

# Effect of single embryo transfer on the risk of preterm birth associated with in vitro fertilization

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## Abstract

**Purpose** To determine whether elective single embryo transfer (eSET) reduces the risk of preterm delivery associated with in vitro fertilization (IVF).

**Methods** This is an observational study of 3125 eSET cycles performed from 2008 to 2009 and reported to the Society for Assisted Reproductive Technology (SART) database. Preterm delivery rates were compared to the overall preterm delivery rate among all patients undergoing IVF over the same time period.

**Results** The 3125 eSET cycles resulted in 1507 live births (live birth rate 48.2 %). Among these deliveries were 27 twins (1.8 %) and one set of triplets (0.07 %). The overall preterm delivery rate (20–37 weeks gestation) following eSET was 17.6 % (269/1527). This is significantly greater than the

preterm birth rate for all patients undergoing IVF over the same time period (12 %,  $P < 0.001$ ).

**Conclusions** Elective single embryo transfer does not reduce the risk of preterm delivery associated with in vitro fertilization (IVF).

**Keywords** Single embryo transfer · Preterm delivery

## Introduction

Despite efforts to reduce the incidence of preterm delivery, greater than 12 % of all pregnancies in the United States still result in premature birth [1]. While numerous factors are responsible for this high incidence, one significant contributor is IVF, which leads to an increased risk of preterm delivery in part because of the high incidence of multiple gestations.

Traditionally, IVF has involved the transfer of multiple embryos, in order to maximize patients' chances for a live birth. While IVF success rates have increased over the years, this improvement has come at the expense of an unacceptably high risk of twins and higher order multiples, conditions that put the patient and the pregnancy at risk. The number of embryos transferred has steadily declined in the US: In 2010, an average of 2 embryos were transferred per cycle to patients under age 35. However, in this age group 32.4 % of all live births were twins, with an additional 1.5 % resulting in triplets [2].

Elective single embryo transfer (eSET), in which one embryo is transferred following ovarian stimulation with any remaining good quality embryos frozen for later use, has been proposed as a possible solution to reduce the risk of multiple pregnancies and, as a result, preterm delivery. However, while eSET does significantly reduce the incidence of multiple gestations, multiple meta-analyses have demonstrated that singletons born after IVF, whether after single or multiple

**Capsule** Elective single embryo transfer does not reduce the risk of preterm delivery associated with in vitro fertilization.

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embryo transfer, are at significantly greater risk of preterm delivery than spontaneously conceived singletons [3–6]. In a recent meta-analysis of perinatal outcomes following eSET, only two studies met criteria to evaluate the preterm delivery rate following eSET compared with the rate following spontaneous conceptions. Although only 520 patients were included, the analysis demonstrated a greater than 2-fold greater risk of preterm delivery in the eSET group compared to the spontaneous conception group [5]. However, to date, no single large observational study has been specifically designed and performed to evaluate the impact of eSET on prematurity.

## Materials and methods

The data source for this study was the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System (SART CORS) database, which contains data from more than 85 % of all practices providing assisted reproductive technologies in the United States. This was a descriptive analysis of birth outcomes following all fresh non-donor eSET cycles with embryo transfer on day 5 or 6 from 2008 to 2009 reported to SART. Data obtained included gestational age at delivery as well as type of gestation (singleton, twin or higher order multiple). Preterm delivery was defined as delivery occurring between 20 weeks 0 day and 36 weeks 6 days gestation. The preterm delivery rate was calculated as a percentage of the total number of deliveries (including multiple gestations) after 20 weeks following eSET.

### Statistical analysis

Chi-square analysis was used to analyze the difference in preterm delivery rate between eSET cycles and IVF cycles overall from 2008 to 2009.

### Ethical approval

The Institutional Review Board of UMDNJ, Newark approved this study prior to its initiation.

## Results

A total of 3125 fresh non-donor eSET cycles with a day 5/6 embryo transfer were reported to SART from 2008 to 2009. Patients were a mean age of 32-years-old, with 31.5 % (983/3125) reporting a history of full term delivery and 4.5 % (142/3125) reporting a history of preterm delivery. The most common infertility diagnosis was male factor ( $n=1133$ ) followed by PCOS ( $n=734$ ), tubal factor ( $n=552$ ), and unexplained infertility ( $n=426$ ). Patients could have more than one

diagnosis. Among the study population, an average of 18 oocytes were retrieved and 4 embryos were cryopreserved per cycle. All patients underwent embryo transfer on day 5/6, and all patients had at least one embryo cryopreserved. The 3125 eSET cycles resulted in 1527 deliveries after 20 weeks gestation (Table 1). Of these, there were 1507 live births (live birth rate 48.2 %). Twenty-seven pregnancies resulted in twins (1.8 %) and one resulted in triplets (0.06 %). The overall preterm delivery rate following eSET was 17.6 % (269/1527). Over the same time period, the preterm delivery rate from all fresh non-donor IVF cycles was 12 %, a figure significantly lower than the rate following eSET (Chi-square 43.5,  $P<0.001$ ). Excluding the few multiple pregnancies made no change in results (Chi-square 24.7,  $P<0.001$ , Table 2).

## Discussion

These findings, derived from the first large published single cohort, demonstrate that the elevated risk of preterm delivery persists, and is in fact higher, with eSET. The data are extremely robust, drawing from the SART national database over a 2-year period. These results confirm those found in two previous studies of fewer numbers of subjects examining the effect of eSET on prematurity and other perinatal complications. Comparing outcomes from SET singleton pregnancies versus spontaneously conceived singletons, Poikkeus et al. demonstrated a 2.85-fold increased risk of preterm birth in the SET group ( $n=269$ ) [7]. No difference in preterm delivery rate was observed between singletons resulting from single versus double embryo transfer. In another comparison of SET versus spontaneous singletons, De Neubourg et al. found a 10 % risk of preterm delivery in the SET group compared to a 6.8 % risk among spontaneously conceived singletons [ $n=251$ ] [8].

It has long been clear that IVF pregnancies have a greater risk of preterm birth, but much of this risk has been thought to be secondary to the marked increase in multiple pregnancy. However, several meta-analyses [3–6, 9] examined singleton births after IVF, and still noted an elevated risk of prematurity. A large observational study from 2004 utilizing SART data

**Table 1** Gestational age at delivery following elective single embryo transfer

Gestational age at delivery	Number (%)
20–23 weeks 6 days	24 (1.6)
24–31 weeks 6 days	33 (2.1)
32–36 weeks 6 days	212 (13.9)
>37 weeks	1258 (82.4)
<b>Total deliveries 20–36 weeks 6 days</b>	<b>269 (17.6)</b>

**Table 2** Gestational age at delivery of singletons only (multiple births excluded) following elective single embryo transfer

Gestational age at delivery	Number (%)
20–23 weeks 6 days	24 (1.6)
24–31 weeks 6 days	27 (1.8)
32–36 weeks 6 days	193 (12.9)
>37 weeks	1255 (83.7)
<b>Total deliveries 20–36 weeks 6 days</b>	<b>244 (16.2)</b>

from greater than 62,000 singletons born after IVF showed a 1.4-fold increased risk of preterm delivery above that of historical spontaneously conceived controls [9]. Four meta-analyses comparing IVF singletons to those spontaneously conceived found an even higher risk of preterm delivery, from 1.8- to 2.1-fold, among the IVF group [3–6].

As an explanation, the authors of these studies have posited that some aspect of either the IVF treatment itself or the underlying infertility is responsible for the increased incidence of preterm delivery that persists even with singleton gestations. Some have suggested this elevated risk may be related to the transfer of multiple embryos, possibly resulting in unrecognized “vanishing” twins, which are known to have a greater risk of preterm birth than in pregnancies which began as singleton [10]. The fact that the preterm birth incidence remained elevated following eSET, however, argues against this explanation as the vast majority of resulting pregnancies begin as singletons.

Two recent studies have demonstrated an increased incidence of preterm delivery among IVF singletons following blastocyst transfer compared to cleavage-stage embryos [11, 12]. The authors suggest that extended culture could cause genetic and epigenetic alterations that can lead to abnormal implantation and placentation, thereby predisposing to preterm birth. While this hypothesis has not yet been proven, it could provide at least a partial explanation for our current findings given that the vast majority of pregnancies in our study resulted from blastocyst transfers.

Other investigators have proposed that the patient’s underlying infertility may predispose them to preterm delivery. Comparing singletons born after any type of fertility treatment to matched fertile controls, Hayashi et al. demonstrated an increased risk of prematurity among the infertile group [13]. There was no significant difference in preterm birth incidence between the various infertility treatment groups (ovulation induction, unstimulated intrauterine insemination, IVF). Based on these findings, the authors suggest that infertility itself is a risk factor for preterm delivery. However, the data also support the theory that ovarian stimulation may contribute to the prematurity rate. While all fertility treatments resulted in a higher rate of preterm delivery compared to their respective controls, the increased prematurity rate in the ovulation induction and IVF groups compared to their controls

were more highly significant ( $P < 0.001$ ) compared to the infertile group that did not undergo ovarian stimulation (i.e. the intrauterine insemination group,  $P = 0.032$ ) [13].

Our group has previously demonstrated that luteal mass, as well as levels of maternal serum relaxin (a product of the corpus luteum known to be elevated after superovulation), correlate strongly with preterm delivery in singleton pregnancies. This evidence suggests that the risk of prematurity may be due to the ovarian stimulation and excess ovarian steroid and protein products associated with IVF.

During same time period as the current report (2008–2009), data from CDC/SART demonstrates a 12 % preterm delivery rate among IVF singleton pregnancies that began as singletons [1]. This group includes not only the eSET patients from our study group, but also patients in whom one embryo implanted after a multiple embryo transfer. The patients who underwent eSET experienced a preterm birth rate nearly 1.5 times higher than the group as a whole. This remarkable finding suggests that some characteristic of the patients themselves, or their response to ovarian hyperstimulation, must be responsible for the differential risk. Women selected for eSET tend to be younger and have a better prognosis than those patients for whom multiple embryo transfer is planned, and thus would be expected to produce a greater response to controlled ovarian stimulation.

Elective SET not only increased the overall preterm delivery rate, but also appears to increase the percentage of preterm deliveries occurring at earlier gestational ages. According to CDC data on all deliveries in the US between 2008 and 2009 (overall preterm delivery rate 12.3 %), six percent of the preterm deliveries occurred prior to 28 weeks gestation [1]. Among our study population 14.2 % of all preterm deliveries occurred prior to 28 weeks, demonstrating a more than two-fold increase in very early premature births.

These observations are of critical importance, as they demonstrate that moving towards eSET as the primary transfer paradigm during IVF will likely not succeed in reducing the elevated risk of preterm delivery seen in IVF singletons. Performing embryo transfer only in aluteal artificial cycles after embryo freezing, on the contrary, would correct for excess luteal function and be more likely to solve the problem. This hypothesis was confirmed by a meta-analysis which demonstrated a lower risk of preterm delivery after the transfer of frozen thawed versus fresh embryos [14]. In this study, singletons conceived following frozen thawed transfer were 16 % less likely to deliver earlier than 37 weeks compared to those resulting from a fresh IVF cycle. These results are promising as they suggest that there are methods the fertility community can employ to reduce the incidence of preterm delivery. Studies to understand the mechanism of IVF-related prematurity in singleton pregnancies are urgently needed.

The main strength of this study is its size, as over three thousand cycles were included over a 2-year period. There are

however some limitations that must be mentioned. Data on several possible confounding variables were incomplete and thus their possible effects could not be evaluated. These parameters include body mass index (BMI), ethnicity, baseline FSH levels, and maximum estradiol levels. While these last two parameters are especially important indicators of ovarian function, the young age of the patients coupled with the large number of oocytes retrieved and the fact that all patients had at least one embryo to cryopreserve support the argument that the study population generally consisted of healthy responders. Details surrounding the indication for the preterm deliveries were not available for this study, thereby limiting the depth of our analysis. Information regarding whether these premature births were spontaneous versus iatrogenic would certainly enhance the conclusions we could draw from the data. Finally, our control group consisted of all patients undergoing IVF over the same time period, a group that includes our study population. While a more accurate control group would have been only those patients who had more than one embryo transferred, the 1527 deliveries among our study patients accounts for less than 3 % of the greater than 57,000 total births among IVF patients.

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