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Perinatal Outcomes After Single- Or Double-Embryo Transfer

Martin et al from Emory University, Georgia, hypothesized that worse perinatal outcomes for singleton pregnancies achieved with assisted reproductive technology (ART) than for those conceived naturally might be due in part to the transfer of

>1 embryos or a vanishing twin. If so, more adverse outcomes would occur for pregnancies achieved after double-embryo transfer (DET) than for those conceived naturally; rates for those achieved after single-embryo transfer (SET) would compare with rates for those conceived naturally. Also, outcomes might be better if SET was elective (eSET), with ≥ 1 high-quality embryos available, than when there is no choice (non-eSET) because there is only a single acceptable embryo.

To test these hypotheses, perinatal outcomes were compared among singletons conceived naturally and 4 subgroups of those born after ART:

- DET after 1 early fetal heartbeat (DET 1)
- DET after ≥ 2 early fetal heartbeats (DET ≥ 2)
- eSET
- non-eSET

Data were obtained from the States Monitoring Assisted Reproductive Technology (SMART) Collaborative database, which at the time had analyzable statistics from Connecticut, Florida, Massachusetts and Michigan. Through SMART, all singleton births in these states between 2000 and 2010 were identified by birth certificates; births that could not be linked to the National ART Surveillance System (NASS) database were considered non-ART ($n = 4,837,983$). ART births were restricted to fresh, nondonor cycles ($n = 17,364$).

Preterm birth (PTB; <37 weeks) occurred in

- 8.2% of non-ART births
- 11.2% of DET 1 births
- 15.2% of DET ≥ 2 births
- 9.1% of eSET births
- 9.0% of non-eSET births

IN THIS ISSUE

Autumn 2017

Perinatal Outcomes After Single- or Double-embryo Transfer

Successful Robotic Surgery for Endometriosis

Menarche, Parity and Premature and Early Menopause

Interpregnancy Interval and Risk of Recurrent Loss

Adjusted analyses found no difference compared with non-ART in the odds of PTB between eSET and non-eSET singletons, but both DET groups had greater odds of PTB and very preterm birth (VPTB; <32 weeks). The odds were greatest for DET ≥2 (PTB adjusted odds ratio [aOR] 1.58; 95% confidence interval [CI], 1.09–2.29; VPTB aOR 2.46; 95% CI, 1.20–5.04).

This pattern was also found for low birth weight (LBW; <2500 g) and very low birth weight (VLBW; <1500 g). For DET ≥2, the aOR for LBW was 2.17 (95% CI, 1.24–3.79); for VLBW, the aOR was 3.67 (95% CI, 1.38–9.77). There was no difference in the odds of having a small for gestational age infant (<10th percentile) for any ART group compared with those born without ART. Infants conceived after eSET were less likely to have a 5-minute Apgar score <7 than were those conceived without ART (aOR 0.33; 95% CI, 0.15–0.69).

Conclusions and Clinical Implications

This study indicates that eSET is strongly associated with ideal pregnancy outcomes after ART. Risk of adverse perinatal outcomes was not significantly higher for singletons born after SET than for those born without ART. If eSET resulted in singleton births, those infants were less likely than those born without ART to have a 5-minute Apgar score <7. Increased risk of adverse perinatal outcomes for singletons after ART appeared to be related to the transfer of >1 embryos; the risk was highest for pregnancies with >1 early fetal heartbeats established.

Martin AS, Chang J, Zhang Y, et al; States Monitoring Assisted Reproductive Technology (SMART) Collaborative. Perinatal outcomes among singletons after assisted reproductive technology with single-embryo or double-embryo transfer versus no assisted reproductive technology. *Fertil Steril* 2017;107:954-960.

Successful Robotic Surgery for Endometriosis

Successful Robotic Surgery for Endometriosis | Robotic surgery has been used as a less invasive approach than laparoscopy to treat endometriosis. How results from the 2 procedures compare was addressed by Soto et al from the Cleveland Clinic, Ohio, in the first known multicenter, randomized controlled trial. Participating

Robotic surgery has been used as a less invasive approach than laparoscopy to treat endometriosis. How results from the 2 procedures compare was addressed by Soto et al from the Cleveland Clinic, Ohio, in the first known multicenter, randomized controlled trial. Participating

Table 1. QoL outcomes: SF-12

Subscores	Robotic surgery	Laparoscopic surgery
Physical health score		
Baseline	41.5 ± 4.8	42.7 ± 6.4
6 weeks	39.6 ± 3.6	41.9 ± 2.8
6 months	42.4 ± 3.9	41.1 ± 4.3
Mental health score		
Baseline	42.7 ± 7.0	43.2 ± 7.0
6 weeks	46.1 ± 6.1	45.8 ± 5.7
6 months	44.9 ± 7.9	44.7 ± 5.4

Data presented as mean ± SD. Number for robotic and laparoscopic groups at 6 weeks' and 6 months' follow-up: n = 31 and n = 34, n = 25 and n = 26, respectively. No comparisons were statistically significant (p > .05); the physical health score at 6 weeks (p = .055) approached significance.

institutions included the Cleveland Clinic, the Mayo Clinic, and Brigham and Women's Hospital.

A total of 73 patients planning to undergo surgery for endometriosis because of pain or infertility were randomly assigned to laparoscopy (n = 38) or robotic surgery (n = 35) and followed postoperatively for 6 months. For the 2 groups, the most common indications for surgery were pelvic pain, dysmenorrhea and dyspareunia. Patients in both groups had had, on average, 1 previous laparoscopic surgery; few had had previous robotic surgery.

The primary outcome measure was operative time, a significant factor because it is linked to cost. Secondary outcomes were perioperative and intermediate-term quality of life (QoL); this was assessed at 6 weeks and again at 6 months after surgery by patients' responses to 2 questionnaires: the 12-item Short Form Health Survey (SF-12) and the Endometriosis Health Profile-30 (EHP-30).

Mean operative time for robotic surgery was 106.6 ± 48.4 minutes; for laparoscopic surgery, 101.6 ± 63.2 minutes (p = .71). After adjusting for disease stage, there were no statistical differences in operative time, blood loss, or intraoperative or postoperative complications; 2 robotic group patients and 3 in the laparoscopy group were rehospitalized for pain from pyelonephritis, urinary tract infection or ileus.

The mental health scores for the 2 groups on the SF-12 were comparable at each time point, with

no significant changes from baseline. The higher physical health score approached statistical significance for the laparoscopic group at 6 weeks, but the scores were similar at baseline and 6 months postoperatively (Table 1).

At 6 weeks and 6 months, QoL scores on the EHP-30 improved from baseline for all parameters except infertility, which was defined as feelings of anxiety about the ability to conceive. There were no statistical differences between the groups for any parameter.

Conclusions and Clinical Implications

For patients with endometriosis, laparoscopy and robotic surgery resulted in comparable perioperative outcomes and significant improvement in QoL evaluated 6 months postoperatively. Further clinical trials including longer-term evaluation are needed to assess the use of robotic surgery for endometriosis.

Soto E, Luu TH, Liu X, et al. *Laparoscopy vs. Robotic Surgery for Endometriosis (LAROSE): a multicenter, randomized, controlled trial.* *Fertil Steril* 2017;107:996-1002.

Menarche, Parity and Premature and Early Menopause

(ages 40 through 44) are at increased risk for chronic conditions later in life and early death. Genetic and environmental factors may affect the timing of menopause. Several studies have found higher parity associated with older age at menopause, and others have suggested a link between early menarche and early menopause.

The roles of parity and early menarche in the timing of menopause were explored by Mishra et al from the University of Queensland, Australia, using data gathered from 9 observational studies conducted in Australia, the United Kingdom, Scandinavia and

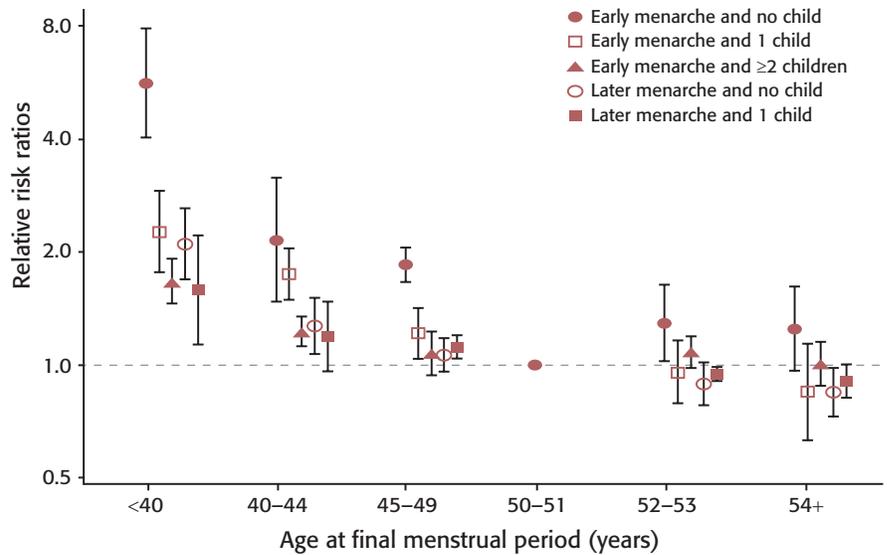


Figure 1. Relative risk ratios and 2-sided 95% CI for menopausal age <40, 40–44, 45–49, 52–53 or ≥54 with reference to age 50–51 among women with early (≤11 years) and later age (≥12 years) of menarche in combination with no child, 1 child or ≥2 children (women with a combination of late age at menarche and ≥2 children were used as a reference group; y-axis on log scale). The estimates were fully adjusted for study cluster, birth year, education, marital status, smoking status and body mass index.

Japan as part of the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE). The study population comprised 51,450 postmenopausal women who reported their age at their final menstrual period, confirmed by 12 months of amenorrhea not due to surgical intervention. Among the participants,

- the median age at final menstrual period was 50 years (interquartile range, 48–53 years)
- the median age at menarche was 13 years (age range, 8–20 years)
- three-quarters of the women had ≥2 children, 11% had 1 child and 12% were nulliparous
- premature menopause was reported by 2.0% of the women
- early menopause was reported by 7.6% of the women

Statistical analyses found that, compared with women who experienced menarche at age 13, those with early menarche had almost twice the relative risk [RR] of experiencing premature menopause (RR 1.80; 95% confidence interval [CI], 1.53–2.12)

and 31% higher risk of early menopause (RR 1.31; 95% CI, 1.19–1.44). Compared with women who had ≥ 2 children, nulliparous women had $>2\times$ the risk of premature menopause (RR 2.26; 95% CI, 1.84–2.77), 32% higher risk for early menopause (RR 1.32; 95% CI, 1.09–1.59) and 13% higher risk for menopause at age 45 to 49 (RR 1.13; 95% CI, 1.03–1.23; Figure 1).

Conclusions and Clinical Implications

This large international study found early menarche a risk factor for both premature and early menopause, with the risk greater for nulliparous women. The authors suggested that nulliparous women who had an early menarche (≤ 11 years) be advised of the risk when they are about 35 years old, and that clinicians begin monitoring and implementing preventive strategies to reduce the possibility of chronic health problems associated with early menopause.

Mishra GD, Pandeya N, Dobson AJ, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Hum Reprod* 2017;32:679–686.

Interpregnancy Interval and Risk of Recurrent Loss

Increased risk of subsequent pre-term birth and recurrent loss after miscarriage has been reported. Women who want to conceive after

a pregnancy loss frequently express concern about another possible loss and ask how long they should wait before attempting to conceive again. Because the interpregnancy interval (IPI) is a modifiable risk factor, Roberts et al from the University of Sydney, Australia, investigated whether the length of the IPI made a difference in pregnancy outcome.

The retrospective study identified 9545 women in New South Wales, Australia, who had had a first pregnancy loss (miscarriage, stillbirth, neonatal death, termination) at 14 to 23 weeks gestation during the years 2003 through 2011. During the following 2 years, 4290 subsequent singleton pregnancies among this group met the study criteria; in 92%, conception occurred within 18 months, with a median IPI of 6.3 months. The pregnancies were categorized according to time (14–19 weeks or 20–23 weeks) and type (spontaneous or termi-

nation) of subsequent loss. The primary outcome measure was any loss or perinatal death <24 weeks.

Only for the 2976 pregnancies ending at 14 to 19 weeks did the type of loss, spontaneous or termination, show a similar pattern of association between the IPI and subsequent pregnancy ending <24 weeks:

- Compared with an IPI of >9 to 12 months, an IPI of ≤ 3 months was associated with an increased rate of recurrence (21.9% vs 11.3%; adjusted relative risk [aRR] 2.02; 95% confidence interval [CI], 1.44–2.83).
- After a spontaneous loss at 20 to 23 weeks, only an IPI of >18 to 24 months showed a statistically significant increase in risk compared with an IPI of >9 to 12 months (aRR 2.15; 95% CI, 1.18–3.91).
- There was no evidence of any increased or decreased risk for an IPI of <6 months.

Conclusions and Clinical Implications

After a pregnancy loss at 14 to 19 weeks' gestation, either spontaneous or by termination, an interval of ≥ 3 months before the next conception reduced the risk of recurrent loss. Women who have had a loss at 14 to 19 weeks would best be advised that waiting 3 months before trying to conceive again might result in a better subsequent pregnancy outcome.

Roberts CL, Algert CS, Ford JB, et al. Association between interpregnancy interval and the risk of recurrent loss after a midtrimester loss. *Hum Reprod* 2016;31:2834–2840.

In the next issue of

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Impact of endometriosis on male partners; fibroids and pregnancy after intrauterine insemination; freeze-only vs fresh embryo transfer success rates

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