GYNECOLOGY

The association between prior cesarean delivery and subsequent in vitro fertilization outcomes in women undergoing autologous, frozen-thawed single euploid embryo transfer

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BACKGROUND: The rates of cesarean deliveries continue to increase worldwide. Previous work suggests an association between a previous cesarean delivery and reduced fertility in natural conception and in vitro fertilization treatment cycles. To our knowledge, there is no published research that explored the relationship between a previous cesarean delivery and the clinical outcomes after in vitro fertilization and the subsequent transfer of a single frozen-thawed euploid embryo.

OBJECTIVE: This study aimed to investigate the relationship between the previous mode of delivery and subsequent pregnancy outcomes in patients undergoing a single frozen-thawed euploid embryo transfer after in vitro fertilization.

STUDY DESIGN: A retrospective cohort study was performed at a single academic fertility center from January 2012 to April 2020. All women with a history of a live birth undergoing autologous, frozen-thawed single euploid embryo transfers were identified. Cases included patients with a single previous cesarean delivery; controls included patients with a single previous vaginal delivery. Only the first embryo transfer cycle was included. The primary outcome was the implantation rate. Secondary outcomes included ongoing pregnancy and live birth rates, biochemical pregnancy rate, and clinical miscarriage rate.

RESULTS: A total of 525 patients met the inclusion criteria and were included in the analysis. Patients with a previous cesarean delivery had a higher body mass index (24.5±4.5 vs 23.4±4.1; P=.004) than those in the vaginal delivery cohort; the rest of the demographic data were otherwise similar. In a univariate analysis, the implantation rate was significantly lower in patients with a previous cesarean delivery (111/200 [55.5%] vs 221/325 [68.0%]; P=.004). After adjusting for the relevant covariates, a previous cesarean delivery was associated with a 48% reduction in the odds of implantation (adjusted odds ratio, 0.52; 95% confidence interval, 0.34—0.78; P=.002). In addition, after adjusting for the same covariates, a previous cesarean delivery was significantly associated with a 39% reduction in the odds of an ongoing pregnancy and live birth (adjusted odds ratio, 0.61; 95% confidence interval, 0.41—0.90; P=.01). There were no differences in the biochemical pregnancy rates or clinical miscarriage rates.

CONCLUSION: This study demonstrated a marked reduction in implantation and ongoing pregnancy and live birth associated with a previous cesarean delivery in patients undergoing a single euploid embryo transfer. Our work stresses the importance of reducing the primary cesarean delivery rates at a national level and elucidating the mechanisms behind the substantially lower implantation rates after a cesarean delivery.

Key words: embryonic aneuploidy, hysterotomy, in vitro fertilization, obstetrical outcomes, preimplantation genetic testing, secondary infertility, uterine niche

Introduction

Cesarean delivery (CD) rates have increased over the last 50 years.[1] In the United States, nearly one-third of all infants are delivered via CD.[2] Although CDs are often necessary surgical interventions, they are also associated with an increased risk for short- and long-term sequelae for both the mother and infant, including an increased risk for abnormal placentation in subsequent pregnancies such as placenta previa, placenta accrete sequence, and uterine rupture.[3]

A CD may also be associated with a subsequent reduction in fertility. Studies evaluating fertility following CD and subsequent natural conception have found mixed results. Smith et al[4] found no association between a woman's likelihood of a second viable pregnancy and a previous CD. However, population-based studies contradicted the findings by Smith et al[4] and concluded that women with a previous CD were less likely to achieve a subsequent live birth than women with a previous vaginal delivery.[5,6]

Recent studies have determined that a CD may adversely affect in vitro fertilization (IVF) outcomes.[7–9] However, these studies evaluated fresh embryo transfers or a combination of fresh and frozen embryo transfers, a combination of single and double embryo transfers, or cycles involving the transfer of genetically untested embryos. Using a frozen-thawed euploid single embryo transfer (euploid SET) model reduces multiple potential sources of bias and may better elucidate any association between a previous CD and subsequent IVF outcomes. To our knowledge, there is no published research exploring the association between previous modes of delivery and subsequent outcomes in a frozen-thawed euploid SET cycle.

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AJOG at a Glance

Why was this study conducted?

This study aimed to investigate the association between a previous cesarean delivery and the subsequent pregnancy outcomes in patients undergoing in vitro fertilization with a single, frozen-thawed euploid embryo transfer.

Key findings

Patients with a previous cesarean delivery demonstrated a lower implantation rate and a lower ongoing pregnancy and live birth rate than patients with a previous vaginal delivery.

What does this add to what is known?

By evaluating only single frozen-thawed euploid embryo transfer cycles, our study minimized the influence of other potential embryonic factors on the subsequent clinical outcomes, which allowed this study to demonstrate a clearer relationship between postcesarean delivery uterine changes and subsequent subfertility in patients presenting with secondary infertility.

Therefore, we aimed to evaluate the relationship between the previous mode of delivery and subsequent pregnancy outcomes in patients undergoing transfer of a single frozen-thawed euploid embryo.

Materials and Methods

Study design

This retrospective cohort study included all patients presenting with secondary infertility who underwent controlled ovarian hyperstimulation, IVF with intracytosplasmic sperm injection (ICSI), and subsequent frozen-thawed euploid SET of autologous embryos from 2012 to 2020. Our study was approved by an academic institutional review board (IRB# 18-00452). Cases included patients with a single previous CD and no previous vaginal delivery, and the controls included patients with a single previous vaginal delivery. All embryos underwent preimplantation genetic testing for aneuploidy (PGT-A) before transfer; mosaic embryo transfers were not included. To avoid selection bias, we included only the first frozen-thawed euploid SET per patient. Only embryo transfers in which a synthetic medicated endometrium preparation was performed were included. Details about the inclusion and exclusion criteria and the demographic data are provided in the Supplemental Methods 1 and Supplemental Methods 2 sections in the Supplement.

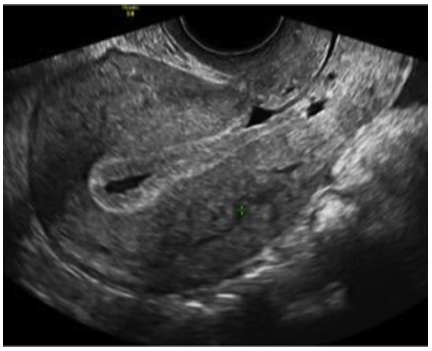
The patient charts were reviewed to confirm the obstetrical history. The available images were also reviewed for each patient who reported a previous CD to determine if a uterine isthmocele was present, which is defined as a wedge-shaped filling defect in the uterine myometrium at the site of a previous CD visualized on a transvaginal ultrasound. Images were reviewed throughout a patient's stimulation cycle and were evaluated individually by 3 study researchers (J.F., C.H.N., and T.A.M.); agreement between the researchers was 99.5%, and Cohen's kappa coefficient was 0.98. Data regarding the presence of blood on the embryo transfer catheter tip, about whether the transfer was marked as "difficult," and the type of embryo transfer catheter utilized were also collected. The difficulty of transfer was evaluated as a combination of blood on the outside of the catheter tip and a transfer marked as "difficult." Transfers were marked as "difficult" if any of the following occurred: multiple attempts to pass the catheter through the cervix, multiple catheters were used, or multiple physicians attempted to perform the transfer. It should be noted that at our center, a transvaginal ultrasound is routinely performed on the day before an embryo thaw and transfer; for any patient in which fluid was visualized in the uterine cavity on the day before transfer, the transfer cycle was cancelled.

Between January 2012 and September 2016, PGT-A was performed using either a quantitative-polymerase chain reaction, array comprehensive genomic hybridization, or next generation sequencing (NGS). Starting in September 2016, all PGT-A analyses were performed using NGS exclusively. Owing to this change, a subanalysis comparing the frozen-thawed euploid SETs before and after September 2016 was performed and included as a covariate in our statistical models in an attempt to control for these changes. All ovarian stimulation protocols, laboratory procedures, and endometrial preparation protocols for the embryo transfers are provided in the Supplemental Methods 3 section in the Supplement.

Outcomes

The primary outcome was the implantation rate, defined as the number of gestational sacs visualized by transvaginal ultrasound divided by the number of single embryo transfers performed. The secondary outcomes included the biochemical pregnancy rate, ongoing pregnancy and live birth rate, and clinical miscarriage rate. The ongoing pregnancy and live birth rates were defined as the number of ongoing pregnancies at the time of a 20 week follow-up call or the live births recorded divided by the total number of SETs performed. The clinical miscarriage rate was calculated as the total number of pregnancies that failed to progress after visualization of an intrauterine gestational sac divided by the total number of clinically recognized intrauterine pregnancies. Biochemical pregnancy was defined as a positive test based on the human chorionic gonadotropin (hCG) levels (defined as an hCG level of >2.5 mIU/mL) approximately 9 days after embryo transfer followed by abnormally rising or subsequently declining hCG levels along with the absence of a visualized gestational sac on a transvaginal ultrasound. The biochemical pregnancy rate was defined as the total number of biochemical pregnancies divided by the total number of positive pregnancy

FIGURE 1
Transvaginal ultrasound image of an isthmocele from a patient in the study cohort



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tests (hCG level of >2.5 mIU/mL) following an embryo transfer.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC). For our power analysis, to detect an effect size of 15% in the implantation rate, 170 cases in each cohort were required, with an alpha of 0.05 and a beta of 0.2. Measures of central tendency and dispersion were utilized to evaluate the data; the normality for all variables was assessed. Analysis of the continuous data was performed using either a Student *t* test for normally distributed data or a Mann-Whitney *U* test for skewed data. The categorical data were analyzed using chi-square tests; the results were expressed as the mean±standard deviation (SD) and as numbers and percentages. In addition, multivariable logistc regression models were used to calculate the odds ratios (ORs) and to adjust for confounding factors; all the variables that showed significance or were thought to be clinically relevant were included and adjusted for as covariates in the models. The adjusted ORs (aORs) with 95% confidence intervals (CIs) were calculated. All the *P* values were 2-sided with a clinical significance level set to $P<.05$.

Results

A total of 551 frozen-thawed euploid SETs were performed for patients with a reported history of 1 previous live birth from 2012 to 2020. It should be noted that during this time period, 30 additional frozen-thawed euploid SETs were initiated but ultimately cancelled before the transfer because of fluid noted in the uterine cavity: 11 in patients with a history of CD and 19 in patients with a previous vaginal delivery. Twenty-six cycles were excluded owing to an inaccurate obstetrical history, leaving 525 cycles for analysis. Of these, 325 embryo transfer cycles were for patients with 1 previous vaginal delivery and 200 embryo transfer cycles were for patients with 1 previous CD. Of the 200 cycles in patients with a previous CD, 188 had imaging available to determine the presence or absence of an isthmocele. Within this cohort, 43.1% (81/188) of the patients had a detectable isthmocele (Figure 1).

The demographic, cycle, and embryo characteristics are presented in Table 1. By design, the parity was the same between the groups. Patients with a previous CD had a higher body mass index (BMI) (24.5±4.5 vs 23.4±4.1; $P=.004$); the rest of the demographic data were similar between the groups. The percentage of good, moderate, and fair embryos was comparable between the cohorts. In addition, when comparing the outcomes before and after September 2016, there was no difference in either the implantation rate (85/149 [57.1%] vs 247/376 [65.7%]; $P=.06$) or ongoing pregnancy and live birth rates (79/149 [53.0%] vs 211/376 [56.1%]; $P=.52$), respectively. In the univariate analysis, the implantation rate was significantly lower in patients with a history of CD (111/200 [55.5%] vs 221/325 [68.0%]; $P=.004$). The ongoing pregnancy and live birth rates were also significantly lower in patients with a history of CD (98/200 [49.0%] vs 192/235 [59.1%]; $P=.02$).

Multivariable logistic regression models, adjusted for the following covariates, were then performed: patient age at the time of retrieval and transfer, BMI, endometrial thickness at the time of transfer, day of embryo biopsy, embryo quality, difficulty of transfer, type of transfer catheter used, and whether the transfer was performed before or after September 2016 (Table 2). In this multivariable model, a previous CD remained significantly associated with poorer implantation rates; having a history of CD was associated with a 48% reduction in the odds of implantation (aOR, 0.52; 95% CI, 0.34−0.78; $P=.002$). In addition, after adjusting for the same covariates, a previous CD was associated with a 39% reduction in the odds of an ongoing pregnancy and live birth (aOR, 0.61; 95% CI, 0.41−0.90; $P=.01$). There were no differences in the biochemical pregnancy rates or clinical miscarriage rates in either the univariate or multivariable analyses.

In a subanalysis in which patients with an isthmocele were compared with patients with a history of vaginal delivery, our findings were even more pronounced. The presence of an isthmocele was associated with a 52% reduction in the odds of implantation (aOR, 0.48; 95% CI, 0.27−0.85; $P=.01$). In addition, the presence of an isthmocele was associated with a 49% reduction in the odds of an ongoing pregnancy and live birth (aOR, 0.51; 95% CI, 0.30−0.89; $P=.02$). Figure 2 illustrates the implantation and ongoing pregnancy and live birth rates in patients with a previous vaginal delivery, a previous CD without an isthmocele, and a previous CD with an isthmocele.

Comment

Principal findings

This study evaluated the association between mode of previous delivery and the subsequent IVF outcomes within a cohort of patients undergoing a frozen-thawed euploid SET. Our results demonstrated that patients with a previous CD experienced decreased implantation rates and a reduction in the ongoing pregnancy and live birth rates after a frozen-thawed euploid SET. These findings are more pronounced when comparing patients with an isthmocele with those with a history of vaginal delivery, suggesting that the presence of an isthmocele is particularly detrimental to subsequent fertility, even among single

TABLE 1
Demographic, cycle, and embryo characteristics of women with previous vaginal or cesarean delivery

Characteristics	Vaginal delivery (n=325)	CD (n=200)	*P* value
Age at oocyte retrieval (y), mean (SD)	36.9 (3.9)	37.4 (3.6)	.11
Age at embryo transfer (y), mean (SD)	37.1 (3.9)	37.7 (3.6)	.06
BMI (kg/m^2), mean (SD)	23.4 (4.1)	24.5 (4.5)	.004
AMH (ng/mL), mean (SD)	2.9 (3.6)	3.3 (4.0)	.32
Gravidity, mean (SD)	1.9 (1.2)	1.9 (1.3)	.50
Endometrial thickness at time of transfer (mm), mean (SD)	9.7 (2.1)	9.5 (1.9)	.13
Embryo quality, n (%)			
Good	195 (60.0)	124 (62.0)	.89
Moderate	33 (10.2)	20 (10.0)	
Fair	97 (29.9)	56 (28.0)	
Implantation rate, n (%)	221 (68.0)	111 (55.5)	.004
Ongoing pregnancy and live birth rate, n (%)	192 (59.1)	98 (49.0)	.02
Biochemical pregnancy rate, n/n (%)	45/266 (16.9)	28/139 (20.1)	.42
Clinical miscarriage rate, n/n (%)	29/221 (13.1)	13/111 (11.7)	.72

AMH, anti-müllerian hormone; *BMI*, body mass index; *CD*, cesarean delivery; *SD*, standard deviation.
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euploid embryo transfer cycles. The exclusive evaluation of transfers using genetically screened embryos is critically important. In the majority of cases of failed implantation and pregnancy loss, embryonic aneuploidy has been identified as the cause.[10,11] By studying only euploid embryo transfers, our results more clearly demonstrate the role of the uterus and its potential injury during CD on subsequent subfertility.

Results

Several studies have been performed and support our study's findings. In a meta-analysis of approximately 600,000 deliveries in the general population, Gurol-Urganci et al[12] found that patients with a history of CD had an approximately 9% reduction in the odds of a subsequent pregnancy and an 11% reduction in the odds of a live birth. Of note, several of the studies included in the meta-analysis failed to control for confounding variables (eg, maternal age, infertility history, indication for CD). More recently, Kjerulff et al[13] performed a prospective cohort study of women who were enrolled before their first childbirth and found that undergoing a previous CD was significantly associated with an approximately 8% reduction in the clinical pregnancy rate and an approximately 7% reduction in the live birth rate.

Among an infertile population, Patounakis et al[14] found that patients with a previous CD undergoing IVF with ICSI and a subsequently fresh day 3 or day 5 embryo transfer had a lower live birth rate than those with a previous vaginal delivery (32% vs 39%), although this result failed to reach statistical significance. However, the authors conceded that the enrollment was cut short and that the study was therefore underpowered to detect statistical differences between the groups. Similar to our results, Wang et al[7] found that the implantation rate was significantly lower (24.01% vs 34.67%; $P<.05$) in women with a history of CD than in those with a previous vaginal delivery; specifically, patients with an isthmocele demonstrated a lower clinical pregnancy rate than either those with a CD and fluid in the cavity or those with a history of vaginal delivery (12.5% vs 40% vs 54.82%). In a larger study by Vissers et al,[9] patients with a previous CD had an approximate 8% to 9% lower implantation and ongoing pregnancy and live birth rate than patients with a previous vaginal delivery ($P<.05$ for both). Again, in a subgroup analysis of women with a documented isthmocele, the authors found a notable difference in the live birth rate between the groups. Recently, in a study published by Wang et al,[15] women with a previous CD had a lower live birth rate (30.1% vs 38.1%) and a higher miscarriage rate (25.9% vs 17.5%) than patients with a previous vaginal delivery.

There are several differences that distinguish the aforementioned studies from our study. First, studies evaluating natural cycles were presumably studying pregnancies that resulted from

TABLE 2
Multivariable logistic regression models according to the obstetrical history

	History of vaginal delivery	History of cesarean delivery	
Outcomes	Ref	Adjusted OR (95% CI)	*P* value
Implantation rate	Ref	0.52 (0.34–0.78)	.002
Ongoing pregnancy and live birth rate	Ref	0.61 (0.41–0.90)	.01
Biochemical pregnancy rate	Ref	1.14 (0.64–2.05)	.65
Clinical miscarriage rate	Ref	0.92 (0.42–2.03)	.84

CI, confidence interval; *OR*, odds ratio; *Ref*, reference.
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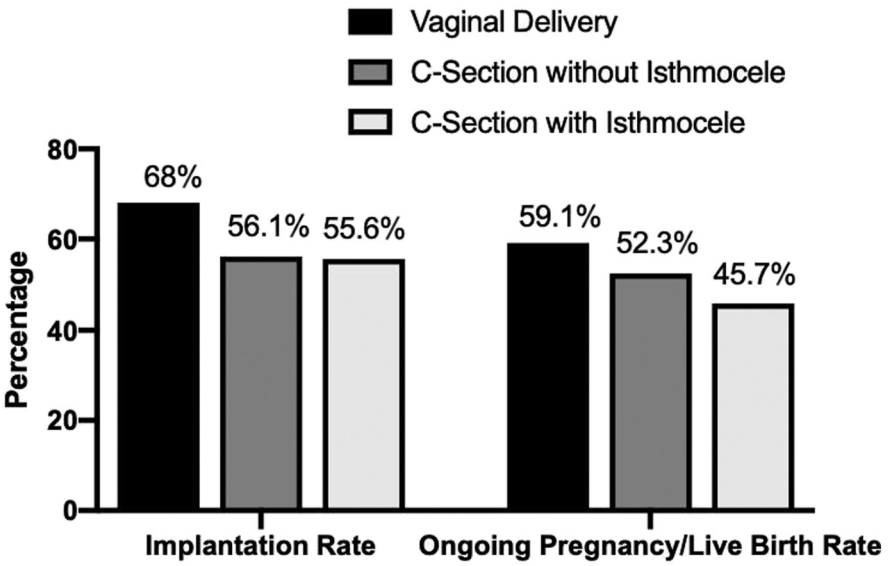
spontaneous conception. These studies do not account for pregnancies among the infertile population or for embryo-related causes of pregnancy failure such as embryonic aneuploidy. In the IVF population, patients in all previous studies underwent either fresh embryo transfers or a mix of fresh and frozen transfers, often including a mix of cleavage stage and blastocyst stage embryo transfers.[7–9] Previous work has already demonstrated a significant improvement in the pregnancy rates in blastocyst vs cleavage stage embryo transfers, even among fresh transfer cycles.[16,17] In addition, studies evaluating differences between fresh transfers vs frozen transfers have shown a significant improvement in the implantation and live birth rates in frozen-thawed transfers.[18–20] Including a mix of cleavage stage and blastocyst transfers in addition to both fresh and frozen transfer cycles may confound previous work and introduce potential biases.[7–9] Previous work on this subject has also included a mix of both single and double embryo transfers. Given the known impact of performing a double vs single embryo transfer on the clinical outcomes,[21,22] utilization of a uniform, single, frozen-thawed blastocyst stage embryo transfer protocol is preferred clinically and further reduces biases in research. Finally, our study included only genetically tested euploid embryos as determined by PGT-A. The advent and utilization of PGT-A have developed as a means of identifying and excluding chromosomally abnormal embryos with the goal of improving the pregnancy rates and reducing the miscarriage rates. Exclusion of untested embryos removes another important source of potential bias and differentiates our study from all other previous work on this subject.

Clinical implications

Although the underlying cause for the differences in pregnancy rates after a CD remains unknown, several theories have been postulated. These include a disturbance of the placental bed by postcesarean delivery scarring,[23] intra-abdominal and intrauterine adhesion formation,[24] and alterations of the endometrial immunobiological milieu.[25] In addition, the development of a CD scar may obstruct the passage of the transfer catheter, which may thereby impact successful implantation.[9,26] In our cohort, neither the difficulty of transfer nor the type of transfer catheter used was associated with our primary or secondary outcomes.

Finally, the presence of a postcesarean delivery isthmocele has been suggested to confer a more pronounced risk with regard to subsequent fertility. In a randomized prospective study evaluating CD suture techniques and the subsequent risk for incomplete uterine healing, the authors found that full thickness closure and suture techniques were associated with reduced odds of incomplete healing.[27] In addition, Hayakawa et al[28] compared uterine closure techniques and found that a double-layer closure was associated with reduced odds of subsequent uterine wedge defects. Previous research has suggested that the existence of an isthmocele may lead to reduced implantation and increased miscarriage rates if implantation occurs in or close to the isthmocele.[29,30] Proposed mechanisms by which a uterine isthmocele may impact subsequent fertility include niche-related endometrial fluid accumulation, increased inflammation at or near the site of the niche, distortion of uterine muscle contractility secondary to niche-related fibrosis, and accumulation of mucus or blood at or near the niche.[25] Similar to previous studies, our results support the notion that the presence of a uterine niche is associated with a more pronounced difference in pregnancy outcomes than patients with a previous vaginal delivery.

FIGURE 2
A comparison of outcomes among patients with a previous vaginal delivery, CD without isthmocele, and CD with isthmocele



CD, cesarean delivery.

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Research implications

Large, prospective studies following all possible sequelae of a CD, including scar formation, development of an isthmocele, immunologic or inflammatory changes, or accumulation of blood, fluid, or mucus in the uterine cavity in response to hormonal stimulation, may better delineate the pathophysiologic effects of a CD on subsequent fertility.

Strengths and limitations

Our study has several strengths. The cohort of patients all underwent single, frozen-thawed euploid blastocyst

embryo transfer cycles. In addition, only the first single frozen-thawed euploid transfer was included, and patients were only included in the study if they reported a single previous delivery, making our results more accurate. The study was performed at a single, high-volume academic center with a team of embryologists all uniformly trained, thereby reducing the inherent variability that may arise from multicenter studies. Finally, each of the single embryo transfers was performed with a PGT-A—tested euploid embryo. By including only euploid embryos, the study controls for one of the most common causes of early pregnancy failure, embryonic aneuploidy.

However, our study is not without limitations. The most notable limitation is its retrospective design. To overcome this, an adjusted, multivariable logistic regression analysis was performed to minimize selection bias. In addition, because of the fact that many pregnancies were ongoing at the time of data collection, ongoing pregnancy and live birth rates were combined as an outcome. Another potential limitation is the change in the PGT-A testing platform utilized in the study period that occurred over time. In an attempt to control for this, the date of the embryo transfer (before or after September 2016) was included as a covariate in the analysis. Data regarding the interval between the date of the previous delivery and date of presentation to the fertility center, in addition to the clinically relevant data related to the first pregnancy and the CD itself (ie, indication for CD), were not available. In addition, because our study focused on patients undergoing IVF for secondary infertility, our findings may have limited generalizability. Finally, the presence of an isthmocele was observed retrospectively by evaluating patient images. Therefore, it is possible that there were patients with an isthmocele that we were unable to visualize based on their saved images and this may have introduced bias in the subanalysis conducted as part of the study. As such, the findings of the subanalysis should be interpreted with caution.

Conclusions

This study demonstrated a significant difference in the implantation rate and ongoing pregnancy and live birth rates associated with the mode of delivery in patients undergoing single, frozen-thawed euploid embryo transfer. Patients who deliver via CD may experience postcesarean delivery scarring and subsequent isthmocele formation, which may alter the uterine milieu and lead to suboptimal implantation. Special care must be taken at the time of CD to optimally re-approximate the original tissue planes and minimize scar formation. In patients presenting with subsequent secondary infertility after a history of CD, infertility specialists should ensure that optimal endometrium preparation has occurred to achieve the best possible outcome. Patients looking to build families with multiple children should be counseled that a previous CD may be associated with significantly lower success rates following euploid single embryo transfer. Our results further stress the importance of a national-level policy to reduce CD rates.

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Supplemental Methods 1

Inclusion and exclusion criteria

We only included embryo transfers in which a synthetic medicated endometrial preparation was performed. Exclusion criteria included patients with a history of either nulliparity or more than 1 previous live birth and donor or recipient cycles in addition to patients with a hydrosalpinx or uterine abnormalities such as fibroids or Asherman's syndrome. Embryo transfers using natural cycles as preparation for embryo transfer were also excluded.

Supplemental Methods 2

Demographic data and embryo grading

Demographic data were obtained, including female patient age (at both the time of retrieval and time of transfer), body mass index, obstetrical history, endometrial thickness at the time of transfer, embryo grade (Modified Gardner[1]), and day of embryo biopsy for preimplantation genetic testing. Embryos were classified as good, moderate, or fair quality as described previously based on the morphologic grading of the following 3 embryonic components: expansion, inner cell mass (ICM), and trophectoderm (TE) at the time of vitrification.[2] Good quality embryos had an expansion grade of 4 or greater with AA, AB, or BA; moderate quality embryos had an expansion grade of 4 or greater and BB; and fair quality embryos had an expansion grade of 3 or less with AC, CA, BC, CB, or CC (ICM and TE respectively).

Supplemental Methods 3

Stimulation protocol and laboratory procedures

Controlled ovarian hyperstimulation protocols were performed as previously described.[3] In our cohort, the majority (86%) of patients utilized an antagonist protocol in which suppression of luteinizing hormone was performed using a gonadotropin-releasing hormone (GnRH) antagonist beginning on approximately day 8 of their cycle; the remainder of patients utilized either a short or long GnRH agonist protocol. When 2 or more follicles reached at least 18 mm, patients were administered either recombinant human chorionic gonadotropin (hCG) alone or a combination, with 1000 IU hCG and 40 IU of a GnRH agonist to trigger final oocyte maturation; transvaginal oocyte retrieval was then performed 36 hours later. All oocytes were evaluated for maturity, and those oocytes that reached metaphase II (MII) underwent ICSI approximately 5 hours after retrieval. Embryos were ultimately cultured to the blastocyst stage at which point they underwent assisted hatching, and a trophectoderm biopsy was performed on day 5, 6, or 7 of development when the embryo reached a morphologic grade of $\geq$4CC (Modified Gardner score) as described previously.[1]

For synthetic endometrial preparation cycles, all patients were administered a combination of estradiol and progesterone before their frozen-thawed embryo transfer. In addition, all patients received imaging via saline sonohysterography and 3-dimensional transvaginal ultrasound before the cycle start. On day 3 of a subsequent menstrual cycle, patients were started on 2 mg micronized oral estradiol (Estrace, Teva Pharmaceutical Industries Ltd, Fairfield, NJ) twice daily for 4 days and continued on estradiol 2 mg 3 times daily thereafter. After approximately 9 to 11 days of estradiol initiation, a transvaginal ultrasound was performed to evaluate the endometrial thickness and pattern. Progesterone was administered either via intramuscular progesterone (Watson Pharma, Parsippany-Troy Hills, NJ) or a combination of oral (Prometrium; Solvay Pharmaceuticals, Princeton, NJ) and vaginal (Endometrin; Ferring Pharmaceuticals, Parsippany, NJ) progesterone according to patient preference and began once the endometrial lining reached 7 mm or greater. Embryo transfer was performed on the sixth day of progesterone administration.

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