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Female Age in ART: When to Stop?

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Key Words
Assisted reproduction technology · Assisted reproduction technology (ART), female age · ART, assessment of age limits · ART, cost-benefit and cost-effectiveness · IVF/ICSI treatment · IUI/STIM treatment · Ovarian reserve tests · Ovarian ageing · Antral follicle count

Abstract
With increasing age the probability of ongoing pregnancy established by the use of assisted reproduction technology (ART) decreases. As a result the question arises whether age limits for the application of ART should be established. From a literature review and ongoing research data it appears that the costs per child born greatly increase after the age of 40 for both intrauterine insemination with mild ovarian stimulation and in vitro fertilisation treatment, while in cases of 44 and over, prognosis is flat zero. The willingness to pay for extra costs will greatly determine whether and at what age strict limits should be applied. Fortunately, predictive factors for success, like the antral follicle count, may enable the identification of women over 40 and under 44 that still have favourable prospects, thereby decreasing the necessary costs per childbirth and allowing couples into ART programs that are often denied based solely on female age.

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Introduction

It is well known that fertility in the female gradually decreases with age. The best documentation for this phenomenon is found in studies on historical populations, where no contraceptive measures were used, and studies on women undergoing donor insemination [1, 2]. From these studies it appears that the monthly chance of achieving a pregnancy decreases gradually after the age of 30, rapidly from 36 years onwards, while a woman loses her natural fertility at a mean age of 41 [2]. It needs to be stressed that age at loss of natural fertility can vary from 33 to 48 years. Apparently, the rate of fertility decrease varies considerably among women. This implies that approximately half of the women of 40 years of age will still have the capacity of becoming pregnant and give birth, although the monthly fecundity and the quality of the conceptus have become diminished.

Fertility decrease is mostly explained by quality loss of the oocyte, as documented by an increase in embryonic aneuploidy, decreased embryo implantation rate and enhanced risk of abortion [2, 3]. Parallel to this, the number of primordial follicles present in the ovaries will clearly decrease with advancing age [4, 5]. In addition, small contributions to the reproductive ageing process are made by changes in menstrual cycle quality, decrease in endometrium function, decay in coital frequency and loss in endosalpinx function [6].

In couples suffering from subfertility the age of the woman plays a pronounced role. This is true for estima-

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tions of the spontaneous conception probability in couples with otherwise unexplained infertility [7]. Also, in infertility treatments like IVF female age will dictate the chances of success [8]. In this review the central question is to what extent the age of the woman should play a role in the use of limits to the availability of assisted reproduction technology (ART).

Ovarian Reserve Tests

The variation of the age at which a woman reaches her natural infertility is highly congruent to the variation in age at menopause [3]. There is growing evidence that reaching menopause early implies that loss of female fertility is antedated to the same degree [9, 10]. It is hypothesized that on an individual level the time relation between age at loss of fertility and the occurrence of menopause is fixed at an interval of 10 years. In the years when female fertility falls down to zero, menstrual cycle regularity is still maintained. As a consequence of this, it is difficult to assess a woman's reproductive status on the basis of her age alone.

Several tests have been proposed as part of the infertility work-up to assess an individual's ovarian reserve. Ovarian reserve can be defined as the combination of the number of follicles present in the ovaries at a given age and the quality of the oocytes held within these follicles. Apart from a woman's age, age at menopause for her mother provides useful information, as genetic factors play a major role in determining age at menopause [11]. Measuring basal FSH is another way to identify cases with a clearly reduced reproductive capacity. Elevated FSH above a certain threshold implies that in such an individual the chance of having severely reduced fertility is high, especially in older women [12–15]. However, other explanations for elevated FSH, such as familial dizygotic twinning, are to be considered, especially in younger women, where chances for pregnancy may not be dramatically reduced [16, 17]. Several other ovarian reserve tests have been advocated, of which the ultrasound-based antral follicle count (AFC) and recently serum anti-Müllerian hormone need to be mentioned. Both tests, either alone or in combination with basal FSH, are reliable predictors for the occurrence of poor response in IVF treatment [18–21]. Unfortunately, none of the tests that have been studied in the last 15 years is capable of predicting the occurrence of pregnancy in such a reliable way that patients can be strongly advised or forced to refrain from further treatment [22–24].

Assessment of Age Limits for ART

In many centres across the world, women over the age of 38 will undergo specific tests to assess their reproductive status, and women of 41 and over are often denied any assisted reproduction treatment. All this is based on the fact that the probability of occurrence of pregnancy in infertility treatments becomes reduced with increasing age [25] and declines to approach the zero line after the age of 40 years. In the view of complication risks of IVF and the assumed low cost-benefit ratio, treatment in women over 40 is considered unjustified [26, 27], leading to denial of participation in an IVF program.

Several other arguments may play a role in the age limits applied. Pregnancy, especially first pregnancy, in the age group over 40 may bear an increased risk of complications both for the mother and the newborn [28–37]. Especially the probability of occurrence of pre-eclampsia, preterm birth and perinatal death seems to be clearly raised. Also, raising children in this phase of life may be hampered by decreasing physical fitness and mental flexibility. Research on this topic, however, is scarce [38]. Finally, survival statistics on men and women will show a considerable increase in the rate of mortality between the ages of 40 and 60 years. This implies that consequences of the loss of 1 parent for a 5-, 10- or 15-year-old child should be incorporated into the view on parenthood initiated by the use of ART in the fourth or fifth decade of life [25]. Although it is desirable to address all these specific points of view extensively, the main aim of the present work is to inventarise efficacy and cost aspects of ART for women above 40 years of age. The other aspects will not be further discussed.

Cost-Benefit and Cost-Effectiveness of Assisted Reproduction Treatment in Women over 40 Years of Age

There exist no studies that have systematically analysed at what age ART in fact has become (cost-) non-beneficial. Ideally, such a study should firstly assess the efficacy of treatment compared to no treatment, in several age classes. In addition, comparisons of different treatment modalities in terms of efficacy should be made. Cumulative probability of pregnancy after several treatment cycles should be included in the efficacy analysis, while assessment of predictive factors should enable the development of models from which the individual prospects for a couple can be estimated. For decision making

costs necessary for the creation of 1 healthy baby (cost-effectiveness [39]) need to be assessed in which calculation both costs for treatment and costs related to pregnancy and pregnancy outcome should be included. Expert opinion shall be necessary to decide to what level the cost per born baby may rise before treatment can be denied from the regulatory point of view (cost-benefit analysis [39]). Moreover, the patient as an expert herself may be asked to participate in such an inventory of minimal cost-effectiveness (willingness to pay analysis) [39].

Studies that have analysed these issues are quite rare and in fact not any study has performed analyses that fully cover the range of aspects that contribute to a proper decision, as described above. Randomised studies comparing assisted reproduction treatments, like in vitro fertilisation (IVF) and intrauterine insemination (IUI), with no treatment are scarce [40–43]. Predictive models providing information on success rates for individual couples have been shown to be not universally applicable [44]. Therefore, predictive information applied in practice is often more or less empirical and not based on systematic research. Cost-effectiveness comparative studies do exist but are often non-randomised [41, 45–52], while expert inquiries on a desired level of cost-benefit are almost lacking [51].

In the paragraphs ahead, the issue to what extent the age of the woman should play a role in decisions on assisted reproduction treatment will be tackled in a systematic fashion. Separately, attention will be paid to intrauterine insemination with mild ovarian stimulation (IUI/STIM) and in vitro fertilisation (IVF/ICSI). Firstly, an estimate will be made of the clinical pregnancy chances for couples where the woman is aged over 40 in both treatment modalities. For that purpose, studies addressing this issue will be searched for in the literature. Key words used in various combinations for a Medline search are 'in vitro fertilisation', 'intra uterine insemination', 'age', 'miscarriage', 'live birth', 'prognostic factors', 'cumulative pregnancy rates'. On the basis of read titles and abstracts, full articles were studied and selected if they provided information on all or several of the following key points: *pregnancy rate per started cycle, ongoing pregnancy rate per started cycle, cumulative pregnancy rate for 4 (IUI/STIM) or 3 (IVF/ICSI) treatment cycles, predictive factors for success in the over 40 age group.* Finally, from the selected studies, cross-references were identified and added to the selection if appropriate.

Studies addressing the issue of cost-effectiveness were searched for by using combinations of the following key words: 'cost-effectiveness', 'in vitro fertilisation', 'intra uterine insemination', 'economic analysis'.

Finally, preliminary results will be presented from a prospective study on the issue whether predictive factors can identify patients above 40 years of age that have an acceptable prognosis.

Pregnancy Rates for Women over 40 Years in IUI/STIM Treatment

With the search strategy described above, 29 studies were identified from reading titles and abstracts. Of these, 14 studies did not provide any of the key points as described above. Check of cross-references did not reveal any additional studies. Therefore, 15 studies were finally selected to contribute to the analysis.

Table 1 summarizes the key information extracted from these studies [49, 53–66]. The vast majority of the intrauterine insemination cycles were combined with mild to moderate ovarian stimulation by the use of exogenous gonadotropins and/or oral clomiphene citrate and/or sequential clomiphene citrate/gonadotropins. Comparison of the efficacy of gonadotropin versus clomiphene citrate only therapy was not feasible due to the fact that the most studies used various stimulation schemes or sequential regimens only and did not stratify for the type of stimulation. Only in a very small part of the treatment cycles no use was made of ovarian stimulation.

For the comparison of treatment in women over 40, cycles of women under 40 were grouped together in one age class. Table 1 shows that in all studies in women under 40, the pregnancy rate per cycle was a little more than twice as high as in the age group over 40. Although not all studies contribute to the data on ongoing pregnancy rates per cycle, the same relation is seen between the two age classes. The rate of early loss of pregnancies by miscarriage is ~33% in the high age class, compared to ~14% in the lower age group. To assess the real cumulative probability of pregnancy in a series of 4 treatment cycles, the data provided in the studies are far too insufficient to come to a proper conclusion.

In women over the age of 40 who undergo a treatment with intrauterine insemination with mild ovarian stimulation, several predictive factors for success are identified. However, different studies will reveal different predictive factors and the effects identified cannot be described quantitatively. Elevated basal FSH is a clear unfavourable factor, while in women of 44 years and older the chances for ongoing pregnancy are diminished to a level close to zero. In addition, semen abnormalities also exert a negative influence on the probability of pregnancy which

Table 1. Pregnancy rates for IUI treatment and predictive factors for success for couples with female age over 40 years

Author/year	Age group, years	Pregnancy	Cycles	Treatment	Stimulation	Preg rate/ cycle, %	Ong preg/ cycle, %	Preg rate/ 4 cycles, %	Predictive factors > 40 years
Haebe, 2002	>40	Biochem	106	IUI/Nat/Stim	Mixed	17.9	8.5		None
	<40		1,011			19.5	12.6		
Houmard, 2002	>40	Clin	208	IUI/Stim	Sequential	2.4			None
	<40		450			9.3			
Khalil, 2001	>40	Clin	39	IUI/Stim	Sequential	10.3			None
	<40		2,434			11.9			
Sahakyan, 1999	>40	Clin	115	IUI/Stim	Gonadotropins	7.0		24.6	None
	<40		502			13.6		36.7	
Nuojua, 1999	>40	Biochem	98	IUI/Stim	Sequential	4.1	3.1		None
	<40		713			13.7	9.7		
Brzechffa, 1998	>40	Clin	85	IUI/Stim	Sequential	5.9	3.5	20.0	Age male partner
	<40		331			16.3	14.9	40.0	
Brzechffa, 1997	>40	Clin	111	IUI/Stim	Gonadotropins	3.6	2.7		Age male partner
	<40		252			16.0	13.0		
Buyalos, 1997	>40	Clin	227	IUI/Stim	Mixed	8.0	5.3		Basal FSH, age female
	<40								
Campana, 1996	>40	Biochem	238	IUI/Nat/Stim	Mixed	6.5			None
	<40		877			2.1			
Corsan, 1996	>40	Clin	469	IUI/Stim	Mixed	6.8	4.4		Infertility type, age female
	<40		210			16.7	13.8		
Vollenhoven, 1996	>40	Biochem	37	IUI/Stim	Gonadotropins	2.7			None
	<40		234			9.4			
Agarwal, 1996	>40	Clin	130	IUI/Stim	CC	5.4		24.0	None
	<40		534			11.6		40.0	
Plosker, 1994	>40	Biochem	25	IUI/Nat/Stim	Mixed	4.0			None
	<40		356			13.2			
Pearlstone,1992	>40	Clin	402	IUI/Stim	Mixed	3.5	1.2		Basal FSH, age female
	<40		1,345			9.8	7.9		
Hull, 1992	>40	Clin	28	IUI/Stim	Sequential	3.6			Semen
	<40		158			18.3			
All studies	>40		2,318			5.5	3.7		
	<40		9,407			12.4	10.7		

Ong preg = Pregnancy advanced beyond 12 weeks; IUI/stim = Intrauterine insemination combined with mild ovarian stimulation; IUI/nat = intrauterine insemination in the natural cycle; Mixed = CC only or sequential CC/HMG/FSH or HMG/FSH only or GnRH agonist with HMG/FSH; Sequential = CC followed by HMG/FSH; CC = clomiphene citrate only; Gonadotropins = HMG or FSH only.

comes to expression also in the effect of the age of the male partner.

On the basis of the data presented, it is not possible to answer the question whether there is any clear efficacy of this treatment modality in females over the age of 40. As predictive models for spontaneous pregnancy, like the Eimers model [67], are not applicable to women in this age category, assessment of the couples' chance for success without medical interference is impossible. Randomized studies comparing treatment with expectant management [41, 42, 68] are quite rare and do not include older aged women. On the basis of existing research, the probability for pregnancy of women over the age of 40 who suffer from unexplained subfertility or subfertility due to mild semen factors [68] can be estimated to be approximately 3–4% per year. On the basis of table 1, the theoretical cumulative probability of ongoing pregnancy after a series of 4 treatment cycles was calculated by the formula $F = 1 - (1 - f)^4$, in which F = the cumulative probability of ongoing pregnancy and f is the cycle probability of ongoing

Table 2. Pregnancy rates for IVF/ICSI treatment and predictive factors for succes for couples with female age over 40 years

Author/year	Age group, years	Cycles	Treatment	Clin preg/ cycle, %	Ong preg/ cycle, %	Clin preg/ 3 cycles, %	Ong preg/ 3 cycles, %	Predictive factors in women >40 years
ASRM, 2002	>40	7,593	IVF/ICSI	13.5	8.1			Na
	<40	55,970		32.9	27.8			
Opsahl, 2001	>40	405	IVF/ICSI	17.7	6.0			Basal FSH, number of replaced embryos
	<40							Age female
Auyeung, 2001	>40	58	IVF/GIFT	19.0	15.5			Na
	<40							
Ron-El, 2000	>40	376	IVF/ICSI	12.0	4.5			Age female
	<40							
Pantos, 1999	>40	62	IVF	13.0	9.6			Na
	<40	231		39.4	32.4			
Engmann, 1999	>40	86	IVF/ICSI	9.3	7.0	24.0	18.0	Na
	<40	449		21.0	18.3	47.0	41.0	
Bar-Hava, 1999	>40	488	IVF/ICSI	9.2		30.0		Na
	<40	1,367		22.0				
Bongain, 1998	>40	194	IVF	8.2	3.6			Flare-up protocol
	<40	209		15.8	13.4			
Lass, 1998	>40	1,088	IVF	11.6	8.5	30.0		Na
	<40	8,233		28.2	24.6			
Grimbizis, 1998	>40	736	ICSI	14.7	7.2			Number of replaced embryos
	<40							Age female
Roest, 1996	>40	169	IVF	16.0	11.0			Ovarian response
	<40	2,419		23.1	18.8			
Widra, 1996	>40	163		16.6	9.2			Basal FSH, number of replaced embryos
	<40	550	IVF	32.0	25.1			
Tan, 1992	>40	155	IVF	7.2	3.2	16.0		Na
	<40	4,800		15.0	10.4			
FIVNAT, 1990	>40	366	IVF	9.0				Na
	<40	4,952		15.8				
Dor, 1990	>40	246	IVF		4.5		13.1	Na
	<40	1,486			15.3		36.5	
Romeu, 1987	>40	64	IVF	22.0	9.3			Na
	<40	819		24.0	16.0			
All Studies	>40	12,249	IVF/ICS/GIFT	12.8	7.2			
	<40	81,485		29.0	23.6			

Ong Preg = Pregnancy advanced beyond 12 weeks; GIFT = gamete intrafallopian transfer; ET = embryo transfer; Na = not analysed.

pregnancy [69]. This resulted in an estimate of ~14% cumulative probability. As real cumulative probabilities may be lower if selection and drop-out of lower prognosis cases is corrected for, this implicates that this treatment modality may be regarded upon as a very modest solution for couples with unexplained or mild male factor-related subfertility.

Pregnancy Rates for Women over 40 Years in IVF/ICSI Treatment

Out of the reading of abstracts and titles and the use of cross-references, a total of 23 studies was identified. From these 23 studies, 7 did not provide any of the key points. Finally, a total of 16 studies was used to collect the data that are summarized in table 2 [70–85]. The vast majority of the studies applied a long GnRH agonist suppression

protocol followed by ovarian hyperstimulation with gonadotropins. As in the IUI data, the information on women under the age of 40 was grouped together in to one age class. As shown in table 2, women over the age of 40 perform clearly worse than their younger counterparts. Pregnancy rates are decreased by a factor 2 while ongoing pregnancy rates in the high age group are only one third of those in the younger age class. The rate of miscarriage is ~40% in the old age group compared to ~19% in the younger women. Cumulative ongoing pregnancy rates are difficult to assess for the group of studies as a whole as is clearly shown in table 2.

Several predictive factors that influence the probability of pregnancy for an individual couple are recognised. Elevated FSH will reduce the probability of pregnancy to approximately zero in this age group. Other factors that worsen the prognosis for the over 40 age group are those who are also related to exhausted ovarian reserve, such as a poor ovarian response to gonadotropin stimulation and a low number of available embryos. In the subgroup of women of 44 years and older the probability of pregnancy appears to be close to zero. Finally, it seems that the negative effect of semen abnormalities, as observed in the IUI/STIM treatment group, is compensated by the application of the ICSI technique.

The data presented do not give an unequivocal conclusion for the group of women over 40. Efficacy again has never been established in randomized trials and to date such studies cannot be expected to be undertaken. Most clinicians will use a number of predictive factors to allow women over 40 to enter an IVF program. The theoretical cumulative probability of ongoing pregnancy on the basis of the data in table 2, calculated in the same way as for the IUI studies, is approximately 20% after a series of 3 treatment cycles. In comparison to the estimate of 14% in 4 cycles for couples in IUI treatment, efficacy of IVF/ICSI seems better than that of IUI/STIM, although clearly these data cannot be compared in a back-to-back fashion. By selecting couples with favourable predictive factors, both these rates may be further raised [86].

Analysis of Cost-Effectiveness

Analysis of cost-effectiveness of infertility treatments should generally take into account the possibility that for the couple being studied an expectant management may be the first choice, because the chances for spontaneous pregnancy are favourable enough to postpone treatment [45]. This may specifically be true for couples of which the female is still young. Expectant management will very much lower the costs per childbirth although from a motivational point of view, this type of management is often hard to realize. Although reliable data on the probability of a spontaneous pregnancy for women above 40, who have tried for more than 1 year to conceive, are lacking, it seems an acceptable choice to omit this specific aspect of the cost-effectiveness analysis.

The cost-effectiveness for the intrauterine insemination with mild ovarian stimulation treatment in older women has been addressed in a few studies. On the basis of these studies [48, 49] and table 1, it can be calculated that one ongoing pregnancy for women over 40 will raise costs that amount to ca. EUR 20,000. The same calculation for women under 40 implies costs to be ca. EUR 7,000. In both calculations it is assumed that one IUI/STIM treatment cycle raises a total cost of ca. EUR 800. An ongoing pregnancy achieved in older women therefore is 3 times as expensive in comparison to the same achievement in younger women.

As for the IVF/ICSI treatment modality, it has already been suggested in the literature that in women over 35, direct initiation of treatment is more cost-effective than applying a period of expected management [45]. This may also be true for women over the age of 40. Assuming that the costs for an IVF/ICSI treatment will amount to ca. EUR 3,000 and making use of the success rates in table 2, it can be calculated that one ongoing pregnancy for women under 40 will raise a cost of ca. EUR 13,000 in comparison to ca. EUR 37,000 for women over 40.

It needs to be stressed that costs for absence due to illness or clinic visits, travelling and medical complications during treatment and in pregnancy have not been incorporated in the calculations above. Also, additional costs related to the occurrence of multiple gestations were not included. As the chance of a twin pregnancy will certainly be much higher in the lower age group it is needless to say that this is to the benefit of the cost-effectiveness of treatment in the older age group.

It can be concluded that treatment of subfertility in older women will raise 2–3 times more costs for the achievement of an ongoing pregnancy in comparison to younger women. This is true for both treatment options under study. If this comparison would have been focused on treatment in the most optimal treatment group, namely those between 30 and 35 years of age, then this difference in cost per ongoing pregnancy will become even larger. To date, no clear insight is present into the question to what level costs may rise to achieve an ongoing pregnancy. Therefore it remains difficult to assess whether the

Table 3. Role of the AFC, basal FSH and female age in the prediction of success in IVF for couples with female age 41 years and over

	AFC < 5 n = 35	AFC ≥ 5 n = 49	Age 41–42 n = 48	Age 43–46 n = 36	All n = 84
Normal response	11/35 (31%)	38/49 (78%)**	30/48 (62%)	19/36 (53%)	49/84 (58%)
Ongoing pregnancy/cycle	1/35 (3%)	8/49 (16%)**	8/48 (17%)	1/36 (3%)*	9/84 (11%)
Ongoing pregnancy/cycle, FSH > 10 U/l	1/18 (5%)	2/11 (18%)**	2/13 (15%)	1/16 (6%)	3/29 (10%)
Ongoing pregnancy/cycle, FSH ≤ 10 U/l	0/17 (0%)	6/38 (16%)**	6/35 (17%)	0/20 (0%)	6/55 (11%)
Ongoing pregnancy/cycle, AFC < 5			0/14 (0%)	1/21 (5%)	
Ongoing pregnancy/cycle, AFC ≥ 5			8/34 (23%)#	0/15 (0%)*	

* $p < 0.05$ for comparison female age 41–42 vs. 43–46; ** $p < 0.05$ for comparison AFC ≥ 5 vs. AFC < 5; # $p < 0.05$ for comparison AFC ≥ 5 vs. AFC < 5 within age group 41–42.

Ongoing pregnancy = pregnancy advanced beyond 12 weeks.

cost-effectiveness of treatment in those over age of 40 is too low, or to put it another way, whether a child is too expensive.

In the comparison of IUI/STIM with IVF/ICSI treatment the IUI treatment seems more cost-effective than IVF. However, one should realize that these data are not obtained in a direct comparison of the two treatment modalities. Application of IUI/STIM is limited to couples with unexplained and mild semen factor subfertility. This will further hamper the comparison, as these two indications are known to be successful categories in IVF/ICSI albeit after failed IUI/STIM treatment. Moreover, in IVF treatment, information will emerge on the ovarian response to ovarian stimulation and this may help to select cases with a favourable prognosis, to proceed with treatment. Exclusion of so-called ineffective cycles will then rapidly increase a favourable relation between cost and effectiveness. On the whole, IVF/ICSI treatment will raise 2–3 times more costs for achieving a delivery compared to IUI/STIM, confirming data in the literature [41, 48, 50, 87].

The Utrecht Experience

In the research project 'Ovarian Ageing' carried out in the Department for Reproductive Medicine, University Medical Center, Utrecht, IVF treatment was offered without restrictions to couples where the female was 41 years of age or older, provided that they had a regular cycle and an indication for assisted reproduction was present. In this patient group, two ovarian reserve tests (AFC and basal FSH) were carried out before treatment was initiated. In this way it was possible to analyse systematically whether within this group of patients a subgroup could be identified in which treatment is useful. In total, 84 couples were treated. Age varied from 41 to 46 years with a mean of 42.9 (SD 1.4). IVF treatment was carried out using a so-called long suppression protocol. Leuprolide was started on day 21 on the previous cycle and after the subsequent menstrual period combined with recombinant FSH in a dose of 150 IU/day (GonalF). On the day gonadotropin stimulation was started an AFC was carried out. Basal FSH was assessed shortly before the treatment cycle was started. During gonadotropin stimulation the dosage of recombinant FSH could be raised from day 8 of the stimulation onwards to as high as 450 IU/day. Criteria for dose adaptation were estradiol <200 pmol/l and/or absent ongoing follicular growth. Cycles were cancelled if there was none or monofollicular growth after 12 days of stimulation. If two or more dominant follicles of 18 mm or larger were present, human chorion gonadotropin was administered and follicle aspiration carried out 36 h later. The occurrence of ongoing pregnancy of 12 weeks was used at the outcome measurement. Also, poor ovarian response was used as outcome measure and defined as having less than 4 oocytes at follicle aspiration or cancellation of the cycle during the stimulation phase due to insufficient follicular response.

In table 3 the most important findings in the study are shown. It appears that in cases with an AFC < 5, the probability of a poor ovarian response to gonadotropin stimulation is clearly increased. This appears to be the same for those with a basal FSH > 10 units/l (data not shown). In addition, the probability of ongoing pregnancy appeared to be very low in women with an AFC < 5. The effect of

having an AFC <5 on the pregnancy rates seems not to be clearly influenced by the level of the FSH, as in both categories of basal FSH with low AFCs the chance for pregnancy is close to zero. If stratification for age group (41–42 and 43–46) is carried out, ongoing pregnancies are more frequent in the younger age group. Within this group the AFC provides vital information on pregnancy prospects as pregnancies occur mostly in the 'younger' age group with a normal follicle count. Neither AFC nor basal FSH measurement seems to be useful in the prediction of pregnancy in women aged 43–46 years.

On the basis of these preliminary results, using factors that relate to the quantitative ovarian reserve, it seems possible to select women in the 41- to 42-year-old age group who still have a reasonable probability of ongoing pregnancy. Assuming a delivery rate per cycle of ~20% in the 41- to 42-year-old age group, the cost for 1 child born will amount to ca. EUR 18,000, a level that may make treatment in this subgroup cost-effective. If selection through tests like AFC, age and FSH or possibly anti-Müllerian hormone [88] is made operational, a patient aged 41 or 42 years may be allowed the opportunity to undergo a series of 3 IVF treatments with a 49% theoretical cumulative probability of an ongoing pregnancy. Studies including a larger number of couples allowing calculation of the predictive values of the AFC should be awaited to confirm the suggestions made in this study.

Conclusion

On the basis of the data shown in this review, it remains difficult to decide whether assisted reproduction treatment should be offered to women of 41 years and over. This is due to the fact that many points of view need to be taken into account before a well-weighted conclusion can be drawn. If issues like obstetrical performance, mental and physical fitness and survival statistics are omitted from the discussion, cost-effectiveness in relation to validation of the costs needed for one childbirth should guide the final judgement. As ovarian reserve is a biological function and not a matter of chronological age alone, factors indicating a woman's true fertility potential should be taken into account. With a theoretical cumulative probability to achieve an ongoing pregnancy of ~49% within 3 cycles for women with a favourable ovarian reserve profile, ART should not be routinely denied for women aged 41 or 42 years, while the age of 43–44 seems to be a solid biological limit for ART. As for cases with unexplained or mild semen subfertility, the IUI/STIM treatment may be considered more cost-effective, a series of IUI cycles as first-line treatment may be chosen in this specific group. This all is said with the assumption that the willingness to pay (direct or through insurance) covers the amount of costs needed for one childbirth in this age category.

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