

The effect of age on the outcome of intrauterine insemination: A review

Michaël DE BRUCKER, Herman TOURNAYE

Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium. Tel.: +32-2-477-66-99; fax: +32-2-477-66-49

Correspondence at: tournaye@uzbrussel.be

Abstract

Aim: Postponing childbearing has led to an increasing demand for treatments due to age-related subfertility. While intrauterine insemination (IUI) is widely used for different indications, here too the age of women in need of this treatment is increasing. Success rates after IUI in relationship to age are often expressed per cycle, but for patient counselling, cumulative delivery rates are to be preferred. We reviewed the literature to assess the impact of age on IUI, and the role of ovarian hyperstimulation in improving the success rates.

Methods: A review of the literature was performed using Medline. We used the UK National Health Service levels of evidence (and grades of recommendation) to categorise all studies.

Results: Overall, controlled ovarian stimulation (COH) resulted in significantly higher live-birth rates when compared to IUI in natural cycle. Since age was not always taken into consideration in many studies, differences among them may account for inconsistent conclusions. For older women aged > 37 years, natural cycle IUI resulted in a significantly higher pregnancy rate and live birth rate than IUI with COH. In women aged 37 and younger, COH resulted in a significantly higher pregnancy rate and live-birth rate compared to natural cycle IUI ($p = 0.025$).

Conclusions: Above the age of 37, success rates decline, but despite this fact, women up to 40 years, may be encouraged to continue IUI treatment, in case of donor insemination even up to 42 years of age. Overall, superovulation with IUI yields better results than unstimulated IUI, but not in women over 37 years who may rather benefit from natural cycle IUI. When the female partner is older than 35 years, a synergistic adverse effect of paternal age has been reported.

Key words: Male age, female age, success rates, clomiphene citrate, gonadotrophins, natural cycle.

Introduction

From the sixties onwards, the large-scale availability of reliable methods for contraception has greatly influenced the number of children born per family in Western societies (Broekmans *et al.*, 2007). In the developed world, postponement of marriage and childbearing resulted in unprecedented numbers of couples who desire pregnancy at a relatively later stage in life. This is a social trend, which has led to an increase in treatments for age-related female subfertility (te Velde *et al.*, 2002; Broekmans *et al.*, 2007). By postponing childbearing, a growing proportion of women attempting to conceive will fail in achieving this goal within a time frame of 12 months, a condition referred to as subfertility

(Evers *et al.*, 2002). An increasing number of couples will depend on ART to achieve a pregnancy, solely on the basis of postponing childbearing. Unfortunately, there is an age-related decrease in success rates of ART treatments (van Noord-Zaadstra *et al.*, 1991).

Patients undergoing fertility treatment need to be clearly informed about their chances of having a baby. Therefore, it is important for both the candidate couples and the fertility specialists who treat them to know the probability for pregnancy and delivery after a defined number of treatment cycles. There have been many reports about the success rates per cycle, but cumulative delivery rates in different age groups for artificial insemination on large patient populations are scarce. Especially for older

Table 1. — Level of evidence and grade of recommendation.

Grade of recommendation	Level of evidence	
A	Level 1a:	Systematic review of randomised, controlled clinical trials (RCT)
	Level 1b:	Individual randomised controlled trial
	Level 1c:	All or none
B	Level 2a:	Systematic review of cohort studies
	Level 2b:	Individual cohort study (including low-quality RCT)
	Level 2c:	Outcomes research
	Level 3a:	Systematic review of case-control studies
	Level 3b:	Individual case-control study
C	Level 4:	Case series, poor quality cohort and case control studies and review of poor quality
D	Level 5:	Expert opinion without explicit critical appraisal

patients, these data are very important. Therefore, the aim of this review is to overview the impact of age on the outcome of intrauterine insemination (IUI) and to analyze whether ovarian superovulation may have any benefit on the success rates.

Methods

Systematic review of the literature was performed on Medline for each topic. We used the UK National Health Service levels of evidence (and grades of recommendation) to categorise all studies (see Table 1).

Age effect on IUI using Husband's sperm

As shown in Table 2, our literature search revealed only one level 1 study (1b, grade A of recommendation) dealing with the age impact on IUI outcome: Goverde *et al.* (2000) wrote a prospective, randomized, parallel trial. The authors stated in their paper that women's age is the most important factor influencing the likelihood of pregnancy, whatever treatment is chosen (IUI or IVF) and that the indication, i.e. male factor or unexplained infertility, had no impact at all. A mean pregnancy rate per cycle as a function of women's age in fictional groups of 100 patients in each age category was calculated and more important, the authors investigated the cumulative delivery rates after six cycles of IUI.

All other studies retrieved on age impact on IUI were retrospective studies (level 2b of evidence and less). We will briefly discuss some of them but refer to Table 2 for specific details.

In the retrospective cohort study of Merviel *et al.* (2008) (level 2b), the woman's age significantly influenced the ongoing pregnancy rate per couple, i.e. 38.5% under 30 years old versus 12.5% for over

40 years old. Frederick *et al.* (1994) performed a retrospective case-control study (level 3a, grade B of recommendation) in which IUI results for women aged 40 years were compared with results obtained for younger women. Because of very poor success rates in women over 40 years of age, they suggested that IUI should not be used in women aged over 40 years and that a prompt recommendation for IVF should be made soon after the failure of a few attempted cycles of IUI combined with ovarian stimulation treatment.

Surprisingly, Ibérico *et al.* (2004) reported in their cross-sectional multivariate retrospective review (level 2b) lower pregnancy rates among women aged 30-39 years compared to women younger than 30 years of age, while no decline in pregnancy rates was found among women 40-43 years old. Overall, female age was not significantly associated with pregnancy rates ($P = .18$). These results are in contradiction with most trials published in the literature, so the authors suggest further research.

Other retrospective studies show similar pregnancy results (Nuojuua-Huttunen *et al.* 1999 (level 2b), Bronte *et al.* 1999 (level 4), Belloc *et al.* 2008, (level 2b)). The number of patients was not reported in these papers and received therefore a grade C of recommendation. Bronte *et al.* (1999) reported an age-related difference in the pregnancy rate per cycle but the authors failed to provide cumulative delivery rates. Nuojuua-Huttunen *et al.* (1999) and Belloc *et al.* (2008) had similar conclusions, and both achieved to report cumulative pregnancy rates. In 2002 a retrospective chart review (level 2b) was published to determine the age-related decline in live birth rates after insemination (Haebe *et al.*, 2002). The authors performed a retrospective analysis of 1117 IUI cycles in women age 40 years or more, resulting in an overall pregnancy rate of 19,4%. The

Table 2. — Overview of studies describing impact of age on success rates after IUI

Reference	Study sample (n)	Study design analysis	Level of evidence	Grade of recommendation	Number of IUI cycles (n = number of patients)	Pregnancy rates (%)	Delivery rates (%)	Cumulative delivery rates (%)	Miscarriage rates (%)	Results
IUI using husband's sperm										
Goverde <i>et al.</i> 2000	258 couples were treated either IUI in spontaneous cycle, either IUI after mild ovarian stimulation or IVF.	Prospective randomized parallel controlled trial	1b	A	693 cycles (n = 258)	7.4% per cycle (IUI alone) 8.7% per cycle (IUI with stimulation) (12.2% per cycle (IVF))	Not analysed	31% (IUI alone, max. 6 cycles) 37% (IUI with stimulation) (38% (IVF))	Not analysed	Couples with idiopathic or male subfertility have the same likelihood of successful pregnancy as IVF. The woman's age was the only factor that influenced a couple's chance of success.
Iberico <i>et al.</i> 2004	To identify predictors of pregnancy rate (PR) in 470 women	Cross-sectional, retrospective	2b	B	1010 (n = 470)	Overall 9.2% per cycle * 30-34 years (n = 537): 7.6% per cycle * 40-43 years (n = 49): 12.2% per cycle	Not analysed	Not analysed	Overall 11.8%	Female age was not significantly associated with PR in multivariate analysis (P = .18). The authors suggest further research.
Merviel <i>et al.</i> (2008),	Determination of predictive factors for pregnancy after IUI in 353 couples	Retrospective cohort trial	2b	B	1038 (n = 353)	* overall 14.7% ongoing PR per cycle	Not analysed	Ongoing pregnancy rate /couple (6cycles) * ≤=30: 38.5% * 31-35: 31.7% * 36-40: 26.3% * ≥40: 12.5%	* overall 20.3%	Women's age was the strongest predictor of success in all indications, with an ongoing pregnancy rate per couple of 38.5% for the under 30s and 12.5% for the over 40s (P < .000001).
Frederick <i>et al.</i> , 1994	Conception rate in 77 women who were > or = 40 years old and who received ovarian stimulation treatment and IUI	Retrospective case-control study	3b	B	210 (n = 77)	14% per patient and 5% per cycle	3.9% per patient and 1.4% per cycle	Not analysed	73% rate of miscarriage (cumulative)	This report compares IUI results for women > or = 40 years with those obtained previously for younger women, and shows the very poor success rate in women > 40 years of age.
Nuojua-Huttunen <i>et al.</i> (1999)	Analysis of factors affecting outcome after IUI treatment.	Retrospective cohort	2b	C	811 (n = unknown, median female age was 32)	* overall: 12.6% per cycle * < 40 years: 13.7% per cycle * > 40 years: 4.1% per cycle	* > 40 years (n = 98): 3.1%	* overall 70.6% cumulative pregnancy rate after six cycles.	* overall 23.5% spontaneous abortion * overall 5.9% ectopic pregnancy	Pregnancy rate in women < 40 years was significantly higher than in older women.
Haebe <i>et al.</i> 2002	Pregnancy rates and live birth rates per insemination cycles according to female age.	Retrospective cohort	2b	C	1117 (n = unknown)	Overall 19.4% per cycle	* overall 12.9% per IUI cycle * 40-42 years (n = 82) 9.8% per cycle * 43 years or more (n = 24) limited to 4.2%	Not analysed	Miscarriage rate per insemination (%) * ≤25 y = 20.0 % * 25-29 y = 29.6% * 30-35 y = 35.5% * 36-39 y = 46.2 % * ≥40 y = 52.6 %	These results may demonstrate that IUI is an appropriate treatment for women 40-42 years old.

Belloc <i>et al.</i> (2008)	Effect of maternal and paternal age on pregnancy and miscarriage rates after IUI (n= unknown)	Retrospective	2b	C	10034 (n = unknown)	* <30 y: 14.4% per cycle * 30-34 y: 14.5% per cycle * 35-37 y: 12.6% per cycle * 38-41 y: 10% per cycle * > 42 y: 8.9% per cycle	Not analysed	Overall 64% cumulative pregnancy rates after 6 cycles.	* <30 y: 11.1% per cycle * 30-34y: 16.1% per cycle * 35-37 y: 21.6 % per cycle * 38-41 y: 28.3 % per cycle * >42 y: 46.4 % per cycle	Pregnancy rate decrease with maternal and parental age.
Bronte <i>et al.</i> (1999)	To determine which factors influence the effectiveness of IUI.	Retrospective	4	C	9963 (approx. 3200 patients)	* <26 y: 18.9% per cycle * 26-30 y: 13.9% per cycle * 31-35 y: 12.4% per cycle * 36-40 y: 11.1% per cycle * 41-45 y: 4.7% per cycle, > 45 years old: 0.5% per cycle	Not analysed	Not analysed	Not reported	Overall pregnancy rates have increased from 5.8% per cycle in 1991 to 13.4% per cycle in 1996, during which time the average of patients undergoing intrauterine insemination has increased from 36.1 to 39.2 years.
Donor sperm										
De Brucker <i>et al.</i> (2009)	Analysis of cumulative delivery rates in different age group after IUI with donor sperm (n = 1654)	Retrospective cohort trial	2b	B	6630	Not analysed	14 % per cycle	Expected cumulative delivery rates after 12 cycles: * 20-29 years: 87% * 30-34 years: 77% * 35-37 years: 76% * 38-39 years: 66% * 40-45 years: 52%	Miscarriage rate after six cycles * 20-29 years: 6.4% * 30-34 years: 8.0% * 35-37 years: 10.4% * 38-39 years: 20.8% * 40-45 years: 31.9%	Acceptable cumulative delivery rates have been reached up until 42 years of age.
Botchan <i>et al.</i> (2001)	Results of 18 years of IUI with donor sperm in 1001 women	Retrospective cohort trial	2b	B	6139	12.6% per cycle	Not analysed	Cumulative PR calculated for 3, 6 and 12 months were 36, 53 and 75%. CPR according to age were: (i) * < 37 years: 44, 61 and 82% * 37-40 years: 24, 44 and 61% * > 40 years: 13, 22 and 50%	Miscarriage rate (undefined number of cycles per age group) * <37 years: 14.5%, * 37-40 years: 22.3% * >40 years: 42.9%	Age was found to be a major determinant for success rates. Satisfying cumulative pregnancy rates have been reached even in women older than 40.
Schwartz <i>et al.</i> , 1982	Report on 2193 nulliparous women who were receiving IUI with donor sperm.	Retrospective cohort trial	2b	B	n = 2193	Mean pregnancy rate per cycle. * < 25 y: 11% * 26-30 y: 10.5% * 31-35 y: 9.1% * > 35 y: 6.5%	Not analysed	Cumulative pregnancy rates after 12 cycles. * < 25 y: 73% * 26-30 y: 74% * 31-35 y: 61% * > 35 y: 54%	Not analysed	Cumulative pregnancy rates after 12 cycles revealed acceptable success rates in all 4 age groups.

number of patients included was not reported. These results may demonstrate that IUI is an appropriate treatment for women 40–42 years old.

Nearly all level 2, 3 and level 4 studies report results as pregnancy rate per cycle. The only level 1 study (Goverde *et al.*, 2000) expressed results as cumulative delivery rates. Overall, a sharp decline of IUI success rate after the age of 40 is observed in almost all studies, irrespective of their quality.

Age effect on IUI using donor sperm

In the literature only limited data are available on the age effect on intrauterine insemination with donor sperm. Only few retrospective studies have been published. In total we found 4 studies assessing the age effect on IUI success rates when donor sperm is used. Providing an accurate answer about the success rates for older women remains thus hampered by a lack of power associated to the small numbers included and the limited number of deliveries included.

De Brucker *et al.* (2009) report on the largest retrospective cohort analysis (level 2b of evidence, level B of recommendation) to calculate cumulative delivery rates after 6630 donor insemination cycles in 1654 women. Overall, a delivery rate of 14% per cycle with an expected cumulative delivery of 77% after 12 cycles was reached. Subgroup analysis in the oldest subgroup (40–45 years; $n = 223$ patients) revealed an expected cumulative delivery after 12 cycles of 55% for women aged 40, 58% for those aged 41, 32% for those aged 42 and 20% for those over 43 years. Dropout analysis in the latter subgroup showed that only one patient discontinued treatment because of medical reasons. In contrast to age, neither indication nor ovarian stimulation protocol had any significant effect on the delivery rates.

Botchan *et al.* (2001) and Schwartz *et al.* (1982), both level 2b of evidence, reported results only on the cumulative pregnancy rates but not on the cumulative delivery rates. A statistically significant, age-related decline in pregnancy rates was found ($P < 0.0001$) in Botchan *et al.* As shown in Table 2, these results were more pronounced when subdividing the population into three groups: age < 37 , 37–40 and > 40 years. Schwartz *et al.* (1982) reported on 2193 women undergoing IUI in the period 1973–1980 at the Centres d'Etude et de Conservation du Spermé Humain (CECOS). The women were divided into 4 age subgroups. Overall, their study shows that a decrease in pregnancy rate per cycle as a function of a woman's age is present and significant after 30 years of age but only relevant after 35 years.

The three level 2b studies show satisfactory success rates in agreement with the large study from

De Brucker *et al.* (2009) and we should advise our patients to continue IUI treatment up to the age of 42.

Has controlled ovarian superovulation any benefit to counteract the age effect?

In the literature, two systematic reviews (Cohlen *et al.*, 2005, Hughes *et al.*, 1997) indicate a benefit for superovulation in combination with IUI in patients with unexplained infertility.

Two level 1b studies were published drawing the same conclusion as mentioned in both systematic reviews (Guzick *et al.*, 1999; Goverde *et al.*, 2000). Studies dealing with IUI in combination with superovulation and the impact of age are scarce and only of level 2b or less. An overview of the results of these studies can be found in Table 3.

Merviel *et al.* (2008) determined pregnancy rates and ongoing pregnancy rates in 353 couples in a retrospective cohort trial (level 2b, Table 3). All cycles were combined with gonadotrophic ovarian stimulation. Acceptable success rates have been shown in all age groups. Harris *et al.* (2009) (level 2b) performed a small retrospective study in women aged > 38 years to determine the success rates in gonadotrophin-induced controlled ovarian stimulation (COH) in conjunction with IUI (COH/IUI). Poor prognosis was demonstrated in these older women. Corsan *et al.* (1996) (level 3b) reviewed retrospectively data, from their ovulation induction with IUI programme for patients aged ≥ 40 years. In women aged ≥ 40 years, ovulation induction with IUI is most likely to result in successful pregnancy in women 40–42 years of age. Women ≥ 43 years should consider other alternatives such as adoption or egg donation.

Although COH in combination with IUI has been shown to result in significantly higher pregnancy rate compared to unstimulated (natural cycle) IUI in some papers (Guzick *et al.*, 1999, level 4 of evidence, retrospective case serie), Kalu *et al.* (2007), level 2b of evidence study, wanted to assess the effect of age on each. Age is an important confounding factor that may affect the outcome of stimulated or unstimulated IUI. This important factor was not always taken into account. In their retrospective cohort paper on 1759 IUI cycles, women age 37 and younger, COH resulted in significantly higher pregnancy rate and live-birth rate compared to natural cycle IUI. However for older women age > 37 years, natural cycle resulted in a significantly higher pregnancy rate and live birth rate than IUI with COH. This difference was even more significant when COH was performed with CC. Thus older women may benefit from natural cycle IUI. See table 3 for

Table 3. — Superovulation in older women. Overview of all level 1, level 2 and level 3 of evidence studies

Reference	Study sample(no.)	Study design analysis	Level of evidence	Grade of recommendation	Number of IUI cycles	Pregnancy rates (%)	Delivery rates (%)	Cumulative delivery rates (%)	Miscarriage rates (%)	Results
Level 1 of evidence										
Goverde <i>et al.</i> 2000	258 couples were treated either IUI in spontaneous cycle, either IUI after mild ovarian stimulation or IVF.	Prospective randomised parallel controlled trial.	1b	A	693	7.4% per cycle (IUI alone) 8.7% per cycle (IUI with stimulation) (12.2% per cycle (IVF))	Not analysed	31% (IUI alone, max. 6 cycles) 37% (IUI with stimulation) (38% (IVF))	Not analysed	Couples with idiopathic or male subfertility have the same likelihood of successful pregnancy as IVF. The woman's age was the only factor that influenced a couple's chance of success. IUI with stimulation gave better success rates than IUI alone.
Guziek <i>et al.</i> 1999	932 couples were randomly assigned to receive intracervical insemination, IUI, superovulation and intracervical insemination, or superovulation and IUI. Treatment continued for four cycles unless pregnancy was achieved.	Prospective randomised controlled trial.	1b	A	4676	* <u>Intracervical insemination</u> : 10% PR/couple * <u>IUI</u> : 18% PR/couple * <u>Superovulation and intracervical insemination</u> : 19% PR/couple * <u>Superovulation and IUI</u> : 33% PR/couple	Not analysed	Not analysed	Not analysed	Among infertile couples, treatment with induction of superovulation and IUI is 3 times as likely to result in pregnancy as intracervical insemination and twice as likely to result in pregnancy as with either superovulation and intracervical insemination or IUI alone.
Level 2 and level 3 of evidence										
Merviel <i>et al.</i> (2008),	Determination of predictive factors for pregnancy after IUI in 353 couples	Retrospective cohort trial	2b	B	1038 (n=353)	* overall 14.7% ongoing PR per cycle	Not analysed	Ongoing pregnancy rate /couple (6cycles) <= 30: 38.5% 31-35: 31.7% 36-40: 26.3% >40: 12.5%	* overall 20.3%	Women's age was the strongest predictor of success in all indications, with an ongoing pregnancy rate per couple of 38.5% for the under 30s and 12.5% for the over 40s (P < .000001).
Corsan <i>et al.</i> (1996)	Analysis of ovulation induction in women > 40 (n = 168) in comparison with an randomly selected group of patients < 40 (210 cycles, n = 180)	Retrospective case-control	3b	C	679	* women 40, 41 and 42 y: 13.3%, 7.9% and 4.8% pregnancy rate per cycle * women < 40 y: 17.95 % PR/cycle	* women 40, 41 and 42 y: 9.6%, 5.2% and 2.4% delivery rate per cycle * women above 43: no delivery rates were reported	Not analysed	* women > 40 y: 34.4% MR/cycle. * women < 40 y: 17.14% MR/cycle	When utilized in women aged > = 40 years, ovulation induction with IUI is most likely to result in successful pregnancy in women 40-42 years of age.

Harris <i>et al.</i> , 2009	To determine the success rates and utility of controlled ovarian hyperstimulation in conjunction with intrauterine insemination (COH/IUI) cycles in 130 women aged 38-39 years versus women \geq 40 years old. 1-3 cycles per patient were performed.	Retrospective cohort	2b	B	262 (n = 130) (*38-39 years (n = 42.6%)) (* \geq 40 years (n = 57.4%))	* 38-39 (42.6%) years: 9.0 % per cycle * \geq 40 (57.4%) years: 7.8% per cycle	* 38-39 (42.6%) years: 6.1 % per cycle * \geq 40 (57.4%) years: 2.0% per cycle	Cumulative live birth rates after 3 cycles. * 38-39 years: 12.3% * \geq 40 years: 4.1%	Overall 23.5% per cycle	The efficacy of COH/IUI cycles significantly decreases with age, but women aged 38-39 years had reasonable success during the first two cycles. However, for women aged \geq 40 years, no benefit after a single cycle of COH/IUI was observed. Women aged \geq 40 years should be considered for in vitro fertilization after one failed COH/IUI cycle.
Kalu <i>et al.</i> , 2007	Analysis of the outcome of IUI with COH and IUI in natural cycle(unstimulated) in women age < 37 and women age > 37.	Retrospective , cohort	2b	B	1759	In women age 37 and younger, COH resulted in a significantly higher pregnancy rate (13.0% vs 6.5%) compared to natural cycle IUI (p = 0.025) * For older women age > 37 years, natural cycle IUI, resulted in a significantly higher pregnancy rate (12.0% vs 8.5%) than IUI with COH (p = 0.0037).	In women age 37 and younger, COH resulted in a significantly higher live-birth rate (10.7% vs 5.2%) compared to natural cycle IUI (p = 0.045). * For older women age > 37 years, natural cycle IUI, resulted in a significantly higher live-birth rate (7.5% vs 3.5%) than IUI with COH (p = 0.0037).	Not analysed	Not analysed	Older women (> 37 y) have a better outcome from unstimulated IUI cycle.

detailed results of this study. Why natural cycle IUI is associated with better outcome in older women is not entirely clear. As the ovarian pool diminishes with age, a dominant follicle selected naturally may be the best in the cohort, hence increasing the likelihood of fertilisation and implantation. COH may encourage the recruitment of suboptimal follicles that may otherwise not have developed.

In addition, a study of Brzechffa *et al.* (1997), level 2b, retrospective cohort trial, examined the influence of female and male patient age and human menopausal gonadotrophin (hMG) on clinical pregnancy rates and live birth rates. This study demonstrated a critical threshold of hMG requirements beyond which pregnancy did not occur. No pregnancies occurred in treatment cycles requiring > 25 ampoules (1875 IU) of menotrophins, independent of female partner age. Furthermore in treatment cycles in which female partner was aged > 40 years no pregnancies occurred when > 20 ampoules (1500 IU) were necessary to achieve follicular maturity. It has to be mentioned that a combination of clomiphene citrate with hMG or FSH (with equivalent results to the use of gonadotropin alone) results in a lower total dose of gonadotropins (Dickey *et al.*, 1993).

And what about male ageing and IUI outcome?

It is well known that virtually no children are born to mothers aged more than 45 years. More and more men of older age will father children with younger partners. (Kühnert and Nieschlag, 2004). The discrepancy in the reproductive span between males and females is astonishing and reduced fertility and higher reproductive risks associated with advancing maternal age prompt the question whether advanced paternal age too is associated with compromised fertility and such increasing risks. A review on this topic was recently written for the Royal College of Obstetricians and Gynaecologists (Tournaye, 2009).

In contrast to female fertility, male fertility is maintained until very late in life, and, in addition to anecdotal reports, it has been documented scientifically up to an age of 94 years (Seymour *et al.*, 1935). Age-dependent decrease of fertility in couples are usually attributed to female ageing, make studies on a male age effect difficult. Besides female age, further confounders, such as reduced coital frequency, an increasing incidence of erectile dysfunction and smoking habits, have to be considered. For natural conception, paternal age has no profound effect whenever the female partner is young. Time to pregnancy is longer than compared to younger men. However, when the female partner too is of age, then a synergistic adverse effect of paternal age has been

reported in a large retrospective multicentre study (de la Rochebrochard *et al.*, 2003).

Only limited data are available about male aging and IUI success rates. By analyzing data from intrauterine artificial insemination with the husband's spermatozoa, Mathieu *et al.* (1995), retrospective (multivariate analysis) concluded that paternal age over 35 years was an important predictive factor of success, after controlling for maternal age. Brzechffa and Buyalos (1997), analyzed in a retrospective cohort trial (level 2b) 184 patients to assess the male impact of male ageing on IUI combined with hMG. The clinical pregnancy rate was significantly lower in males aged 40 years or older compared with males aged less than 40 years whose female partners were 35 years or more (16.3% versus 6.5%, $P = 0,02$). No differences were observed in the clinical pregnancy rates in treatment cycles in which males aged 40 years or older were compared with males aged less than 40 years whose female partners were aged less than 35 years ($P = 0,81$).

Belloc *et al.* (2008) (level 2 b study) found that paternal age led to a decrease in the pregnancy rate from 12.3% before 30 years of age to 9,3% after 42 years of age ($P < 0,0001$) and a doubling of the miscarriage rate from 13.7% before 30 years of age, to 32.4% after 45 years of age, and this independently of women's age. The impact of increased age on necrozoospermia and sperm-DNA structure is a probable direct cause of this paternal effect, but further research about this topic is needed.

Conclusion

A female age effect on the success rates after IUI is evident: above the age of 37, success rates decline, but despite this fact, women up to 40 years, may be encouraged to continue IUI treatment, in case of donor insemination even up to 42 years of age. The adjuvant role of superovulation to counteract the adverse age-effect on IUI results remains unclear since age was not always taken into consideration in many studies and methodological differences among them may account for inconsistent conclusions. When the female partner is older than 35 years, a possible synergistic adverse effect of paternal age too has been reported.

References

- Belloc S, Cohen-Bacir P, Benkhalifa M *et al.* Effect of maternal and paternal age on pregnancy and miscarriage rates after intrauterine insemination. *Reprod Biomed Online*. 2008;17(3): 392-7.
- Broekmans F. J, Knauff E, te Velde E *et al.* Female reproductive ageing: current knowledge and future trends, *Trends in Endocrinology & Metabolism*, Volume 18, Issue 2, March 2007, Pages 58-65.

- Botchan A, Hauser R, Gamzu R *et al.* Results of 6139 artificial insemination cycles with donor spermatozoa. *Human Reprod.* 2001;16:2298-2304.
- Brzechffa P, Buyalos R. Female and male partner age and menotropin requirements influence pregnancy rates with human menopausal gonadotrophin therapy in combination with intrauterine insemination. *Hum Reprod.* 1997;12(1):29-33.
- Bronte A, Stone PD, Ringler GE *et al.* Determinants of the outcome of intrauterine insemination: analysis of outcomes of 9963 consecutive cycles. *Obstet Gynecol.* 1999;180:1522-64.
- Cohlen BJ. Should we continue performing intrauterine inseminations in the year 2004? *Gynecol Obstet Invest.* 2005;59:3-13.
- Corsan G, Trias A, Trout S *et al.* Ovulation induction combined with intrauterine insemination in women 40 years of age and older: is it worthwhile? *Human Reprod.* 1996;5:1109-12.
- De Brucker M, Haentjens P, Evenepoel J *et al.* Cumulative delivery rates in different age groups after artificial insemination with donor sperm. *Hum. Reprod.* 2009;24:1891-9.
- de La Rochebrochard E, Thonneau P. Paternal age > or = 40 years: an important risk factor for infertility. *Am J Obstet Gynecol.* 2003;189(4):901-5.
- de La Rochebrochard E, McElreavey K, Thonneau P. Paternal age over 40 years: the "amber light" in the reproductive life of men? *J Androl.* 2003;24(4):459-65. Review.
- Dickey RP, Olar TT, Taylor SN *et al.* Sequential clomiphene citrate and human menopausal gonadotrophin for ovulation induction: comparison to clomiphene citrate alone and human menopausal gonadotrophin alone. *Hum Reprod.* 1993;8(1):56-9.
- Evers JL. Female subfertility. *Lancet.* 2002;360(9327):151-9.
- Frederick JL, Denker MS, Rojas A *et al.* Is there a role for ovarian stimulation and intra-uterine insemination after age 40? *Hum Reprod.* 1994;9(12):2284-6.
- Goverde AJ, McDonnell J, Vermeiden JP *et al.* Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. *Lancet.* 2000;355(9197):13-8.
- Guzick DS, Sullivan MW, Adamson GD *et al.* Efficacy of treatment for unexplained infertility. *Fertil Steril.* 1998;70(2):207-13.
- Guzick DS, Carson SA, Coutifaris C *et al.* Efficacy of superovulation and intrauterine insemination in the treatment of infertility. *N Engl J Med.* 1999;340:177-83.
- Harris I, Missmer SA, Hornstein M. Poor success of gonadotropin-induced controlled ovarian hyperstimulation and intrauterine insemination for older women. *Fertil Steril.* 2009 [Epub ahead of print].
- Haebe J, Martin J, Tekepety F, Tummon I *et al.* Success of intrauterine insemination in women aged 40-42 years. *Fertil Steril.* 2002;78(1):29-33.
- Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. *Hum Reprod.* 1997;12(9):1865-72.
- Ibérico G, Vioque J, Ariza N *et al.* Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. *Fertil Steril.* 2004;81(5):1308-13.
- Kalu E, Thum M, Abdalla H. Intrauterine insemination in natural cycle may give better results in older women. *J Assist Reprod Genet.* 2007;24:83-6.
- Kühnert B, Nieschlag E. Reproductive functions of the ageing male. *Hum Reprod.* 2004;10:327-9.
- Lannou DL, Lansac J. Artificial procreation with fresh donor semen: the French experience of CECOS, Chapter 11. In Barret CRL, Cooke ID (eds.). *Donor insemination.* Cambridge: Cambridge University Press, 1993, 153-169.
- Mathieu C, Ecochard R, Bied V *et al.* Cumulative conception rate following intrauterine artificial insemination with husband's spermatozoa: influence of husband's age. *Hum Reprod.* 1995;10:1090-7.
- Merviel P, Heraud MH, Grenier N *et al.* Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature. *Fertil Steril.* 2010;93(1):79-88. Review.
- Nuojua-Huttunen S, Tomas C, Bloigu R *et al.* Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. *Hum Reprod.* 1999;14(3):698-703.
- Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. *Federation CECOS. N Engl J Med.* 1982;18:306(7):404-6.
- Seymour FI, Duffy C, Koerner. A case of authenticated fertility in a man, aged 94. *J Am Med Assoc.* 1935;105:1423-4.
- te Velde ER, Pearson PL. The variability of female reproductive ageing. *Hum. Reprod. Update* 2002;8:141-154.
- Tournaye H, Reproductive ageing, eds. Susan Bewling, William Ledger and Dimitrios Nikolaou, published by RCOG Press at the Royal College of Obstetricians and Gynaecologists, pp.95-104, 2009.
- van Noord-Zaadstra BM, Looman CW *et al.* Delaying childbearing: effect of age on fecundity and outcome of pregnancy. *Br Med J.* 1991;302:1361-5.