

Elective single-embryo transfer in women aged 40–44 years

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STUDY QUESTION: Is an elective single-embryo transfer (eSET) policy feasible for women aged 40 or older?

SUMMARY ANSWER: For older women (aged 40–44 years) with a good prognosis, an eSET policy can be applied with acceptable cumulative clinical pregnancy rates and live birth rates.

WHAT IS KNOWN ALREADY: Various studies have shown the effectiveness of eSET in women aged <35 years with high cumulative pregnancy rates and low rates of multiple births.

STUDY DESIGN, SIZE, DURATION: This retrospective cohort study included 628 women treated between 2000 and 2009.

PARTICIPANTS, SETTING, METHODS: Women aged 40–44 years underwent a fresh cycle of IVF or ICSI treatment with eSET ($n = 264$) or double-embryo transfer (DET) ($n = 364$). In the subsequent frozen-thawed embryo transfer cycles, SET/DET was performed in both groups according to the number of embryos available and the opinion of the couple. The study was performed at the Family Federation of Finland Helsinki Fertility Clinic.

MAIN RESULTS AND THE ROLE OF CHANCE: In the fresh cycles, the clinical pregnancy rates were 23.5 and 19.5% in the eSET and DET groups, respectively, and live birth rates were 13.6 and 11.0%, respectively. In the fresh cycles with eSET, there were no twin pregnancies, but in the DET group, there were three sets of twins (7.5%). The cumulative clinical pregnancy rates per oocyte retrieval were 37.1 and 24.2% in the eSET and DET groups, respectively ($P < 0.001$), and the cumulative live birth rates were 22.7 and 13.2%, respectively ($P = 0.002$). Cumulative twin rates were 6.7% ($n = 4$) in the eSET group and 8.3% ($n = 4$) in the DET group ($P = 0.726$). All of the twin pregnancies in the eSET group resulted from frozen and thawed DET embryo transfer cycles.

LIMITATIONS: The characteristics of the two patients groups are not comparable because the suitability of eSET was individually assessed by a clinician based on both clinical prognostic factors and the outcome of IVF or ICSI, i.e. the number and quality of embryos.

WIDER IMPLICATIONS OF THE FINDINGS: This study may be generalized to IVF units having experience in eSET and cryopreservation.

STUDY FUNDING/COMPETING INTEREST(S): This study received no funding and there are no conflicts of interests to be declared.

Key words: *in vitro* fertilization / single-embryo transfer / cumulative pregnancy rate

Introduction

The high occurrence of multiple pregnancies is the most common complication of assisted reproductive technology (ART), as multiple pregnancies significantly increase the chances of maternal morbidity and mortality and perinatal complications. Single-embryo transfer (SET) is the only effective strategy to decrease multiple pregnancies (ESHRE, 2012). In randomized studies, elective SET (eSET) has been

proved to reduce multiple births significantly without compromising cumulative pregnancy rates (Martikainen *et al.*, 2001; Thurin *et al.*, 2004). Despite the encouraging research data, the eSET policy is not widely accepted and large differences exist between European countries in terms of multiple births. In 2010, a European Society of Human Reproduction and Embryology (ESHRE) report estimated that the twin rate in ART was still 20.8% in Europe (ESHRE, 2012). In Finland, the eSET policy has been well adopted without provision

of law, and the practise has lead to reduced numbers of twin deliveries after ART treatment. In 2009 in Finland there were only 8.8% multiple births from all IVF, ICSI and frozen embryo transfer (FET) treatments (THL, 2010).

The age of the woman at the time of IVF affects the probability of live birth rates (Templeton et al., 1996). The number of embryos needed to achieve maximum live birth rates depends on the age of the woman and the number of embryos cryopreserved (Schieve et al., 1999). In a recent meta-analysis, younger women (aged <33 years) had higher odds of a live birth than older women (>33 years) (37 versus 29%, $P = 0.02$). However, the effect of eSET compared with double-embryo transfer (DET) on live birth rates did not differ significantly between younger and older women (28 and 45% versus 23 and 35%, $P = 0.60$). Furthermore, the incidence of multiple live birth was similar for younger when compared with older women (19 versus 18%, $P = 0.86$) (McLernon et al., 2010). In fresh IVF cycles, women aged 36–39 years with eSET or DET had similar pregnancy rates per embryo transfer and similar live birth rates, while cumulative pregnancy rates (pregnancies per oocyte pick-up, including fresh and frozen embryo transfers) and live birth rates were significantly higher in the eSET group compared with women in the DET (Veleva et al., 2006).

The incidence of multiple live birth rates from eSET and DET in women aged 39 years or older is not well established. In an earlier cohort study performed in the USA, the multiple birth rate decreased by age and was 10.8% in the age group of 40–44 years when two embryos were transferred (Schieve et al., 1999). A recent study by Scotland et al. (2011) found the twin live birth rate to be 1.9 and 19.1% in 39-year-old women in eSET and DET cycles, respectively.

The present study was therefore carried out to elucidate the feasibility of eSET in women aged 40 years or older. To the best of our knowledge, current data on the suitability of eSET in this older age group is scarce. The study was conducted to compare clinical pregnancy rates, live birth rates and twin pregnancy rates in fresh cycles, as well as cumulative pregnancy rates, among women with eSET or DET.

Materials and Methods

This retrospective cohort study included all women aged 40–44 years, who received IVF or ICSI treatment at the Family Federation of Finland Helsinki Fertility Clinic during 2000–2009. Data on the fresh and frozen embryo transfers following one oocyte retrieval were included. The results were analysed per IVF/ICSI cycle, including both fresh and frozen embryo transfers. Women receiving donor oocytes were excluded. The database for each ART cycle performed at the Family Federation of Finland has been used as a data source for all parameters of this study.

The women were divided into two groups. The women in the eSET group had one single-embryo transferred in the fresh cycle, and one or more embryos cryopreserved. In the DET group, all women had two embryos transferred in the fresh IVF/ICSI cycle. The decision to electively transfer one embryo was based on several variables, including clinical factors such as the outcome of previous treatment cycles, number of previous embryo transfers, outcome of stimulation (number of large follicles) and embryological factors such as the number of oocytes retrieved, number of cleaved embryos and, most importantly, the quality of the embryos. Furthermore, the couples received careful counselling regarding chances of pregnancy after eSET compared with DET as well as the possibility of twins after DET. Couples were also informed about risks involved in multiple pregnancies at the age of 40 years or older. The

couples' opinion regarding the number of embryos to be transferred was taken into consideration. This means that even in good prognosis patients, if they insisted on having two embryos transferred, DET was performed, as long as there was no medical contraindication for a multiple pregnancy.

The criteria for cryopreservation of a Day 2 embryo were two to five blastomeres without multinucleated blastomeres and fragmentation <50%, and for a Day 3 embryo, the criteria were five or more blastomeres without multinucleated blastomeres and fragmentation <50%.

For all subjects, age, body mass index (BMI), main diagnosis for infertility and the duration of infertility at the time of IVF were obtained. Data on primary or secondary infertility was not analysed, as it was considered to be inconsistently documented. The characteristics of the index treatment (protocol, type of ART, total gonadotrophin dose, total days of gonadotrophin treatment, number of oocytes retrieved and number of frozen embryos) were gathered by using the database. The primary outcome measures were the rates of clinical pregnancies and live births in the fresh ART cycle, and the cumulative clinical pregnancy and live birth rates per oocyte retrieval. The data on twin pregnancies were also retrieved.

For statistical analysis, continuous variables (age, duration of infertility, total gonadotrophin dose, number of gonadotrophin treatment days, number of oocytes and number of frozen embryos) were compared using the Mann–Whitney test, as the data were skewed. Categorical variables were compared by using the χ^2 test, except for twin pregnancy rates which were compared by using Fisher's exact test. P -values of <0.05 were considered to be statistically significant. Predictive Analysis Software (PASW) Statistics 18 was used for the analysis.

Results

During the study period, altogether 628 women aged 40–44 having IVF or ICSI were included in the study. Of them, 264 had eSET and 364 had DET in the fresh ET cycle. The clinical characteristics are shown in Table I. Women in the eSET group were significantly younger than those in the DET group ($P < 0.001$). Other characteristics (BMI, main diagnosis and duration of infertility) did not differ significantly between the groups, although the data for duration of infertility were available for only 25% in the eSET and 20% in the DET group. The characteristics of the index treatment (fresh IVF/ICSI cycle) are shown in Table II. Women in the eSET group needed less gonadotrophins ($P < 0.001$), and had more oocytes retrieved ($P < 0.001$) and more embryos frozen ($P < 0.001$).

The primary outcome results are shown in Table III. In the fresh cycles, the clinical pregnancy rates were 23.5 and 19.5% in the eSET and DET groups, respectively. Live birth rates were 13.6 and 11.0%, and miscarriage rates were 37.5 and 36.1%, respectively. In the fresh eSET cycles, there were no twin pregnancies, whereas the fresh DET cycles resulted in three twin pregnancies (7.5%). In the FET cycles, 46 women in the eSET group and 28 women in the DET group had a clinical pregnancy, and 27 of the eSET group and 11 of the DET group resulted in live births. Sometimes these FET pregnancies were in women who had a fresh IVF/ICSI cycle pregnancy as well. Altogether the cumulative clinical pregnancy rates per oocyte retrieval were 37.1 and 24.2% after eSET and DET, respectively ($P < 0.001$), and the live birth rates were 22.7 and 13.2%, respectively ($P = 0.002$). Cumulative twin rates were 6.7% in the eSET group and 8.3% in the DET group ($P = 0.726$). In the eSET group, all twins were from the FET cycles with two embryos transferred.

Table I Characteristics of the women in the study groups.

	eSET (n = 264)	DET (n = 364)	P-value
Age (years)			
Mean (median), range	40.8 (41.0), 40–44	41.1 (41.0), 40–44	<0.001
BMI (%)			
<20.0	17 (6.4)	46 (12.6)	0.082
20.0–24.9	150 (56.8)	175 (48.1)	
25.0–29.9	57 (21.6)	73 (20.1)	
30.0–34.9	12 (4.5)	13 (3.6)	
35.0 or more	1 (0.4)	2 (0.5)	
Main diagnosis			
Tubal only	30 (11.4)	40 (11.0)	0.584
Female only, hormonal	0 (0)	1 (0.3)	
Female only, other	38 (14.4)	65 (17.9)	
Male factor only	48 (18.2)	78 (21.4)	
Unexplained	76 (28.8)	92 (25.3)	
Multiple causes	69 (26.1)	86 (23.6)	
Duration of infertility (months)			
Mean (median), range	43.0 (39), 2–127	39.0 (32), 1–205	0.050

Table II Characteristics of the ART in study groups.

	eSET (n = 264)	DET (n = 364)	P-value
Protocol (%)			
Agonist	212 (80.3)	280 (76.9)	0.519
Antagonist	50 (18.9)	79 (21.7)	
Other	2 (0.8)	5 (1.4)	
ART (%)			
ICSI	54 (20.5)	89 (24.5)	0.239
IVF	210 (79.5)	275 (75.5)	
Total gonadotrophin dose (IU)			
Mean (SD)	2400 (905)	2834 (1105)	<0.001
Total days of gonadotrophin treatment			
Mean (SD)	10.5 (1.6)	10.5 (1.8)	0.916
Number of oocytes			
Mean (SD)	11.1 (5.9)	8.4 (4.5)	<0.001
Number of frozen embryos			
Mean (SD)	4.6 (3.1)	1.5 (2.3)	<0.001

Discussion

Women in many western countries are increasingly postponing their attempt for first pregnancy. Our study question is increasingly relevant as a growing number of women in their 40s require ART (Te Velde

et al., 2012). The present study shows that even in the age group of 40–44 years, eSET is a feasible method when supported by an effective embryo freezing and thawing programme. We suggest that despite age, eSET should be considered for women who have good ovarian response to stimulation with moderate doses of gonadotrophins and additional embryos available for freezing. This requires an individualized assessment of each cycle.

ART outcomes are usually presented as pregnancies or live births per embryo transfer or per cycle started. This is a favourable way to present the results, if several embryos are transferred in one cycle and only a few are cryopreserved. This policy increases the pregnancy rate per transfer, but also increases risks of multiple pregnancies. In the eSET programme, the idea is to transfer one embryo at a time in fresh cycle and subsequent frozen cycles giving similar cumulative outcomes, but with fewer risks.

We acknowledge some limitations of this study, including the fact that the data on the duration of infertility were incomplete (22% missing). Furthermore, in this retrospective data, it was not possible to reliably distinguish between primary and secondary infertility. Also, the quality of embryos was not available in the database, even though the decision about cryopreservation was made taking this into account, as described in the section Materials and methods. All these parameters reflect the prognosis of the infertility treatment and were used in the clinical decision-making. Overall, the groups (eSET and DET) studied here are not comparable by their backgrounds or ART-related characteristics, because the aim was to choose the women with good prognosis for eSET to avoid multiple births.

A concern has been raised about restricting the possibility of having twins if a couple desires two children (Gleicher and Barad, 2009). On the other hand, a twin pregnancy and having twins at the age of 40–44 years might be burdensome in many ways and all couples at this age do not necessarily want to take that risk. In the present study, all couples received thorough counselling by an experienced doctor on the benefits and risks of both DET and SET. The opinion of the couple was taken into account in the decision-making.

Cumulative pregnancy rates are known to decline with age. During 1995–2010, in all IVF/ICSI eSET cycles (n = 1011) at the University

Table III Outcomes in eSET and DET groups.

	eSET (n = 264)	DET (n = 364)	P-value
Fresh cycle			
Clinical pregnancy (%)	62 ^a (23.5)	71 ^b (19.5)	0.228
Live birth (%)	36 (13.6)	40 (11.0)	0.315
Miscarriage (%)	24 (37.5)	26 (36.1)	0.735
Twins (%)	0 (0)	3 (7.5)	0.135
Cumulative results			
Clinical pregnancy (%)	98 (37.1)	88 (24.2)	<0.001
Live birth (%)	60 (22.7)	48 (13.2)	0.002
Twins ^c (%)	4 (6.7)	4 (8.3)	0.726

^aOne pregnancy ended in induced abortion and one pregnancy outcome was unknown.

^bFive pregnancies were ectopic.

^cAll twins in the eSET group were from frozen embryo transfer cycles.

Hospital of Oulu, the cumulative live birth rates per oocyte retrieval were 54% in women younger than 30 years, 49% in women aged 30–34 years and 39% in women aged 35–39 years (unpublished data). It was reassuring that the cumulative pregnancy rate was as good as 37% in the age group of 40–44 years even though only one embryo was transferred in the fresh cycle.

With increasing maternal age, miscarriages tend to become more common. Also, maternal age at conception is a strong and independent risk factor for fetal death, irrespective of previous reproductive outcomes (Nybo Andersen et al., 2000). These unfavourable pregnancy outcomes are mainly a consequence of the increasing number of fetal aneuploidies in older women. In a recent study, women with poor responses in IVF had more miscarriages than normal responders among women aged >36 years, suggesting a connection between quantitative ovarian reserve and oocyte quality (Haadsma et al., 2010). In this respect, the groups were similar in our study: 37.5% of pregnancies in the eSET group and 36.1% in the DET group in the fresh IVF/ICSI cycles ended in miscarriage.

In the UK, the authority regulating IVF, The Human Embryology and Fertilization Authority has made a recommendation for the national target of twin live birth rates to be below 10% (HFEA, 2012). Recently, a large prospective study concerning the effect of age on live birth and multiple birth rates showed that the risk of preterm birth and low birthweight, associated with multiple births, were lower among women older than 40 years, and thus older age would support the choice of transfer of two embryos (Lawlor and Nelson, 2012). However, as the authors pointed out, the data on cumulative pregnancy and live birth outcomes was missing in that study. In the present study, the cumulative twin pregnancy rates were similar between the two groups. All of the twins in the eSET group were the result of DET transfers in the frozen cycles. As described above, the number of embryos transferred was evaluated individually in each treatment cycle. The low number of twins in both groups shows that the selection of patients to an eSET or DET approach has been successful in terms of the twin pregnancy rate. However, that does not mean that DET should be performed for all women, as this misinterpretation would probably lead to increasing twin rates. It has been indicated that the risk of preterm birth, low birthweight and perinatal death is higher in ART twins than in spontaneously conceived twins of different genders (Hansen et al., 2009). Moreover, the risks of maternal hypertension, gestational diabetes and pre-eclampsia increase in multiple pregnancies (Dodd and Crowther, 2005), and at the same time, age alone increases the maternal risks. Based on these previous studies, to minimize additional maternal and neonatal problems, twin pregnancies in women over 40 should actively be avoided. This policy requires proper counselling of the patients and a good ethical approach of the IVF clinics.

As the increasing age of the woman reduces her chance to conceive even with ART, we do not recommend SET for every woman in her 40s. However, the clinical decision between eSET and DET should not be based solely on the age of the woman, but also on other prognostically favourable characteristics of the treatment cycle (e.g. good response to stimulation and at least two good-quality embryos). The present study suggests that an eSET policy can be applied with gratifying cumulative clinical pregnancy and live birth rates in older women (40–44 years) with a good prognosis. We hope that these results will encourage other providers to

consider eSET in women aged 40 years or older in situations where there is a high chance of pregnancy.

Authors' roles

All authors participated in the study design and drafting the manuscript. M.N. conducted the data analysis. The final version of the manuscript was approved by all the authors.

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Conflict of interest

None declared.

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