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ARTICLE

Pregnancy and twinning rates using a tailored embryo transfer policy

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Abstract A tailored embryo transfer policy based on the prognostic profile of the couple was prospectively evaluated. Single-embryo transfer (SET) was performed, followed by double-embryo transfer (DET) in frozen–thawed embryo transfer cycles in women with a good prognosis (<35 years, first cycle, ≥1 top-quality embryo). DET was performed in both fresh and frozen cycles in women with an intermediate prognosis (<35 years, first cycle and no top-quality embryo available, or <35 years and ≥1 failed cycles, or 35–38 years). Triple-embryo transfer (TET) in both fresh and frozen cycles was performed in women with a poor prognosis (≥39 years). The cumulative ongoing pregnancy rate in the cycles of women with a good prognosis was 43% with a multiple pregnancy rate of 2%, in the cycles of women with an intermediate prognosis 27% and 23% and in the cycles of women with a poor prognosis 18% and 13%, respectively. These findings can be used to guide current practice: i.e. performing SET in women with a good prognosis and TET in women with a poor prognosis. The embryo transfer strategy in women with an intermediate prognosis requires further improvement, possibly by refining the prognosis according to the ovarian response after ovarian stimulation.

KEYWORDS: cohort study, embryo transfer, IVF, multiple pregnancy, pregnancy

Introduction

In the last decades, improvements in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have resulted in higher embryo implantation rates (Thurin et al., 2004). These higher implantation rates in combination with the transfer of multiple embryos have led to a substantial increase in multiple pregnancy rates (HFEA, 2007; Kingsland et al., 1990; Steptoe et al., 1986). These high multiple pregnancy rates caused great concern, since

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maternal and perinatal morbidity and mortality as well as healthcare costs became unacceptable (Bergh, 2005; Gerris, 2005; Thurin et al., 2004). As the number of embryos transferred is the most important factor influencing multiple pregnancy rates, the only way to reduce these high multiple pregnancy rates was to reduce the number of transferred embryos.

The first randomized trial to compare elective single-embryo transfer (SET) and double-embryo transfer (DET was performed by Gerris et al. (1999) in women under 34 undergoing their first IVF/ICSI cycle. Since then, two systematic reviews and meta-analyses of randomized trials have synthesized aggregated data and individual patient data on elective SET versus DET in women with a good prognosis. These reviews showed that elective SET not only reduces the odds of multiple pregnancies but almost halves the odds of a live birth per fresh cycle. These reduced live birth rates after elective SET were restored by the subsequent transfer of a single frozen–thawed embryo yielding cumulative live birth rates comparable to those after DET (McLernon et al., 2010; Pandian et al., 2009).

The implementation of a SET policy in countries such as Sweden and Belgium for women with a good prognosis resulted in a dramatic decrease in multiple pregnancy rates. In Sweden there was a decrease from 35% to around 5% and in Belgium from 19% to 3%, while maintaining similar pregnancy rates (Gordts et al., 2005; Karlstrom and Bergh, 2007).

Although elective SET is now an accepted policy for women with a good prognosis, the majority of women currently undergoing IVF have an intermediate or poor prognosis, such as women aged ≥35 years with one or more failed IVF cycles. For these women, data from randomized trials are lacking and existing cohort studies have not been able to provide robust evidence on how many embryos to transfer to obtain high pregnancy rates but low multiple pregnancy rates. This is because only women with good response after ovarian stimulation or women with at least two or more good-quality embryos have been included in the cohort studies conducted thus far (Kovacs et al., 2003; Veleva et al., 2006).

In view of this lack of data on this important issue, this article reports on the results of a prospective cohort study on the implementation of a differentiated embryo transfer policy based on the age of the woman, the number of previous cycles and embryo quality, in terms of ongoing pregnancy rates and multiple pregnancy rates.

Materials and methods

In 2006, the Academic Medical Center implemented a tailored embryo transfer strategy as standard clinical care and prospectively monitored the effects of this strategy on relevant clinical outcomes. All consecutively performed IVF/ICSI cycles between August 2006 and April 2011 were evaluated.

All couples had been trying to conceive for at least 12 months and underwent a basic fertility workup according to the guidelines of the Dutch Society of Obstetrics and Gynaecology (NVOG, 2012). The indication to start IVF or ICSI treatment was determined according to the Dutch IVF guideline (NVOG, 1998). If subfertility was caused by tubal pathology, such as two-sided tubal blockage and severe endometriosis, or severe oligozoospermia (post-wash total motile sperm count <3 million), IVF/ICSI was offered directly (Repping et al., 2002). In case of one-sided tubal pathology, minimal endometriosis, cervical hostility, mild male oligozoospermia and unexplained subfertility, at least six intrauterine inseminations were applied before IVF/ICSI was offered. In case of ovulation disorders, mainly caused by polycystic ovary syndrome, 12 cycles of ovulation induction were applied before IVF/ICSI was offered.

The embryo transfer policy was based on the prognostic profile of the women. The prognostic profiles (i.e. good/intermediate/poor) were based on three important predictive factors for pregnancy with IVF: female age, number of previous cycles and embryo quality (Nelson and Lawlor, 2011; Templeton et al., 1996; van Loendersloot et al., 2010).

Women with a good prognosis were women <35 years undergoing their first cycle of IVF/ICSI with at least one top-quality embryo. In these women, SET was performed. In the frozen embryo transfer cycles (FET) following these fresh cycles, DET was performed (**Table 1**).

Women with an intermediate prognosis were women aged <35 who did not have a top-quality embryo in the first cycle, women aged <35 who failed to get pregnant in their first cycle of IVF/ICSI or women aged 35–38 years. In these women, DET was performed in the fresh and frozen cycles (**Table 1**). This transfer strategy was based on a combination of the Practice Committee of the American Society for Reproductive Medicine guidelines and the Belgian embryo transfer legislation (ASRM, 2004, 2006).

Women with a poor prognosis were women aged ≥39 years. In these women, three embryos were transferred (triple-embryo transfer, TET) in the fresh and frozen cycles (**Table 1**). This strategy was also based on a combination of the Practice Committee of the American Society for Reproductive Medicine guidelines and the Belgian embryo transfer legislation (ASRM, 2004, 2006).

Fresh and frozen–thawed IVF/ICSI cycles were included for analysis if the embryo transfer criteria were met: i.e. women eligible for SET had at least one top-quality embryo, women eligible for DET had at least two embryos and women eligible for TET had at least three embryos.

IVF/ICSI procedures

Women underwent ovarian stimulation after down-regulation with the gonadotrophin-releasing hormone agonist triptorelin (Decapeptyl; Ferring) in a long protocol with a midluteal start. Ovarian stimulation was started on cycle day 5 with recombinant FSH or human menopausal gonadotrophin in daily doses ranging from 75 to 450 IU depending on the antral follicle count. Follicular maturation was induced by 10,000 IU human chorionic gonadotrophin (Pregnyl; Organon). Cumulus–oocyte–complexes were recovered by transvaginal ultrasound-guided follicle aspiration 36 h thereafter. Oocytes were inseminated with 10,000 or 15,000 progressively motile spermatozoa (IVF) or injected with a single spermatozoon (ICSI) 2–4 h after