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DOES THE ULTRASOUND APPEARANCE OF THE ENDOMETRIUM DURING TREATMENT WITH ASSISTED REPRODUCTIVE TECHNOLOGIES INFLUENCE PREGNANCY OUTCOMES?

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Abstract

We evaluated endometrial pattern (defined as the relative echogenicity of the endometrium on a longitudinal uterine ultrasonic section) as a surrogate for endometrial receptivity in an attempt to evaluate the association between endometrial pattern and pregnancy outcome in women who underwent ART treatment. The primary outcome was live birth and secondary outcomes were clinical intrauterine pregnancy and miscarriage. Potential associations were evaluated using cluster-weighted generalized estimating equations to account for within-couple correlation among repeated ART cycles while adjusting for potentially confounding variables. There were 1034 ART cycles with embryo transfer (778 fresh, 256 frozen) among 695 women (median age: 31.0 (6.0) years). The average number of embryos transferred per cycle was 2.1 embryos. The clinical intrauterine pregnancy rate per transfer was 56.0% for fresh and 54.3% for frozen cycles. The overall live birth rate per embryo transfer was 48.4%. Live birth rates were unchanged when the endometrium was semi-trilinear (RR:0.91 CI:0.74,1.12) or unilinear (RR:1.15 CI:0.89,1.49) in comparison to trilinear endometrium after controlling for potentially confounding variables. Results were similar when analysed separately for fresh and frozen cycles and when evaluating associations with clinical intrauterine pregnancy and miscarriage rates. It appears that endometrial pattern does not significantly affect live birth in ART and our data do not support cancelling an ART cycle if the endometrium is less than trilinear.

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

This study was approved by the University of Oklahoma Health Sciences Centre Institutional Review Board and was performed in accordance with the ethical standards as established in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

INTRODUCTION

Despite advancements made since the introduction of assisted reproductive technology (ART), fewer than 40% of ART treatment cycles result in a live birth (Craciunas et al., 2019; De Geyter et al., 2018; Kushnir et al., 2017; Sunderam et al., 2018). Endometrial receptivity remains a crucial rate-limiting step affecting the success of ART treatment (Craciunas et al., 2019; Nastri et al., 2015). However, direct measures of endometrial receptivity are not feasible during embryo transfer cycles due to the negative impact of invasive endometrial biopsies on implantation (Karimzade et al., 2010). High-resolution transvaginal ultrasonography offers a non-invasive alternative for assessing endometrial pattern as a marker of endometrial receptivity (Fanchin et al., 2000; Hershko-Klement & Tepper, 2016; Mahajan, 2015; Wu et al., 2014). During an ART treatment cycle, the most prevalent endometrial pattern observed before embryo transfer is a trilinear endometrial pattern (Sadro, 2016), which exhibits a triple-striped pattern consisting of a hypoechoic endometrium with a central echogenic line and well-defined hyperechoic outer walls. Other less common endometrial patterns are characterized as unilinear or semi-trilinear, but it remains unclear whether pregnancy rates differ by sonographic characteristics.

Such a potential relationship has been examined, with mixed results (Ahmadi et al., 2017; Barker et al., 2009; Bassil, 2001; Chen et al., 2010; Fanchin et al., 2000; Gingold et al., 2015; Yang et al., 2018; Yuan et al., 2016; Zhang et al., 2018; Zhao et al., 2012). While some studies have failed to observe an association between endometrial pattern and pregnancy outcome (Barker et al., 2009; Bassil, 2001; Chen et al., 2010; Yuan et al., 2016), others have reported poorer outcomes among women with non-trilinear endometrial patterns (Ahmadi et al., 2017; Fanchin et al., 2000; Gingold et al., 2015; Zhao et al., 2012). These mixed results may be due to the small sample size of most studies (Ahmadi et al., 2017; Barker et al., 2009; Bassil, 2001; Fanchin et al., 2000; Gingold et al., 2015), with limited precision and reduced statistical power to detect associations. Furthermore, larger studies (Chen et al., 2010; Yang et al., 2018; Yuan et al., 2016; Zhang et al., 2018; Zhao et al., 2012) failed to account for the correlation between multiple ART treatment cycles within the same couple; likely underestimating the standard errors. Few studies have examined associations with live birth outcomes (Yang et al., 2018; Zhang et al., 2018) despite the obvious importance of the endometrium in the maintenance of pregnancy (Granot et al., 2012) and the ultimate ART treatment goal of delivering a baby.

With the goal of addressing the limitation in previous studies, we aimed to evaluate endometrial pattern as a marker of endometrial receptivity by examining associations with pregnancy outcomes and a focus on live birth.

MATERIALS AND METHODS

Study Design and Population

This was a retrospective cohort study among patients who underwent ART treatment between Jan 1, 2008 and Dec 31, 2014, at a university-based infertility clinic. Clinical information including treatment outcome for each ART cycle was obtained from the clinic ART database. Out of the 1182 cycles in the clinic database, 106 cycles were excluded due

to missing outcome data and 42 cycles due to cancelled cycles that did not result in an embryo transfer. Most cycles that were cancelled or did not result in an embryo transfer were due to complications from ovarian response to the stimulation protocol or patient withdrawal from treatment. Three patients had their cycle cancelled due to endometrial receptivity concerns / inadequate endometrial response. Hence, complete records on 1034 ART cycles (778 fresh & 256 frozen cycles) for 695 women were analysed.

Stimulation Protocol and ART Procedures

At the start of treatment, all patients had a baseline ultrasound to evaluate their uterus. Patients who underwent fresh embryo transfer received recombinant follicle stimulating hormone (FSH) in combination with human menopausal gonadotropin (hMG) for ovarian stimulation. Different stimulation protocols were utilized for patients undergoing a fresh embryo transfer during the study period, including gonadotropin releasing hormone (GnRH) antagonist, micro-dose flare, and long GnRH agonist protocols. Ovarian follicles and endometrium were serially monitored via transvaginal ultrasound and adjustments were made to gonadotropin (FSH and hMG) dosage based on the ovarian response. All fresh embryo recipients underwent endometrial assessment shortly before triggering the final oocyte maturation with human chorionic gonadotropin (hCG), which was performed when two or more follicles 18 mm were observed. Follicular aspiration was performed using transvaginal ultrasound-guided puncture of follicles 35 hours following trigger. Fertilization was accomplished using conventional in-vitro fertilization (IVF) method, intracytoplasmic sperm injection (ICSI), or a combination of both. The luteal phase was supported with daily administration of intramuscular progesterone. The decision whether to do a day 3 or day 5 transfer was made on day 2 of embryo development. This decision was based on the total number of embryos, their quality, and the anticipated number to transfer. Subsequent transvaginal ultrasound examinations were performed five weeks after embryo transfer at approximately seven weeks gestation.

Patients undergoing embryo transfer of cryopreserved blastocysts underwent endometrial preparation with oestradiol patches in increasing doses. To assess the endometrial thickness and pattern, an ultrasound was performed at approximately two-and-a-half weeks after initiation of oestradiol patches. In addition to oestradiol patches, intramuscular progesterone was administered and an embryo transfer was performed six days later.

Endometrial Assessment

Sonographic evaluation of the endometrial pattern and thickness were performed in the longitudinal plane of the uterus, using a 4–9 MHz variable frequency transvaginal transducer, after patients had emptied their bladder. All fresh embryo recipients underwent endometrial assessment the same day that the hCG trigger shot was administered. Patients undergoing frozen embryo transfer underwent an endometrial assessment one to two days prior to initiating intramuscular progesterone.

The endometrial pattern was classified as a trilinear pattern (a triple-line pattern consisting of a hypoechoic endometrium with a central echogenic line and well-defined hyperechoic outer walls), a semi-trilinear pattern (an intermediate pattern consisting of an isoechoic

endometrium that has a central echogenic line with poorly defined outer walls), or a unilinear pattern (a hyperechoic endometrium with a homogenous pattern). Endometrial thickness was measured in the median longitudinal plane of the uterus as the maximum anteroposterior distance between the interfaces at the endometrial-myometrial junction. All ultrasounds were performed by one of three providers (two board certified physicians and one certified physician assistant).

Outcome

The primary outcome was live birth, defined as the delivery of a newborn > 20 weeks in comparison to the non-live birth group, which included patients that were not pregnant, had a miscarriage, ectopic, or biochemical pregnancy. The secondary outcomes were clinical intrauterine pregnancy, defined as the presence of an intrauterine gestation with foetal cardiac activity, and miscarriage defined as spontaneous loss of a foetus before the 20th week of gestation.

Covariates

Variables considered as potential confounders included endometrial thickness at final ultrasound prior to embryo transfer (<8 mm, 8–14 mm, >14 mm), number of embryos transferred (1–2 or 3), ovarian reserve (normal or low based on criteria of day three FSH >10 IU/ml, oestradiol >80 pg/ml, or AMH < 1.0 ng/ml), stimulation protocol (long GnRH agonist; microdose flare; GnRH antagonist or endometrial preparation for frozen transfers using exogenous oestrogen/progesterone), day of transfer (cleavage stage or blastocyst stage), body mass index (BMI) [underweight (< 18.5kg/m²), normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²) and obese (> 30kg/m²)], age at oocyte retrieval (<35 years, 35–37 years, 38–40 years or ≥ 41 years), parity (nulliparous or parous), peak oestradiol (<1704pg/ml, 1704–3162pg/ml, ≥ 3162pg/ml), assisted hatching (yes/no), tobacco use within last three months (yes/no), fresh or frozen cycle, number of fertilized embryos (continuous), and the quality of the embryo(s) transferred (graded as good, fair or poor).

Statistical Analyses

Unadjusted comparison between the endometrial patterns for both cycle-specific and patient-specific covariates were tested using chi-square for categorical covariates, and Kruskal-Wallis test for continuous covariates. The crude and adjusted associations between endometrial pattern and pregnancy outcomes were evaluated using a modified Poisson regression model. The crude and adjusted associations were estimated using a generalized estimating equation (GEE) approach weighted for cluster size, and robust standard errors were calculated to account for within-couple correlation among observations from multiple ART cycles. The risk ratios (RR) and 95% confidence intervals (CI) were adjusted for potential confounders of pregnancy outcome. Covariates were selected for model adjustment based on *a priori* evidence of associations with clinical pregnancy. Due to substantial missing data for parity, this covariate was not retained in the final adjusted models upon confirming a lack of association with the characteristic of interest (endometrial pattern) and the outcome (live birth) in these data (i.e., both risk ratios near 1.0). The proportion of live births with complete information on endometrial pattern and the proportion of live births missing information about this variable were compared to determine if the endometrial

pattern was differentially missing between these two groups. Sensitivity analysis was also conducted by assigning all cycles with missing values to one of the endometrial pattern categories to determine if omitting cycles with missing endometrial patterns might have biased the results. The significance level was assessed at $p < 0.05$. All analyses were conducted using SAS v9.4 (Cary, NC).

RESULTS

Patient and Cycle Characteristics

During the study period, 695 women underwent 1034 ART cycles (778 fresh, 256 frozen) with embryo transfers. Patient age at oocyte retrieval ranged from 20 to 46 years (median 31.0 (interquartile range (IQR) 6.0), with similar age distributions observed for frozen embryo transfers (median 31.0 years (IQR 7.0)) and fresh cycles (median 32.0 years (IQR 6.0)). Median BMI was 24.7 (IQR 7.8) kg/m^2 .

There were 778 fresh IVF cycles and 256 frozen cycles. The overall clinical intrauterine pregnancy rate was 55.6% per cycle (56.0% in fresh cycles and 54.3% in frozen cycles), the live birth rate was 48.4% (50.5% in fresh cycles and 41.8% in frozen cycles), and the multiple birth rate per transfer was 16.4%. Among all ART treatment cycles, the endometrium was trilinear in 80.0%, semi-trilinear in 16.2% and unilinear in 3.8% of cycles.

Endometrial pattern was not reported for 64 cycles. However, the live birth rate did not differ when comparing those with missing endometrial pattern to those without missing data (54.7% vs 45.3%, respectively; $p=0.30$).

Comparisons of Cycle Characteristics by Endometrial Pattern

Cycle characteristics are compared by endometrial pattern in Table 1. Cycles with unilinear endometrial patterns had higher peak serum oestradiol levels ($p<0.0001$). Despite this, the endometrial thickness across the three endometrial patterns was not significantly different ($p=0.79$). The number of retrieved oocytes ($p=0.43$), number of fertilized embryos ($p=0.12$) and the number ($p=0.74$) and quality ($p=0.84$) of embryos transferred into the uterus also did not differ between the three endometrial patterns. Embryo transfers in trilinear endometrial cycles were more likely to have occurred at the cleavage stage ($p=0.002$).

Bivariable and Multivariable Analysis

In unadjusted comparisons, the proportion of live births among cycles with semi-trilinear and unilinear endometrial patterns was not significantly different compared to the trilinear endometrial pattern (Table 2). Results were unchanged after adjusting for endometrial thickness, number of embryos transferred, ovarian reserve, stimulation protocol, transfer day, BMI, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use, embryo quality and type of ART cycle (Table 2). Similar findings were observed when fresh and frozen cycles were analysed separately (Table 2). Consistent with findings for live births, there were no associations with clinical intrauterine pregnancy (Table 3) or miscarriage (Table 4) in unadjusted or adjusted analyses. The small number of miscarriage events, however, precluded separate analysis for fresh and frozen cycles.

Similarly, no associations were observed in unadjusted or adjusted analyses after collapsing the unilinear and semi-trilinear patterns into a single group for comparison with the trilinear pattern (data not shown).

Sensitivity Analysis

We conducted a sensitivity analysis to determine if omitting cycles with missing endometrial patterns may have biased results. Analyses were repeated after assigning all cycles with missing values to one of the endometrial pattern categories. Conclusions were unchanged whether all missing values were assigned to the unilinear, semitrilinear or trilinear categories (data not shown).

DISCUSSION

This study asked whether endometrial pattern as a surrogate marker of endometrial receptivity was associated with pregnancy outcomes. In order to do this, transvaginal ultrasound examination of the endometrium was used to determine endometrial pattern because this non-invasive technique has been shown to be reliable in evaluating the changes undergone by the endometrium (Fanchin et al., 2000; Heger et al., 2012; Hershko-Klement & Tepper, 2016; Kim et al., 2000; Strowitzki et al., 2006; Wu et al., 2014). In addition, ultrasound evaluation does not have the risks associated with other invasive approaches such as pelvic infection and uterine perforation.

In our study, endometrial pattern was not associated with pregnancy outcomes in ART. The results were consistent with the findings of several previous studies (Barker et al., 2009; Bassil, 2001; Chen et al., 2010; Shibahara et al., 2002; Singh et al., 2011; Zhang et al., 2018). Our findings, however, did differ from the conclusion of Ahmadi et al., who reported higher pregnancy rates among women with trilinear endometrial pattern, compared to those with semitrilinear or unilinear endometrial patterns (Ahmadi et al., 2017). Similarly, Fanchin and colleagues observed significantly lower pregnancy rates among cycles with unilinear endometrial pattern (Fanchin et al., 2000). In this research, the study was conducted on young women, below age 40, with good quality embryos, and a disproportionately larger number of their study population had a trilinear endometrial pattern. In contrast, our study population was not restricted by these characteristics, but was adjusted statistically for the heterogeneity in these variables. Study population selection may explain the discrepancy between their results and our findings. Zhao et al. also reported significantly lower pregnancy rates among women with unilinear endometrial pattern (Zhao et al., 2012), which was similar to the findings of Fanchin et al., but these studies failed to account for within-couple associations among observations from multiple IVF cycles, which could result in poor estimates of standard errors and lead to erroneous conclusions (Littell et al., 2000). Contradictory results may also be due to methodological inconsistencies. Our study incorporated appropriate methods to account for the lack of independence across repeated ART cycles and within-cluster correlation. Fanchin et al. used a computer-assisted module to assess endometrial pattern objectively, which likely minimized operator-dependent variability when classifying endometrial pattern (Fanchin

et al., 2000). In our study, the endometrial pattern was evaluated by different personnel, potentially causing variability in endometrial characterization.

A recent meta-analysis of several studies with a total of 15,653 fresh IVF/ICSI treatment cycles reported similar clinical pregnancy rates between women with trilinear echo pattern and those without trilinear echo pattern on the day of hCG injection (Craciunas et al., 2019), which is consistent with our findings. This meta-analysis also reported similar clinical pregnancy rates between the different endometrial patterns for women undergoing a frozen thawed transfer (Craciunas et al., 2019), which is consistent with our findings. While the ultimate aim of ART treatment in both fresh and frozen embryo transfer cycles is to deliver a baby, the association between endometrial patterns and live birth has been evaluated in only a few studies of frozen thawed transfers (Yang et al., 2018; Zhang et al., 2018), and no studies in fresh cycles. Assessment of live birth outcomes arguably provides the best information on the embryo's ability to tolerate the environment to which it has been exposed throughout the entire period of gestation.

Studies that evaluated live birth rates in cycles with frozen thawed transfer reported similar rates irrespective of the endometrial echotexture on the day of hCG injection (Yang et al., 2018; Zhang et al., 2018), which is consistent with our findings. However, these researchers failed to account for the lack of independence across repeated cycles and the possibility of informative clustering which occurs when the outcome of treatment influences the number of treatment cycles. Since there might have been a slight advantage conferred by transferring the best embryo during the first transfer of a fresh cycle, we adjusted for the type of cycle and other factors, and still observed no significant difference in pregnancy outcomes including live birth rates, clinical intrauterine pregnancy or miscarriage rates across the different endometrial patterns.

Chen and colleagues also found no association between endometrial pattern and clinical pregnancy (Chen et al., 2010), which is consistent with our findings. However, unlike Chen's study we did not find a significant association between trilinear endometrial pattern and reduced risk of miscarriage. The changes in oestrogen to progesterone ratio may affect endometrial structure and pattern (Bourgain & Devroey, 2003; Dockery & Rogers, 1989), and thus may affect how the endometrium prepares for implantation (Bourgain & Devroey, 2003; Macklon & Fauser, 2000). Additionally, the function of the corpus luteum in providing a suitable hormonal milieu that will help the uterus to sustain pregnancy, thereby preventing miscarriage, is impaired when premature regression of the corpus luteum occurs via the negative feedback of high oestrogen concentrations (Barbosa et al., 2016; Fatemi, 2009; Macklon & Fauser, 2000; Martins et al., 2016). Despite this, Chen and colleagues, in their study did not control for oestradiol level, nor did they adjust for embryo quality, a significant predictor of pregnancy outcome (Nastri et al., 2015). This may explain the discrepancy between their results and our own.

Our initial categorical analysis (Table 1) shows that cycles with unilinear endometrial pattern had higher serum oestradiol levels. The oestradiol level in cycles with a semitrilinear endometrial pattern was in the lowest oestradiol tertile, and in cycles with trilinear endometrial pattern, serum oestradiol levels was mostly observed to be within the middle-

tertile ($p < 0.0001$). Despite the observed difference in the oestradiol level among the different endometrial patterns, there was no significant difference in the thickness of the endometrium, nor a significant difference in the number of oocytes retrieved across the different endometrial patterns. While it has been suggested that the negative feedback of oestradiol on the pituitary arising from the supra-physiological oestradiol levels is associated with poor pregnancy outcomes (Barbosa et al., 2016; Fatemi, 2009; Martins et al., 2016), , we observed no significant difference in live birth rates, clinical intrauterine pregnancy or miscarriage rates across the different endometrial patterns after adjustment for serum oestradiol level and other factors.

A further consideration for endometrial receptivity is the potential effect of elevated progesterone during the late follicular phase of a stimulation cycle. While some studies have reported poor pregnancy outcomes in cycles with high progesterone levels during this phase of the cycle (Bosch et al., 2010; Bu et al., 2014; Kolibianakis et al., 2012; Mio et al., 1992; Xu et al., 2012), others have shown no significant effect on pregnancy outcomes (Givens et al., 1994; Hofmann et al., 1996; Martinez et al., 2004; Vanni et al., 2017; Venetis et al., 2007). Elevated progesterone levels toward the end of the follicular phase may lead to a premature transformation of a proliferative endometrium to secretory endometrium; which appears on ultrasound as a homogenous hyperechoic (unilinear) endometrial pattern (Killick, 2007; Mahajan, 2015). This premature transformation may indicate that the embryo is not in sync with the development of the endometrial cavity, and thus cause failure of implantation. However, no histological difference among the different endometrial patterns has been found (Sterzik et al., 1997). Sterzik and colleagues conducted a study on 53 patients who had no fertilization during an ART treatment cycle and therefore no embryo transfer. On the day of intended embryo transfer, an ultrasound and endometrial biopsy was performed, however, Sterzik and colleagues observed no histological differences between the endometrial patterns. The absence of a significant difference in pregnancy outcomes between the different endometrial patterns in our study suggests there may be other paracrine or autocrine factors affecting the endometrium and implantation (Bourgain & Devroey, 2003; Kawamura et al., 2012).

While the ultimate aim of ART treatment in both fresh and frozen thawed cycles is to deliver a baby, research seeking associations between endometrial characteristics and live birth has previously been limited to evaluations of frozen thawed transfers. No prior studies have examined associations with live birth outcomes in fresh cycles despite the importance of the endometrium in the maintenance of pregnancy (Granot et al., 2012). Another strength of our study was that we accounted for the lack of independence between the number of repeated ART cycles among couples and the treatment outcome (i.e., informative cluster size), thereby reducing the possibility of an erroneous inference. Our study also comprised a larger sample size and as such had more power to detect existing differences. Although the overall sample size of our study was large, we nevertheless had few cycles with unilinear endometrial pattern, which may have decreased the precision of the estimates in cycles with this endometrial pattern. However, when cycles with unilinear and semi-trilinear patterns were combined into a single group for comparison with the trilinear pattern, the conclusion of no association remained. Because of the retrospective nature of our study, we were limited by the unknown genetic composition of embryos since preimplantation genetic

testing was rarely utilized by our clinic during the study period. However, based on our clinical practice during the study period, it is likely that very few included cycles used embryos known to be euploid. Another limitation of our study was that there might have been inter-individual variation in transvaginal ultrasound assessment of the endometrium among the three providers. Similarly, we did not collect information nor control for the position of the uterus (anteverted, retroverted, or mid-position), which could have affected the ability to visualize the endometrial pattern on ultrasound.

In conclusion, our work suggests that endometrial pattern on an ultrasound does not affect pregnancy outcomes in ART cycles, both fresh and frozen. This may be explained by significant bio-variability that exists in the response of the endometrium to endocrine factors. Similarly, other paracrine or autocrine factors may affect endometrial receptivity and thus make the endometrium favourable for implantation. Hence, our findings indicate that ART cycles should not be cancelled based on the echopattern of the endometrium.

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Table 1:

Cycle Characteristics among the three groups defined by Endometrial Pattern observed during a Cycle.

Variable	Endometrial pattern (n=970)*			p value
	Trilinear (n=776)	Semitrilinear (n=157)	Unilinear (n=37)	
Cycle, n (%)				
Fresh	639 (82.3)	86 (54.8)	28 (75.7)	<0.0001
Frozen	137 (17.7)	71 (45.2)	9 (24.3)	
Number of oocytes retrieved**	17.0 (12.0)	17.0 (9.0)	19.0 (14.0)	0.43
Number of fertilized embryo**	8.0 (7.0)	7.0 (9.0)	8.0 (8.0)	0.12
Stimulation Protocol, n (%)				
GnRH antagonist	66 (8.5)	8 (5.2)	3 (8.1)	<0.0001
E2/P4	170 (22.0)	81 (52.6)	11 (29.7)	
Long GnRH agonist	387 (50.1)	45 (29.2)	17 (46.0)	
MicroDose	150 (19.4)	20 (13.0)	6 (16.2)	
Endometrial thickness (mm), n (%)				
<8.0	45 (5.9)	10 (6.4)	1 (2.8)	0.79
8.0–14.0	598 (77.4)	117 (74.5)	27 (75.0)	
>14.0	130 (16.8)	30 (19.1)	8 (22.2)	
Peak serum oestradiol (pg/mL), n (%)				
< 1716	209 (27.1)	79 (52.0)	11 (29.7)	<0.0001
1716–3161	276 (36.0)	35 (23.0)	9 (24.3)	
3162	282 (36.8)	38 (25.0)	17 (46.0)	
# of embryo transferred, n (%)				
1–2	665 (85.7)	134 (85.4)	30 (81.1)	0.74
3–5	111 (14.3)	23 (14.6)	7 (18.9)	
Quality of the embryo, n (%)				
Good	390 (58.0)	76 (58.0)	22 (66.7)	0.84
Fair	236 (35.1)	45 (34.4)	10 (30.3)	
Poor	46 (6.9)	10 (7.6)	1 (3.0)	
Stage at embryo transfer, n (%)				
Cleavage stage	362 (46.7)	49 (31.2)	15 (40.5)	0.0016
Blastocyst stage	414 (53.4)	108 (68.8)	22 (59.5)	
Assisted Hatching, n (%)				
Yes	218 (28.3)	90 (57.3)	13 (35.1)	<0.0001
No	553 (71.7)	67 (42.7)	24 (64.9)	
Reduced Ovarian reserve, n (%)				
Yes	89 (11.5)	21 (13.4)	6 (16.2)	0.57
No	687 (88.5)	136 (86.6)	31 (83.8)	

* Endometrial pattern not reported on 64 cycles.

** Median (IQR).

Percentages are column percentages.

Chi-square and Kruskal-Wallis tests were used as appropriate.

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Table 2:

Crude and Adjusted Risk Ratios and 95% Confidence Intervals for the Association between Endometrial Pattern and Live birth.

Endometrial Pattern	Cycles (n)	Live Births (n)	Live Birth Rates (%)	Crude Risk Ratio (95% CI) ^d	Adjusted Risk Ratio (95% CI) ^d
ALL CYCLES^a					
Semitrilinear	157	59	37.6%	0.81 (0.65,1.02)	0.91 (0.74,1.12)
Unilinear	37	23	62.2%	1.06 (0.78,1.43)	1.15 (0.89,1.49)
Trilinear (ref)	776	383	49.4%	Referent	Referent
FRESH CYCLES^b					
Semitrilinear	86	35	40.7%	0.82 (0.63,1.07)	0.90 (0.70,1.14)
Unilinear	28	18	64.3%	1.15 (0.84, 1.57)	1.25 (0.98,1.61)
Trilinear (ref)	639	326	51.0%	Referent	Referent
FROZEN CYCLES^c					
Semitrilinear	71	24	33.8%	0.89 (0.54,1.48)	0.96 (0.58,1.59)
Unilinear	9	5	55.6%	1.07 (0.41, 2.77)	0.83 (0.33, 2.07)
Trilinear (ref)	137	57	41.6%	Referent	Referent

^aModel was adjusted for endometrial thickness, # embryos transferred, ovarian reserve, stimulation protocol, transfer day, BMI, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use, embryo quality and type of ART cycle.

^bModel adjusted for endometrial thickness, # embryos transferred, ovarian reserve, stimulation protocol, transfer day, BMI, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use, embryo quality, IVF technique and number of fertilized eggs.

^cModel adjusted for endometrial thickness, # embryos transferred, ovarian reserve, BMI, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use and embryo quality.

^d95% CI = 95% Confidence Interval.

Table 3:

Crude and Adjusted Risk Ratios and 95% Confidence Intervals for the Association between Endometrial Pattern and Clinical Intrauterine Pregnancy.

Endometrial Pattern	Cycles (n)	Clinical Pregnancies (n)	Pregnancy Rate (%)	Crude Risk Ratio (95% CI) ^d	Adjusted Risk Ratio (95% CI) ^d
ALL CYCLES^a					
Semitrilinear	157	75	47.8%	0.85 (0.69,1.02)	0.92 (0.76,1.10)
Unilinear	37	25	67.6%	1.02 (0.76,1.36)	1.07 (0.85,1.36)
Trilinear (ref)	776	436	56.2%	Referent	Referent
FRESH CYCLES^b					
Semitrilinear	86	39	45.4%	0.83 (0.66,1.06)	0.90 (0.72,1.12)
Unilinear	28	18	64.3%	1.05 (0.77, 1.44)	1.11 (0.86,1.42)
Trilinear (ref)	639	363	56.8%	Referent	Referent
FROZEN CYCLES^c					
Semitrilinear	71	36	50.7%	0.86 (0.57, 1.29)	0.87 (0.57,1.33)
Unilinear	9	7	77.8%	1.33 (0.76, 2.32)	1.18 (0.59, 2.34)
Trilinear (ref)	137	73	53.3%	Referent	Referent

^aModel was adjusted for endometrial thickness, # embryos transferred, ovarian reserve, stimulation protocol, transfer day, BMI, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use, embryo quality and type of ART cycle.

^bModel adjusted for endometrial thickness, # embryos transferred, ovarian reserve, stimulation protocol, transfer day, BMI, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use, embryo quality, IVF technique and number of fertilized eggs.

^cModel adjusted for endometrial thickness, # embryos transferred, ovarian reserve, BMI, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use and embryo quality.

^d95% CI = 95% Confidence Interval.

Table 4:

Crude and Adjusted Risk Ratios and 95% Confidence Intervals for the Association between Endometrial Pattern and Miscarriage.

Endometrial Pattern	Clinical Pregnancies (n)	Miscarriage (n)	Miscarriage Rate (%)	Crude Risk Ratio (95% CI) ^b	Adjusted Risk Ratio (95% CI) ^b
ALL CYCLES^a					
Semitrilinear	75	16	21.3%	1.32 (0.60, 2.91)	1.01(0.47, 2.16)
Unilinear	25	2	8.0%	0.61 (0.13, 2.85)	0.45(0.11, 1.84)
Trilinear (ref)	436	48	11.0%	Referent	

^aModel was adjusted for # embryos transferred, ovarian reserve, stimulation protocol, transfer day, age at egg retrieval, peak oestradiol, assisted hatching, tobacco use, embryo quality and type of ART cycle.

^b95% CI = 95% Confidence Interval.