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Birth Rates Using Single Embryo Transfer

In recent years, the number of high-order multiple gestations (triplets or more) for women undergoing in vitro fertilization (IVF) has declined as a result of reductions in the average

number of embryos transferred. Rates of twin births, however, along with premature births and associated complications, have remained high due to the practice of transferring ≥ 2 embryos. In some countries, elective single embryo transfer (eSET) is common, but physicians in the United States have been slow to adopt this practice, mainly out of fear it will lower pregnancy rates.

Mancuso et al from the University of Iowa Carver College of Medicine compared rates of live births and multiple births at clinics in the United States that perform eSET with those that do not. The data collected by the Centers for Disease Control and Prevention National Assisted Reproductive Technology Surveillance System for 2013 included 94% of all IVF clinics in the country. The comparison focused on the rate of eSET performed at a clinic for all fresh autologous cycles in patients aged < 35 years and from 35 years to 37 years. An eSET was defined as a cycle in which 1 embryo was transferred and ≥ 1 additional embryo was cryopreserved.

The clinics were divided into groups based on eSET rates for each age group, aggregate rates of live births per embryo transfer and multiple births per delivery. Live-birth rate was defined as the percentage of live births of ≥ 1 child at > 20 weeks gestational age divided by the total number of embryo transfer cycles in a clinic. Multiple-birth rate was defined as the percentage of multiple births (twins and higher-order multiples) per live birth conceived by IVF in a clinic. Also compared were eSET and double embryo transfer (DET), based on total number of embryos available, embryo stage and patient age.

Calculations showed a marked linear decrease in the multiple-birth rate as the eSET rate increased, and no significant difference in clinic-level live-birth rate for each age group (Figure 1). Live-birth rates were slightly higher with DET, mainly in women aged 35 years to 37 years or with ≥ 3 embryos available for transfer.

IN THIS ISSUE

Summer 2017

Birth Rates Using Single Embryo Transfer

How Prevalent Is Ovarian Cancer After Endometrioma Excision?

Pregnancy Complications in Women With Endometriosis

Effect of First-line Cancer Treatment on Young Girls' Ovaries

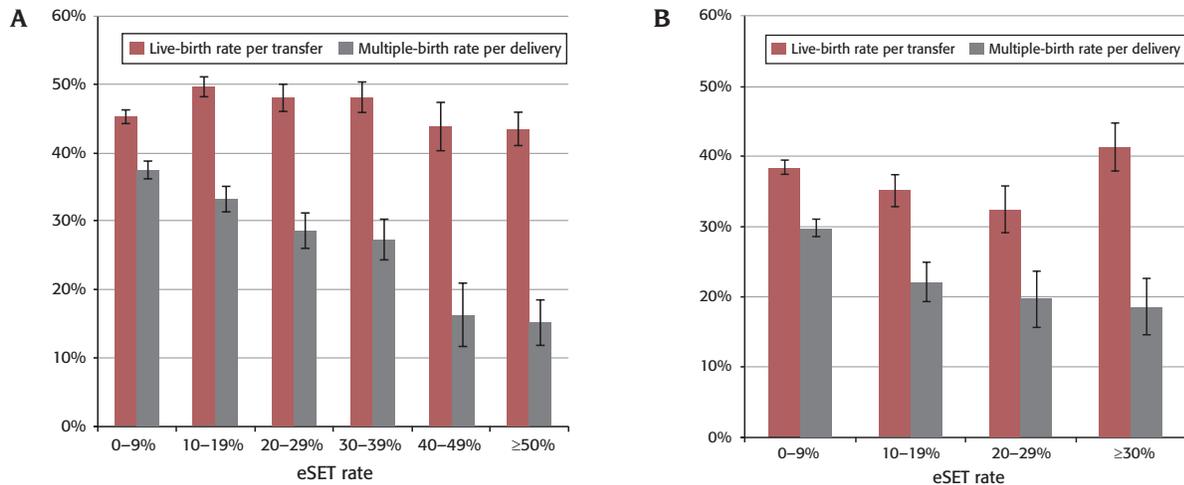


Figure 1. Live-birth rate and multiple-birth rate by clinic eSET rate for fresh IVF cycles in patients aged (A) <35 years and (B) 35–37 years, U.S. fertility clinics, 2013; estimated means with standard error bars for live-birth rates and multiple-birth rates after adjusting for significant confounding variables. Live-birth rates for patients aged <35 adjusted for blastocyst transfer rate. Multiple-birth rates for patients aged <35 years adjusted for blastocyst transfer rate and parity. Live-birth rates for patients aged 35–37 years adjusted for blastocyst transfer rate, intracytoplasmic sperm injection rate and patient race. No significant confounding variables were found for multiple-birth rates for ages 35–37 years.

Conclusions and Clinical Implications

The benefits of increasing eSET use are clear, the authors concluded. This study’s findings add to the growing evidence that eSET effectively decreases the high multiple-birth rates associated with IVF, which create a “significant financial burden to healthcare delivery systems” and have little or no effect on live-birth rates. Continuing advances in embryo cryopreservation, embryo genetic analysis and selection should lead to further improvement in IVF outcomes for patients undergoing eSET.

Mancuso AC, Boulet SL, Duran E, et al. Elective single embryo transfer in women less than age 38 years reduces multiple birth rates, but not live birth rates, in United States fertility clinics. *Fertil Steril* 2016; 106:1107-1114.

How Prevalent Is Ovarian Cancer After Endometrioma Excision?

The most common form of endometriosis is ovarian endometrioma, which has been estimated to account for 55% of cases. Haraguchi et al from the University of

Tokyo, Japan, investigated the prevalence of ovarian cancer development following excision of ovarian endometrioma (cystectomy), surgery frequently

performed when medical treatment has been inadequate to alleviate pain and infertility.

Records of 485 patients who underwent laparoscopic excision of endometriomas ≥ 4 cm in diameter from 1995 through 2004 were reviewed. At the time of laparoscopy, the patients ranged in age from 13 to 48 years (mean age, 32.8 years); 383 patients (79.0%) were experiencing pain, and 186 patients (38.4%) were being treated for infertility.

During the follow-up period of 1 to 221 months (median follow-up, 48 months), 121 patients (24.9%) experienced recurrence of endometriosis, and 4 (0.8%) of the total cohort were diagnosed with ovarian cancer. At the time of laparoscopy, these 4 patients were aged 32 to 41 years. All experienced endometriosis recurrence after periods ranging from 12 to 140 months; their cancers were diagnosed between the ages of 42 to 45 years at 7 to 93 months after recurrence.

Conclusions and Clinical Implications

The study’s findings indicated that ovarian cancers developing after excision of ovarian endometrioma are most likely to arise from recurrence of endometrioma. The authors urged that special care and rigorous follow-up be given to patients who experience recurrence. Further research is needed about

other possible variables and whether preventing recurrence could prevent cancer development.

Haraguchi H, Koga K, Takamura M, et al. *Development of ovarian cancer after excision of endometrioma*. *Fertil Steril* 2016;106:1432-1437.

Pregnancy Complications In Women With Endometriosis

The possible association between endometriosis and adverse pregnancy outcomes has received increasing attention, but study results have been inconclusive.

Investigating the question further, Glavind et al from Aarhus University Hospital, Denmark, conducted a population-based study using data from the Aarhus Birth Cohort, which was established in 1989 and has been described as the largest European birth cohort.

The data analyzed were based on 82,793 live singleton births to 55,829 women between September 1989 and December 2013. Diagnosis of endometriosis was recorded in the Danish National Patient Registry for 1213 (2.2%) of these women, who had 1719 (2.1%) of the pregnancies. On average, the pregnant women with endometriosis

- were older than those without endometriosis
- had a higher prevalence of using assisted reproductive technology (ART)

The women with endometriosis were found to be at greater risk for preeclampsia, preterm birth (defined as live birth at <37 weeks gestation) and cesarean section. No association was seen between endometriosis and small for gestational age (SGA); defined as ≥ 2 standard deviations below the mean) or postpartum hemorrhage (Table 1). These risks were essentially the same for women who received ART and those who did not.

The risk of preterm birth in women with endometriosis was higher for very preterm deliveries compared with those that were moderately preterm; when all induced deliveries were excluded, this risk decreased slightly. Women with endometriosis had elective cesarean section deliveries more often; for those having acute cesarean section, the adjusted odds ratio (AOR) was 1.72 (95% confidence interval [CI], 1.47–2.01). When, in secondary analysis, pregnancies complicated by preeclampsia, preterm birth or SGA were excluded, the AOR for any cesarean section decreased slightly to 1.74 (95% CI, 1.50–2.01).

Conclusions and Clinical Implications

These data support the hypothesis that endometriosis is a risk factor for preeclampsia, preterm birth and cesarean section. The results “strongly suggest that the obstetric risks associated with endometriosis should be taken seriously,” the authors stated. They cited the need for further research into the underlying mechanisms.

Glavind MT, Forman A, Arendt LH, et al. *Endometriosis and pregnancy complications: a Danish cohort study*. *Fertil Steril* 2017;107:160-166.

Table 1. Adjusted odds ratios for pregnancy complications in women with endometriosis among 82,793 live singleton births in Aarhus, Denmark, between 1989 and 2013

Variable	Distribution of adverse pregnancy outcome (%)		AOR ^a (95% CI)
	Endometriosis (n = 1719)	No endometriosis (n = 81,074)	
Preterm birth (<37 wk)	7.27	4.33	1.67 (1.37–2.05)
Small for gestational age	2.45	2.35	1.00 (0.73–1.37)
Preeclampsia	4.30	3.07	1.37 (1.06–1.77)
Postpartum hemorrhage	9.23	9.42	0.95 (0.80–1.14)
Cesarean section	24.08	14.14	1.83 (1.60–2.09)

^aAdjusted for maternal age (≤ 19 , 20–24, 25–29, 30–34 and ≥ 35 years), maternal body-mass index before pregnancy (<20, 20–24.9, 25–29.9 and ≥ 30 kg/m²), parity (nulliparous or parous), ethnicity (based on the place of birth, categorized as Denmark or other countries), years of school (≤ 9 , 10–11, or ≥ 12 years), and year (categorized as before 1994 or 1994 and later). CI, confidence interval.

Effect of First-line Cancer Treatment on Young Girls' Ovaries

For young girls who undergo cancer treatment, the pool of ovarian follicles may be severely reduced or disappear. The only available option

to preserve fertility for a prepubertal girl is cryopreservation of ovarian tissue. Then, if ovarian activity is destroyed and premature ovarian insufficiency occurs, the tissue might be transplanted to restore ovarian function. The first published report of a child born after transplantation of ovarian tissue obtained before menarche but after puberty appeared recently.

The problem is deciding whether a young girl needs to undergo this invasive procedure. Fertility preservation is recommended when there is an estimated risk of premature ovarian insufficiency >50%. El Issaoui et al from the University of Copenhagen, Denmark, assessed the impact of first-line drugs considered to be relatively gonadotoxic, such as ABVD (Adriamycin, bleomycin, vincristine and dacarbazine).

The retrospective case-control study included 63 girls aged <18 years (range, 1.5–17.9 years) who were diagnosed with cancer and had been referred for ovarian tissue cryopreservation between 2002 and 2014. Of these, 31 (group 1) had not received chemotherapy before the procedure, while 32 (group 2) had received low-risk gonadotoxic agents, then, after experiencing a relapse of their cancer, underwent ovarian tissue cryopreservation before further treatment. There was no significant difference in mean age between the groups. The most frequent diagnoses in group 1 were Hodgkin lymphoma and Ewing sarcoma; in group 2, acute lymphoblastic leukemia and acute myeloid leukemia.

Ovarian tissue cryopreservation involved excision of a single ovary. The ovary was weighed before freezing, had a small cortical biopsy examined histologically and was then cut into sections. Follicular density (follicles/mm³) was measured by counting follicles in every second section, and ovarian volume (mL) was calculated from the weight.

The 2 patient groups were compared by

- follicular density
- ovarian volume
- number of ovarian cortex pieces

No statistically significant difference was found between the groups in follicular density ($334 \pm 476/\text{mm}^3$ vs $327 \pm 756/\text{mm}^3$; $p > .1$). However, ovarian volume was significantly higher in group 1 than in group 2 (5.3 ± 3.3 mL vs 2.9 ± 2.1 mL; $p < .05$), as was the number of cryopreserved ovarian cortex pieces (21.3 ± 8.1 mL vs 15.2 ± 7.1 mL; $p < .05$).

Conclusions and Clinical Implications

From the reductions in ovarian volume and total number of cryopreserved cortex pieces of the patients who had received prior cancer treatment, the authors calculated that the reduction in estimated ovarian reserve was 10% to 20% in girls aged <6 years and up to 30% in those aged 10 to 18 years. Thus, for young girls, first-line cancer treatment may not have long-term consequences for fertility. The exact consequences of a 30% reduction in ovarian reserve are unknown, but the information could be important for counseling patients and their parents about whether to undergo fertility preservation.

El Issaoui M, Giorgione V, Mamsen LS, et al. Effect of first line cancer treatment on the ovarian reserve and follicular density in girls under the age of 18 years. *Fertil Steril* 2016;106:1757-1762.

In the next issue of

Infertility Treatment Update™

Laparoscopy vs robotic surgery for endometriosis; interpregnancy interval and recurrent loss; singletons' outcomes after assisted reproductive technology (ART) vs not using ART

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