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Predictive factors influencing pregnancy rates after intrauterine insemination with frozen donor semen: a prospective cohort study

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KEY MESSAGE

Female age, non-smoking or smoking fewer than 15 cigarettes a day, secondary infertility, low progesterone levels at day zero of the cycle and use of ovarian stimulation with HMG and recombinant FSH are the most important factors influencing the success rate after intrauterine insemination with frozen donor semen.

A B S T R A C T

The extent to which certain parameters can influence pregnancy rates after intrauterine insemination with frozen donor semen was examined prospectively. Between July 2011 and September 2015, 402 women received 1264 IUI cycles with frozen donor semen in a tertiary referral infertility centre. A case report form was used to collect data prospectively. The primary outcome measure was clinical pregnancy rate (CPR), confirmed by detection of a gestational sac and fetal heartbeat using ultrasonography at 7–8 weeks of gestation. Statistical analysis was carried out using generalized estimating equations (GEE) to account for the correlation between observations from the same patient. Overall, CPR per cycle was 17.2%. Multivariate GEE analysis revealed the following parameters as predictive for a successful pregnancy outcome: female age ($P = 0.0003$), non-smoking or smoking fewer than 15 cigarettes a day ($P = 0.0470$ and $P = 0.0235$, respectively), secondary infertility ($P = 0.0062$), low progesterone levels at day zero of the cycle ($P = 0.0164$) and use of ovarian stimulation with HMG and recombinant FSH compared with clomiphene citrate and natural cycle ($P = 0.0006$ and $P = 0.0004$, respectively). These parameters were the most important factors influencing the success rate in a sperm donation programme.

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Introduction

Intrauterine insemination (IUI) with frozen donor semen is indicated for couples suffering from severe male factor infertility, including azoospermia, men with sexually transmitted infectious diseases, in men with genetic disorders linked to the Y chromosome that might be transmissible to the progeny, as well as lesbian women and women without a male partner (Zuzuarregui et al., 2004). In recent years, the request for IUI with frozen donor semen has increased in parallel with the rise in the number of lesbian couples and single women relying on donor insemination and a high inflow of patients seeking cross-border reproductive care to avoid restrictive laws in their home country (Pennings, 2004; Pennings et al., 2009; Thijssen et al., 2014).

Furthermore, demand for more cost-effectiveness in health care is ever increasing. Therefore, it is important to determine the factors influencing pregnancy rates after IUI with frozen donor semen to increase success rates and decrease costs per treatment cycle. For donor inseminations, only frozen sperm can be used. Cryopreserved donor semen is quarantined for a minimum of 6 months to prevent transmission of sexually transmitted diseases, such as human immunodeficiency virus and hepatitis B and C (American Fertility Society, 1990; American Society for Reproductive Medicine, 2012). Cryopreservation of donor semen and the use of cryoprotective agents, however, reduce post-thaw sperm survival, motility and pregnancy rates (Botchan et al., 2001; DiMarzo et al., 1990; Ritcher et al., 1984).

The influence of different parameters such as female age, ovarian stimulation protocols, sperm parameters, on pregnancy rates after IUI with frozen donor semen has been described thoroughly in the past, however, with diverging results. Mostly, female age has been indicated as one of the most important prognostic factors for predicting pregnancy rate after donor insemination (Allamaneni et al., 2004; Botchan et al., 2001; De Brucker et al., 2009; Ecochard et al., 1999; Ferrara et al., 2002; Kang and Wu, 1996; Khalil et al., 2001; Mokdad et al., 2013; Williams and Alderman, 2001; Zuzuarregui et al., 2004). Recently, a study by Koh et al. (2013) also revealed sperm donor age as a factor influencing clinical pregnancy rate (CPR) in donor insemination cycles. Matorras et al. (2002) and Zuzuarregui et al. (2004) reported that the use of FSH for ovarian stimulation results in significantly higher pregnancy rates compared with clomiphene citrate or natural cycle. Ferrara et al. (2002) and De Brucker et al. (2009) concluded that ovarian stimulation did not significantly improve pregnancy rates and delivery rates. Numerous sperm parameters have also been suggested as possible predicting factors, ranging from pre-freezing sperm motility (Guan et al., 2015), to post-thaw sperm motility (Clarke et al., 1997), forward progression (Freour et al., 2009; Kelly et al., 1997), inseminating motile count (IMC) (Kang and Wu, 1996; Williams and Alderman, 2001; Zuzuarregui et al., 2004) and total motile sperm counts (TMSC) (Dong et al., 2011; Freour et al., 2009). Many studies, however, were unable to detect such relationships (Clarke et al., 1997; Ferrara et al., 2002; Guan et al., 2015; Kang and Wu, 1996; Kelly et al., 1997; Sidhu et al., 1997).

These widely conflicting data are mainly the result of differences in study design and methodology (Ombelet et al., 2014). Most previously published studies are retrospective, and statistical analysis does not account for the multivariate nature of the dataset and the fact that the same patients are returning for treatment after previous failed attempts.

This study aimed to prospectively evaluate the extent to which different parameters can influence the success rate in a donor insemination programme. Although this was a cohort study, the nature of the study was prospective as patient-specific data were recorded by means of a case report form (CRF) at the time of insemination. Furthermore, as patients are returning for further treatment after previously failed attempts, these data cannot be analysed as independent, which is mostly assumed in classical statistical analysis, such as t-tests, linear regression models and logistic regression models. Therefore, a novel form of multivariate logistic regression analysis, i.e. generalized estimating equations (GEE), was used on the data to take into account the correlation between observations from the same patient.

Materials and methods

Patients

Between 1 July 2011 and 30 September 2015, data from 402 women with a total of 1264 IUI cycles with frozen donor semen were collected prospectively in a tertiary referral infertility centre. A CRF was used to review all possible contributing factors to IUI outcome. This was completed by a midwife together with the patient during the 20 min of mandatory bedrest after insemination (Custers et al., 2009; Saleh et al., 2000). The results of the CRFs were examined by a third person for possible lack of data on a monthly basis.

The average age of the patient population was 33 ± 5 years (range 20–46 years). All women were either single or lesbian, or heterosexual couples with an azoospermic partner or a partner with a y-linked chromosome genetic disorder. In all patients, a complete infertility work-up was carried out, including a medical history, physical examination, pelvic ultrasound, serum hormone assays between day 2 and 4 of the menstrual cycle and mid-luteal serum progesterone in women with regular menstrual cycles. If an implantation abnormality or uterine abnormality was suspected on ultrasound, a hysteroscopy, laparoscopy, or both, was carried out. Tubal patency was assessed either by hysterosalpingography, laparoscopy, or both. Biochemical and ultrasound screening was conducted in all IUI cycles. Institutional Review Board approval was obtained for this study from the Committee of medical Ethics, Ziekenhuis Oost-Limburg on 31 May 2013 (reference number 13/054U).

Parameters studied

Data analysed included female age (years), female smoking (non-smoking, one to 14 cigarettes a day, ≥15 cigarettes a day), female body mass index (BMI) (kg/m^2), primary or secondary infertility, cycle number, ovarian stimulation method (natural cycle, clomiphene citrate, HMG or recombinant FSH), day 0 oestradiol (ng/l) and progesterone (µg/l) levels, HCG-insemination time interval (h), easy or difficult insemination with difficult being defined as multiple attempts needed to enter the uterus (easy-clamp (C), easy+C, difficult+C, difficult+C+dilator, intracervically), occurrence of obvious uterine bleeding during or after insemination (yes, no), post-thaw sperm quality parameters, i.e. concentration (million/ml), motility grade A (%), motility grade A + B (%), TMSC grade A (million), TMSC grade A + B (million), and IMC (million) and sperm washing procedure (wash, density gradient centrifugation [DGC]).

The primary outcome measure was clinical pregnancy rate (CPR), defined as a pregnancy with ultrasound visualization of a

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