EJ, Harman C, Baschat AA, Visser GH.
Am J Perinatol. 2010 Aug;27(7):573-7. Epub 2010 Mar 1.

A validation of electrohysterography for uterine activity monitoring during labour.
Jacod BC, **Graatsma EM**, Van Hagen E, Visser GH.
J Matern Fetal Neonatal Med. 2010 Jan;23(1):17-22.

Average acceleration and deceleration capacity of fetal heart rate in normal pregnancy and in pregnancies complicated by intrauterine growth restriction.
Graatsma EM, Mulder EJH, Lobmaier SM, Pildner von Steinburg S, Schneider KTM, Schmidt G, Visser GHA
Submitted for publication

Glycaemic control throughout pregnancy in women with type 1 diabetes.
Graatsma EM, de Valk HW, Kerssen A, Visser GHA
Under review

Continuous simultaneous monitoring of maternal glucose and fetal heart rate in diabetic pregnancy.
Graatsma EM, Mulder EJH, de Valk HW, Visser GHA
Submitted for publication

Left ventricular cardiac function in fetuses with congenital diaphragmatic hernia and the effect of fetal endoscopic tracheal occlusion.
Van Mieghem T, Gucciardo L, Doné E, Van Schoubroeck D, **Graatsma EM**, Visser GH, Verhaeghe J, Deprest J.
Ultrasound Obstet Gynecol. 2009 Oct;34(4):424-9.

Addendum

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Dankwoord

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Addendum

Curriculum Vitae

Curriculum Vitae

Margo Graatsma werd op 16 april 1979 geboren te Gouda. In 1997 behaalde zij haar VWO diploma aan het Rotterdams Montessori Lyceum. De numerus fixus voor de studie Geneeskunde zorgde door tweemaal uitloten voor enkele omzwervingen. Zij werkte een jaar als au pair in Parijs en behaalde tevens haar propedeuse Psychologie aan de Universiteit Utrecht. Na een derde maal meeloten begon zij in 1999 zeer gemotiveerd aan de opleiding Geneeskunde, ook ditmaal aan de Universiteit Utrecht. De studie werd in 2002 een jaar onderbroken door haar functie als praeses van het Bestuur van de Utrechtsche Vrouwelijke Studenten Vereeniging (UVSV/NVVSU).
Na de doctoraalfase van haar studie heeft zij haar wetenschappelijke stage uitgevoerd bij Prof. Dr. G.H.A. Visser. Na het artsexamen in 2006 kreeg zij de gelegenheid het wetenschappelijk onderzoek voort te zetten in een promotie-onderzoek, dat zij onder leiding van Prof. Dr. G.H.A. Visser heeft afgerond.
In het kader van een uitwisselingstraject heeft zij in 2008 onder leiding van Prof. Dr. W. Steyn in het Tygerberg ziekenhuis te Stellenbosch, Zuid Afrika, 3 maanden onderzoek gedaan. Verder was zij in 2009 gedurende 7 maanden werkzaam als AGNIO op de afdeling Verloskunde van het Universitair Medisch Centrum Utrecht.
In mei 2010 is zij begonnen met haar opleiding tot gynaecoloog in het Diakonessenhuis te Utrecht (Opleider Dr. P.C. Scholten).
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