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ARTICLE

Influence of paternal age on ongoing pregnancy rate at eight weeks' gestation in assisted reproduction

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Aukje Marieke Meijerink obtained her degree as a Medical Doctor at the Rijks University Groningen (the Netherlands) in 2012. She worked as a resident in Obstetrics and Gynaecology for one year. After that, she started her scientific career in the field of reproductive medicine in Radboud University Medical Center (the Netherlands). Her special interest is safety of assisted reproductive techniques in severe male infertility, in terms of reproductive outcome. She also works as a physician of reproductive medicine in this field.

Abstract A retrospective cohort study was performed with the followings aims: to evaluate the influence of paternal age on best embryo quality available for embryo transfer on the third day; biochemical pregnancy rate; miscarriage rate and ongoing pregnancy rate at 8 weeks' gestational age, after IVF or intracytoplasmic sperm injection (ICSI) treatment, respectively, including treatment with non-ejaculated spermatozoa. In total, 7051 first IVF/ICSI cycles in Radboud university medical center, between 1 January 2001 and 1 June 2013 were included in this study. A statistical model was used to analyse the effect of paternal age and maternal age. No statistically significant differences between the paternal age groups were found with respect to the probability of an ongoing pregnancy after the first cycle (35–44 years: odds ratio [OR] = 0.97 [95% confidence interval [CI]: 0.86 to 1.10] and ≥45 years: OR = 1.01 [95% CI: 0.82 to 1.26]), respectively, compared with <35 years of age (control). Similar results were found with respect to paternal age and the availability of a top quality embryo for transfer, biochemical pregnancy and miscarriage. However, live birth was not taken into account. In conclusion, paternal age did not affect ongoing pregnancy rates in first IVF/ICSI cycles.

KEYWORDS: assisted reproductive techniques, male infertility, paternal age, pregnancy rate, semen, spermatozoa

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Introduction

In Western society and developed countries, there is a tendency for delayed parenthood as a consequence of social economical welfare, personal education development, increased life expectancy, divorce and restarting new families. Nowadays, not only women are delaying parenthood; men's ages for parenthood have also increased in the last decade. In the Netherlands in 2000, 11.1% ($n = 22,981$) of the children born had a father over 40 years old; in 2012 this percentage was 16.4% ($n = 28,888$) (CBS, 2011).

While for women their biological clock will determine the end of their fecundity, men's biological clocks do not play such a prominent role, as men can produce spermatozoa until a very advanced age. Currently, there are no legal or biological restrictions given to participation of elderly men in assisted reproductive programmes. The focus on factors affecting the outcome of assisted reproductive techniques is mainly related to the influence of female factors, including age, diagnosis, co-morbidity and ovarian stimulation. It is well known that women older than 35 years have a higher risk of spontaneous abortion, pregnancy complications and chromosomal abnormalities, but couples with men over 40 years of age also seem to have a higher risk for miscarriage (de La Rochebrochard and Thonneau, 2002). Another study found a 4.5-fold higher risk of having a child with trisomy 21 in men over 45 years of age compared with men younger than 30 years (Zhu et al., 2005). They suggest that this could be induced by biological or environmental factors causing gamete mutations in men. It seems that reproductive function in both women and men declines with age (Wiener-Megnazi et al., 2012).

Fathers in couples undergoing assisted reproductive techniques are older than their fertile counterparts (Stern et al., 2014), but only limited or controversial results about the influence of paternal age on reproductive outcome after assisted reproductive techniques have been published. Previous studies show discordant findings in terms of effects on embryo quality, pregnancy rate and live born delivery (de La Rochebrochard et al., 2006; Ferreira et al., 2010; Klonoff-Cohen and Natarajan, 2004). In these studies the use of non-ejaculated spermatozoa (of epididymal or testicular origin) was not included. However, older men who had a previous vasectomy, in particular, are candidates for intracytoplasmic sperm injection (ICSI) with non-ejaculated spermatozoa for assisted reproductive treatment. Studies using an ovum donation model reveal that embryo implantation rates decline with increasing paternal age, but show no agreement regarding pregnancy outcome and have not been adjusted for recipient age (Humm and Sakkas, 2013; Robertshaw et al., 2014). The aim of this study is to look at the influence of paternal age on best embryo quality available for embryo transfer (ET), biochemical pregnancy rate (BPR), miscarriage rate and ongoing pregnancy rate (OPR) up to 8 weeks' gestational age, after IVF or ICSI treatment, respectively, including treatment with non-ejaculated spermatozoa. To this end, a large retrospective cohort study of first assisted reproductive treatment cycles was performed.

Materials and methods

Study population

A retrospective cohort study was performed to investigate the influence of paternal age on reproductive outcome when using assisted reproductive techniques. Data were collected for all first cycles of assisted reproductive treatment at the Radboud university medical center (Radboudumc) between 1 January 2001 and 1 June 2013. Data were obtained with respect to: the age of men and women at the time of oocyte retrieval; type of assisted reproductive technique (IVF or ICSI); type of spermatozoa used for the treatment (ejaculated or non-ejaculated: percutaneous epididymal sperm aspiration [PESA]; microsurgical epididymal sperm aspiration [MESA] or testicular sperm extraction [TESE]); condition of spermatozoa (fresh or cryopreserved); FSH dose; number of follicles and oocytes; fertilization rate; embryo quality of transferred embryos; single embryo transfer (SET) or double embryo transfer (DET); number of good quality embryos for cryopreservation; and pregnancy results (biochemical and ongoing pregnancies).

Of all first cycles ($n = 7246$), the study excluded couples who underwent assisted reproductive treatment in a modified natural cycle ($n = 51$); women who did not have ET for risk of ovarian hyperstimulation syndrome (OHSS); or assisted reproductive treatment in oncology patients because of fertility preservation ($n = 74$) or for oocyte vitrification ($n = 70$). As a result, 7051 first assisted reproductive technique cycles were included in this study. Ethical committee approval was not required for this retrospective study according to the Medical Treatment Agreements Act (Medical Treatment Agreements Act, 1994, book no. 7, article 446–468).

Procedures

Patients underwent assisted reproductive treatment in a long agonist protocol as described previously by Dam *et al.* (Dam et al., 2012). Briefly, stimulation was initiated by injections with FSH with doses depending on anti-Müllerian hormone concentrations and/or antral follicle count. Oocyte retrieval was planned when ≥3 follicles with a diameter of ≥17 mm were observed by ultrasound examination, and was performed 36 h after human chorionic gonadotrophin (HCG) injection. ICSI was performed as described previously by Palermo *et al.* (Palermo et al., 1992).

Luteal phase support was started on the day of oocyte retrieval by vaginal administration of 200 mg progesterone (Utrogestan) three times daily, continued until pregnancy test.

Three days after oocyte retrieval, one or two embryos were transferred. SET or DET was performed depending on national policy, the woman's age, the woman's medical history and the couple's preference. Transfer policy has changed over time, the last 3 years into SET in women <38 years in the first two IVF/ICSI cycles including cryotransfers. No embryo transfer was performed in cases of absence of fertilization, abnormal embryos or in cases of (risk for) OHSS.