

Endometrial pattern, but not endometrial thickness, affects implantation rates in euploid embryo transfers

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Objective: To evaluate the relationship of endometrial thickness (EnT) and endometrial pattern (EnP) to euploid embryo transfer (ET) outcomes.

Design: Retrospective cohort.

Setting: Private academic clinic.

Patient(s): Patients ($n = 277$; age 36.1 ± 4.0 years) whose embryos ($n = 476$) underwent aneuploidy screening with fresh ($n = 176$) or frozen ($n = 180$) ET from July 2010 to March 2014.

Intervention(s): The EnT and EnP were measured on trigger day and at ET. Patients were stratified by age and cycle type (fresh or frozen). Cycle data were combined at trigger day, but separated at ET day.

Main Outcome Measure(s): Outcome measures were implantation rate, pregnancy rate, and clinical pregnancy rate. Analysis was conducted using χ^2 analysis and Fisher's exact test.

Result(s): A total of 234 gestational sacs, 251 pregnancies, and 202 clinical pregnancies resulted from 356 cycles. The EnT (9.6 ± 1.8 mm; range: 5–15 mm) at trigger day ($n = 241$ cycles), as a continuous or categorical variable (≤ 8 vs. >8 mm), was not associated with implantation rate, pregnancy rate, or clinical pregnancy rate. The EnT at day of fresh ET (9.7 ± 2.2 mm; range: 4.4–17.9 mm) ($n = 176$ cycles) or frozen ET (9.1 ± 2.1 mm; range: 4.2–17.7 mm) ($n = 180$ cycles) was not associated with implantation rate, pregnancy rate, or clinical pregnancy rate. Type 3 EnP at trigger day was associated with increased serum progesterone at trigger and a decreased implantation rate, compared with type 2 EnP. The EnP at fresh or frozen ET was not associated with implantation rate, pregnancy rate, or clinical pregnancy rate.

Conclusion(s): Within the study population, EnT was not significantly associated with clinical outcomes of euploid ETs. A type 3 EnP at trigger day suggests a prematurely closed window of implantation. (Fertil Steril® 2015;104:620–8. ©2015 by American Society for Reproductive Medicine.)

Key Words: Endometrial thickness, endometrial pattern, implantation rate, pregnancy rate, preimplantation genetic screening

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The identification of the optimal conditions for controlled ovarian hyperstimulation (COH) and embryo transfer (ET) is of substantial

clinical interest. Improved clinical outcomes have been demonstrated with: particular stimulation protocols (1, 2); embryo handling and culture

conditions (3); technical factors, such as use of the transfer catheter and embryo placement during ET (4–9); and embryo selection techniques (10, 11). However, identification of clinical markers of endometrial receptivity for optimization during COH remains a challenge.

During a natural menstrual cycle, and one in the context of COH, the endometrium develops and matures within a complex hormonal environment, proliferating and thickening

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under the influence of estrogens (Es), and decidualizing under the influence of progestins (12–19). Despite recent advances in molecular assays (20–23), ultrasound assessment is the only noninvasive tool in standard clinical use for assessing the endometrium. Endometrial thickness (EnT) directly reflects histologic thickness, whereas endometrial pattern (EnP) changes in lockstep with the menstrual cycle, correlating closely with morphologic assessment of endometrial biopsies (24, 25). Although endometrial histology has long been recognized to inform the optimal window of implantation (26), the influence of EnT and EnP on endometrial receptivity and pregnancy rates has been intensively explored but not conclusively determined (27, 28).

Ultrasound measurements of endometrium at the day of ovulatory trigger (the earliest point of completed follicular development of oocytes) and at ET day (the first interaction between embryo(s) and the uterine environment) may provide a window into the developing egg and the implantation environment. Studies thus far, focusing on the effect of EnT on embryo implantation and receptivity, have yielded conflicting findings. Some have shown that increased EnT on human chorionic gonadotropin (hCG) trigger day are correlated with improved pregnancy outcomes for patients undergoing in vitro fertilization (IVF) (29–34). An EnT of <6–7 mm (35–37), or >10–14 mm (37, 38), on hCG trigger day, has been reported to adversely affect implantation rate. Similar findings were noted in ovum donation cycles in recipients with an EnT of <8 mm on the day of ET (39).

Other studies have documented no association between implantation rates and EnT at trigger or ET day (40–48). Given reports of successful pregnancy with an EnT of <4 mm (49), a thick endometrium is certainly not a prerequisite for pregnancy. One study found a positive correlation between EnT and pregnancy rates in intrauterine insemination but not IVF cycles (50), although this finding has been challenged (51). Recipient EnT at ET day in ovum donation cycles was not predictive of pregnancy outcomes (52).

Several interventions have been developed and employed clinically to increase EnT as a means of improving endometrial receptivity, primarily by promoting E-dependent endometrial proliferation (53, 54). However, given the conflicting studies mentioned, the question remains of whether EnT is a parameter that should be considered for clinical optimization. A recent survey found that 30% of clinicians would defer ET if EnT were ≤ 6 mm; the percentages were smaller as EnT increased (55).

The EnP reflects the anatomical changes associated with the menstrual cycle after progestin exposure and can be used to track the pre- and peri-implantation uterine environment (19, 56). One possibility is that an optimized EnP will lead to improved reproductive outcomes. However, lack of consensus persists on the predictive power of EnP on reproductive outcomes. A triple-line EnP on ultrasound after ovarian stimulation before or on trigger day has been associated with improved pregnancy rates vs. a homogeneous, hyperechogenic, or intermediate EnP (57–60). Others have failed to observe this association (61), or have

confirmed it only in a subset of patients with an EnT of 7–14 mm (36, 62). Some have highlighted the importance of a homogeneous, hyperechogenic endometrium at ET day for achieving implantation (63); others have observed a triple-line pattern more frequently (64).

In all the aforementioned studies, morphology before ET was used for embryo selection. However, morphologic embryo selection alone carries potential limitations (65, 66). The lack of preimplantation genetic assessment of embryos, a major source of variability in implantation across patients (67), limits the generalizability of findings from previous studies on the role of both EnT and EnP.

With the use of preimplantation genetic screening to detect aneuploid embryos (10, 11), a more standardized and systematic analysis of the role of sonographic endometrial measurements on implantation can be performed. This study sought to evaluate the impact of EnT and EnP, as measured on trigger and ET day, in patients undergoing IVF, on cycle implantation rate and pregnancy rate, after controlling for oocyte age and cycle type.

MATERIALS AND METHODS

Patient Population

A single-center retrospective cohort study was performed on patients whose embryos underwent tuberculosis and preimplantation genetic screening, via comprehensive 24-chromosome screening during IVF cycles between July 2010 and March 2014. Aneuploidy screening was offered during routine infertility care. Patient age at the initiation of the assisted reproductive technology (ART) cycle producing the euploid embryo was recorded as a categorical variable (A: age <35 years; B: age 35–38 years; C: age 38–41 years; D: age 41–43 years; and E: age >43 years).

Treatment Protocol

In vitro fertilization stimulation cycles and hormonal adjustments were performed according to standard clinical practice (68). All cycles were autologous. Patients were treated with 1 of 3 protocols, determined by clinician preference. The antagonist protocol used ganirelix acetate (Antagon; Organon) or cetrorelix acetate (Cetrotide, EMD Serono). The down-regulation protocol and the microflare protocol used leuprolide acetate (Lupron, AbbVie Inc) (Supplemental Table 1, available online). In general, antagonist protocols were used in potential hyper-responders, microflare protocols in poor responders, and down-regulation or antagonist protocols in the remaining patients.

Final oocyte maturation (henceforth referred to as “trigger”) was induced with 6,500 IU of recombinant hCG alone (Ovidrel, EMD Serono), after confirmation of ≥ 2 mature follicles of ≥ 18 mm, using ultrasound. In patients with a strong ovarian response, or at risk for ovarian hyperstimulation syndrome (OHSS), who were undergoing an antagonist protocol, induction was with 40 IU of leuprolide acetate together with 1,000 IU of hCG (Novarel, Ferring Pharmaceuticals). Vaginal oocyte retrieval was performed under transvaginal ultrasound guidance 36 hours later.

For frozen ETs, patients started taking oral estradiol (E₂) (Estrace, Teva Pharmaceuticals): 2 mg twice daily, for 1 week, followed by 2 mg, 3 times daily, with EnT assessed weekly until a thickness of ≥ 8 mm was observed. Immediately thereafter, 50 mg of intramuscular (IM) progesterone (P) (Actavis Inc) was initiated daily. Thawing and transferring of the embryo(s) were performed after 5 days of P supplementation.

Embryos reaching the blastocyst stage at day 5 after fertilization underwent trophectoderm biopsy and overnight preimplantation genetic screening interpretation. They were transferred fresh on day 6 at 8 AM, or frozen immediately after biopsy. All frozen embryos were thawed at 9 AM, for transfer at 1 PM into a day-5 endometrium (i.e., 5 days after starting P), to avoid embryo–endometrium asynchrony. The decision to freeze day-5 embryos was made by patients after clinician consultation. All embryos reaching the blastocyst stage at day 6 were biopsied and frozen in the morning of day 6. The EnT and EnP at trigger, from both fresh and frozen cycles, were considered together; the EnT and EnP at ET, from both fresh and frozen cycles, were considered separately.

The EnT was measured by transvaginal ultrasound on trigger day, and transabdominally at ET to the nearest 0.1 mm. Although transabdominal measurements were imported automatically, transvaginal measurements were manually inputted into our database, rounded to the nearest millimeter. The EnP was recorded as being in 1 of 3 categories, as described by Grunfeld et al. (24): (1) late proliferative (hyperechoic endometrium constituting $< 50\%$ of the EnT, with a hyperechoic basalis and a hypoechoic functionalis); (2) early secretory (hyperechoic basalis and functionalis extending to $> 50\%$ of the EnT, but not encompassing the entire endometrial cavity); and (3) mid-late secretory (homogeneous hyperechoic functionalis extending from the basalis to the lumen). All assessments of EnT and EnP were performed by the clinician who performed the ultrasound. The most commonly observed EnP (type 2 at trigger day, and type 3 at ET day) was used as the reference factor in linear models.

A pregnancy was defined as the detection of β -hCG in serum, 14 days after vaginal oocyte retrieval. A clinical pregnancy was defined as the detection of a gestational sac on an ultrasound examination 22–25 days after retrieval. Monozygotic twins were counted as a single gestational sac. Implantation rates, pregnancy rates, and clinical pregnancy rates were calculated from these statistics, as, respectively: the ratio of the number of gestational sacs to the number of transferred euploid embryos; the ratio of total pregnancies and clinical pregnancies, respectively, to the number of ART cycles entailing ET.

Serum E₂, follicle-stimulating hormone, P, and hCG levels were quantitatively assessed by solid-phase, competitive, chemiluminescent immunometric assay (IMMULITE 2000, Siemens Healthcare Global) with an analytic sensitivity of 15 pg/mL, 0.1 mIU/mL, 0.1 ng/mL, and 0.4 mIU/mL, respectively. Progesterone was considered to be elevated at day of trigger if it was > 1.5 ng/mL (69–71).

Outcomes

The outcome measures were implantation rate, pregnancy rate, and clinical pregnancy rate. Outcomes were regressed against age group, cycle type, EnT (at trigger and ET), and EnP (at trigger and ET). The EnT and EnP at ET were analyzed separately for fresh and frozen cycles. The EnT was analyzed as both a categorical variable (≤ 8 mm or > 8 mm) variable and a continuous variable.

Statistical Analysis

Statistical analysis was performed with the R programming language (The R Project for Statistical Computing). Binomial regression was performed using a logistic link function. Statistical analysis of a binomial regression model was calculated using χ^2 analysis for residual deviance, with significance at $P < .05$. Contribution of model terms was assessed using the Akaike information criterion using the “step” function in R (in better models, the criterion is smaller). Differences between outcomes in 2 groups were assessed using Fisher’s exact test. For implantation rates in binned samples, 95% confidence intervals (CI) were calculated using the Clopper–Pearson method with the R package “binom” (CRAN). Linear correlation was calculated with a variable intercept, and significance was tested using the Pearson correlation coefficient. Power analysis calculations were performed using the R package “pwr” (CRAN). Levels of P across patient samples as a function of EnP were compared using χ^2 analysis in a linear model.

The study was designed for 80% power, with a 5% false positive rate, to detect the difference between a 60% implantation rate if EnT > 8 mm, and a 40% implantation rate if EnT ≤ 8 mm. Power is achieved with 97 euploid embryos in each of 2 equally sized groups if each embryo is considered independent, but it is still $> 79.9\%$ if 1 group has 67 patients and the other group has 173 patients. This research was approved by the Western Institutional Review Board (WIRB). Because the study is retrospective, informed consent was not required.

RESULTS

A total of 476 euploid embryos were transferred into 277 patients over the course of 356 IVF cycles. One ($n = 247$ cycles), 2 ($n = 101$), 3 ($n = 5$), or 4 ($n = 3$) euploid embryos were replaced per cycle. Patients ranged in age from 23.4 to 44.4 years (mean: 36.1 ± 4.0 years) at the day of the initiation of their IVF stimulation cycles (Supplemental Tables 1 and 2, available online). Aggregate implantation rate was 49.5% (234 of 476), and aggregate pregnancy rate and clinical pregnancy rate were 70.5% (251 of 356) and 56.7% (202 of 356), respectively.

Age Group

Implantation rate did not generally change as a function of maternal age group ($P = .08$, .88, and .33 for age groups B, C, and E, relative to group A, respectively), although the implantation rate was higher in patients in age group D

(0.67 [95% CI, 0.46–0.83] vs. 0.45 [0.37–0.52] for group A; $P=.04$) (Supplemental Table 2). The pregnancy and clinical pregnancy rates were not different across all age groups ($P>.05$ for all comparisons). The addition of age group to a model of implantation rate did not improve the Akaike information criterion (611.1 with vs. 610.8 without age group).

Fresh Versus Frozen

Patients who underwent frozen ETs ($n = 180$ cycles in 152 patients) were compared with patients who underwent fresh ETs ($n = 176$ cycles in 166 patients) (Supplemental Tables 1 and 2). Distinction of cycle type did not improve models of implantation rate (Akaike information criterion of 613.7 with, vs. 610.8 without, cycle type), although it led to improved models of pregnancy rate and clinical pregnancy rate. Implantation rates were similar in frozen versus fresh ETs (0.52 [95% CI, 0.45–0.58] vs. 0.47 [95% CI, 0.40–0.53]; $P=.27$). Compared with patients who underwent fresh cycles, the pregnancy rate (0.76 [95% CI, 0.70–0.83] vs. 0.64 [95% CI, 0.57–0.71]; $P=.01$) and clinical pregnancy rate (0.62 [95% CI, 0.55–0.69] vs. 0.51 [95% CI, 0.44–0.59]; $P=.03$) were improved in frozen ETs (Supplemental Table 1).

Endometrial Thickness at Trigger

Endometrial thickness ranged from 5 to 15 mm (mean: 9.6 ± 1.8 mm) at trigger day. The presence of an EnT of ≤ 8 mm at trigger day ($n = 71$ cycles) was not associated with decreased or increased implantation rate ($P=.90$), pregnancy rate ($P=.88$) or clinical pregnancy rate ($P=.78$), compared with an EnT of >8 mm ($n = 170$ cycles) (Supplemental Table 3, available online). Endometrial thickness detected at trigger day and treated as a continuous variable was not associated with implantation rate ($P=.77$), pregnancy rate ($P=.73$) or clinical pregnancy rate ($P=.98$) (Supplemental Table 3; Fig. 1A).

Endometrial Thickness at Embryo Transfer

The EnT ranged from 4.4 to 17.9 mm (mean: 9.7 ± 2.2 mm) at fresh ET day, and from 4.2 to 17.7 mm (mean: 9.1 ± 2.1 mm) at frozen ET day. Presence of an EnT of ≤ 8 mm at ET day in fresh cycles ($n = 48$ cycles) was not associated with a decreased or increased implantation rate ($P=.80$), pregnancy rate ($P=1.00$), or clinical pregnancy rate ($P=.50$), compared with an EnT of >8 mm ($n = 128$ cycles) (Supplemental Table 2). Presence of an EnT of ≤ 8 mm at ET day in frozen ET cycles ($n = 90$ cycles) was not associated with a decreased or increased implantation rate ($P=.52$), pregnancy rate ($P=.86$), or clinical pregnancy rate ($P=.88$), compared with an EnT of >8 mm ($n = 90$ cycles).

The EnT at the time of fresh ET, treated as a continuous variable, was not associated with implantation rate ($P=.44$), pregnancy rate ($P=.19$), or clinical pregnancy rate ($P=.54$) (Fig. 1B). The EnT at the time of frozen ET, treated as a continuous variable, was not associated with

implantation rate ($P=.34$), pregnancy rate ($P=.24$), or clinical pregnancy rate ($P=.61$) (Supplemental Table 3; Fig. 1C).

Endometrial Pattern at Trigger

Most patients had a type 2 EnP ($n = 79, 138,$ and 20 , for types 1, 2, and 3 EnP, respectively) at trigger day (Supplemental Table 1). Patients with a type 3 EnP at trigger day experienced a decreased implantation rate (0.31 [95% CI, 0.14–0.52]), compared with a type 2 EnP (0.54 [95% CI, 0.47–0.62]) ($P=.03$) (Fig. 2A, left). The implantation rate for patients with a type 1 EnP (0.50 [95% CI, 0.40–0.60]) at trigger day did not differ from those with a type 2 or 3 EnP ($P=.49$ and $.08$, respectively) (Fig. 2A, left). No effect was observed of EnP at trigger day on pregnancy rate ($P=.92, P=.22,$ and $P=.18$ for types 1 vs. 2, 1 vs. 3, and 2 vs. 3, respectively) or clinical pregnancy rate ($P=.33, P=.27,$ and $P=.09$, for types 1 vs. 2, 1 vs. 3, and 2 vs. 3, respectively) (Fig. 2A, center and right; Supplemental Tables 3 and 4, available online).

The serum P levels at trigger day were compared across patients grouped by their same-day EnP. Patients with a type 3 pattern at trigger day had higher same-day serum P levels (1.21 ± 0.54 ng/mL), compared with those with a type 2 (0.92 ± 0.39 , $P<.006$) or type 1 (0.94 ± 0.46 , $P<.004$) EnP (Fig. 3). Progesterone levels in type 1 and type 2 patterns at trigger day were not significantly different ($P=.64$).

Progesterone elevation (>1.5 ng/mL) at trigger was associated with a decreased implantation rate (0.43 [95% CI, 0.35–0.50]), compared with nonelevation (0.53 [95% CI, 0.47–0.59]; $P=.04$) (Supplemental Table 2). This effect remained strong in patients with type 2 EnP ($P=.02$), but not in those with type 3 EnP ($P=.62$) (Supplemental Table 5, available online). After controlling for P elevation, the trend toward a decreased implantation rate in type 3 EnP, compared with type 2 EnP, was not significant ($P=.07$). In patients with nonelevated P, the trend toward a decreased implantation rate in type 3 (0.38 [95% CI, 0.09–0.76]), compared with type 2 EnP (0.61 [95% CI, 0.51–0.70]; $P=.21$) was not significant (Supplemental Table 5).

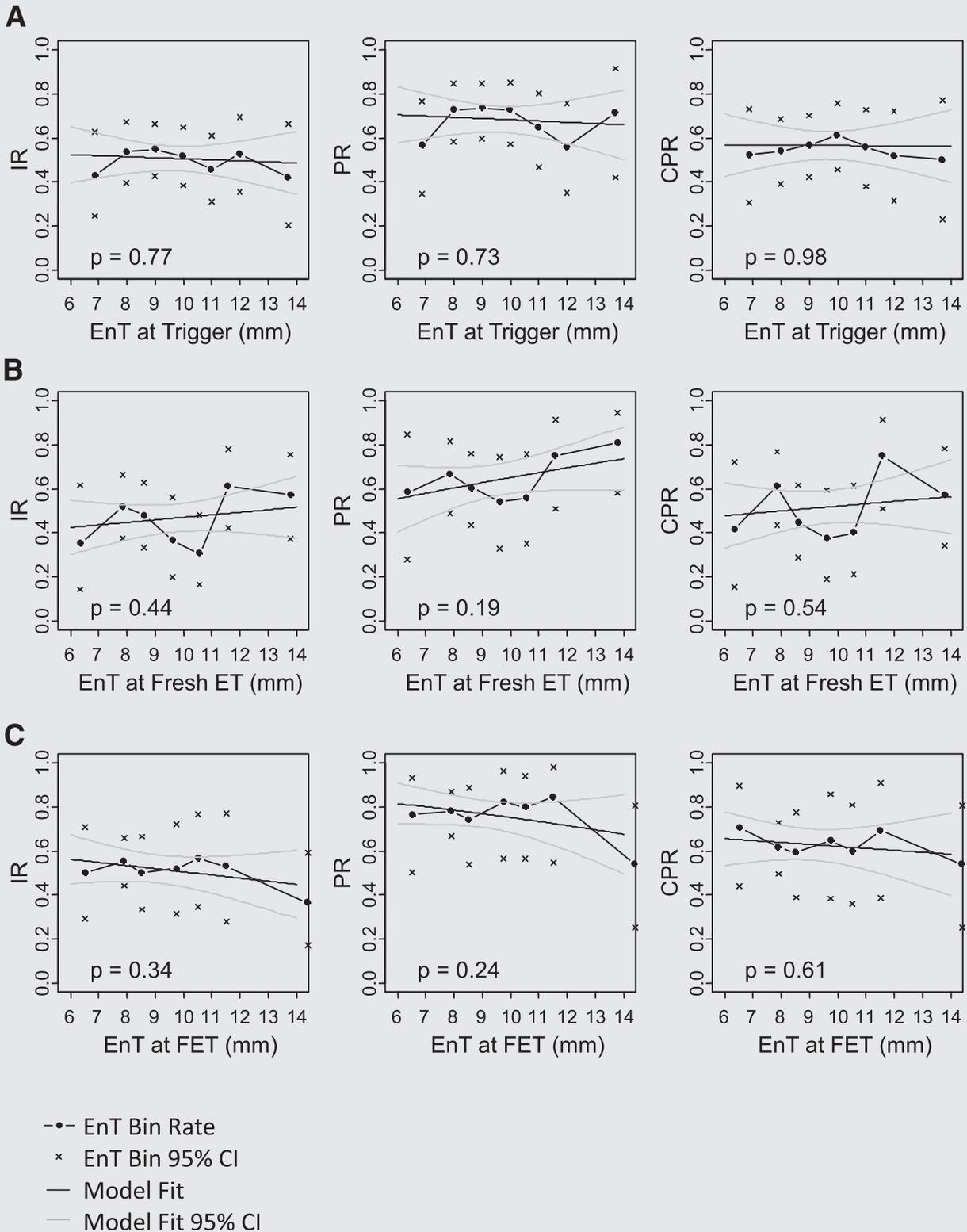
Endometrial Pattern at Embryo Transfer

Most patients had a type 3 EnP at ET day ($n = 1, 25,$ and 150 , for type 1, 2, and 3 EnP in fresh cycles, respectively; and $0, 14,$ and 166 for frozen cycles, respectively) (Supplemental Table 1). The types 2 and 3 EnP at ET day had no detectable differences in regard to implantation rate, pregnancy rate, or clinical pregnancy rate, in either fresh ($P=.47, P=.34,$ and $P=.39$, respectively) or frozen ($P=.41, P=.41,$ and $P=.91$, respectively) ETs (Fig. 2B and C; Supplemental Tables 3 and 4).

DISCUSSION

Although previous studies have suggested a significant effect of EnT and possibly EnP on implantation, they were limited by the unknown genetic composition of embryos before ET.

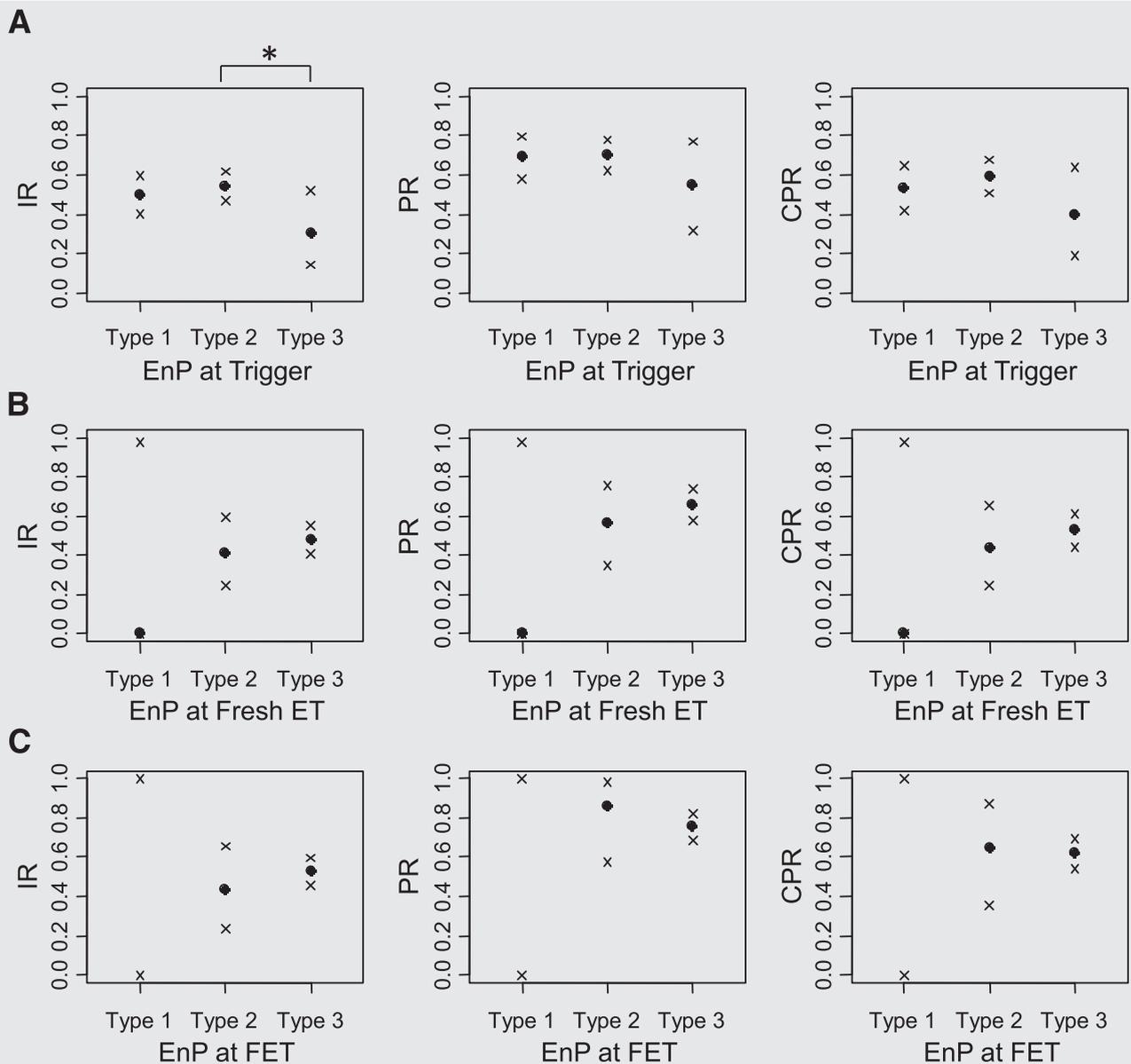
FIGURE 1



The EnT at trigger or ET day does not correlate with IR or PR. Clinical outcomes (black circle points) with their respective 95% CIs (x points) are plotted at the mean EnT of each EnT bin. Model of IR, PR, and CPR vs. EnT treated as a continuous variable at: (A) trigger day; (B) fresh ET day; and (C) FET day is calculated and superimposed in solid black lines. Gray lines represent model 95% CIs. CPR = clinical pregnancy rate; FET = frozen embryo transfer; IR = implantation rate; PR = pregnancy rate.

Gingold. Endometrium in euploid embryo transfers. *Fertil Steril* 2015.

FIGURE 2



The EnP at trigger correlates with IR. The ETs were binned by EnP at: (A) trigger day; (B) fresh ET day; or (C) FET day. Clinical outcomes (black circle points) reflecting IR (left), PR (center), and CPR (right) are plotted for each of the EnP categories with their respective 95% CIs (x points). * $P < .05$. CPR = clinical pregnancy rate; FET = frozen embryo transfer; IR = implantation rate; PR = pregnancy rate.

Gingold. Endometrium in euploid embryo transfers. *Fertil Steril* 2015.

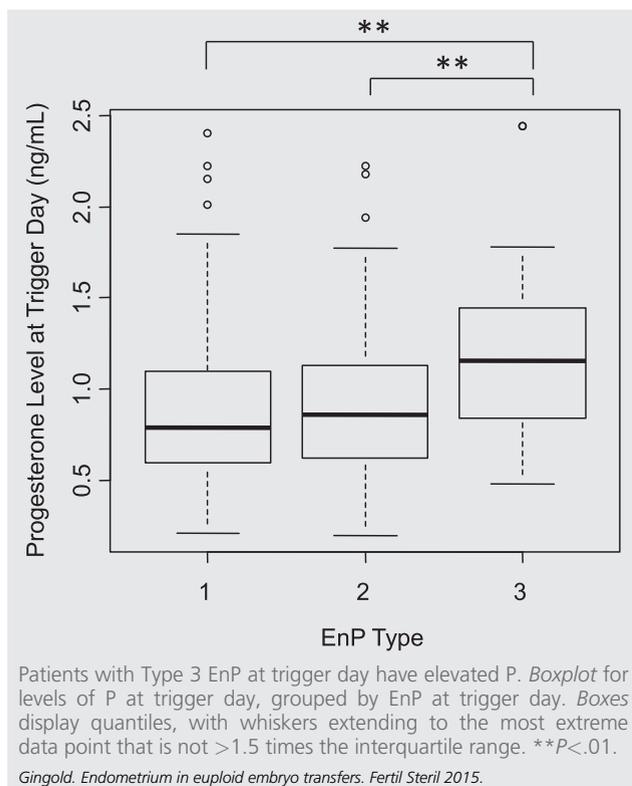
After controlling for embryo quality by aneuploidy screening, we find that EnT, at either trigger or ET day, had no significant correlation with implantation rate or clinical outcomes. However, type 3 EnP at trigger did correlate with a low implantation rate.

The agreement of these findings with the negative findings on the role of EnT in ovum donation cycles (52) likely stems from the low aneuploidy rates of eggs from young donors (67). Given that the primary contributor to age-related fertility decline is aneuploidy (67), the lack of a maternal age effect on implantation rate of euploid embryos

in this study is unsurprising. However, the existence of additional rare oocyte and genetic abnormalities that contribute to embryo failure (72, 73) but are undetectable by current preimplantation genetic screening technology cannot be ruled out. The strong ovarian response in this patient cohort (Supplemental Table 1) is largely a consequence of the use of preimplantation genetic screening in routine infertility care, including for patients with normal ovarian reserve.

This study's findings are consistent with others, indicating the importance of EnP at trigger day in IVF cycles

FIGURE 3



(58). The decreased implantation rate observed in patients with a type 3 EnP at trigger day, compared with those with the typical type 2 EnP, suggests that premature luteinization leading to uterine-embryo asynchrony is a significant contributor to implantation failure. The finding of elevated P levels, a known trigger of premature ovulation (18, 74), in patients with a type 3 EnP, suggests that an early opening of the window of implantation leads to its premature closure, thereby preventing successful embryo implantation. Although the findings from this study may be limited, owing to clinician-to-clinician variability in grading EnP, the association between elevated serum P and a hyperechogenic endometrium with the associated decreased endometrial receptivity has been widely reported (75–77) in ETs performed without aneuploidy screening.

Although 7 mm has been widely reported as a cutoff for a “thin” EnT (46, 62), our clinic generally considered a thin EnT to be ≤ 8 mm. Although none of the protocols required “optimization” of EnT to this target in fresh cycles, most ETs were performed with a greater EnT. An EnT of ≥ 8 mm was explicitly targeted in frozen ETs (68), although achieving it was not always possible. Of the 180 frozen cycles (representing 236 frozen ETs), 30 (39 frozen ETs) needed to be performed with an EnT of < 8 mm at transfer. Consequently, too few patients had an EnT of ≤ 7 mm in all groups to analyze this subset for statistical significance. A future study entailing randomization to various target EnTs, especially in frozen ETs, would better address this limitation.

This study’s findings may not apply to euploid embryos derived from cycles that would have been cancelled in our

clinical practice. Follicles from patients whose procedures were cancelled (before retrieval), in cycles with a thin or thick endometrium or unusual EnP, might have contained oocytes that were less competent for implantation.

The negative findings of this study are unlikely to generalize to patients whose EnT or EnP is altered because of endometrial pathology (e.g., from Asherman’s syndrome, intrauterine tuberculosis, or an autoimmune disorder), in whom an altered endometrium may be a marker of disease. A future study restricted to couples with male-factor infertility might better establish the role of EnT and EnP in implantation into an otherwise normal uterine environment.

Although the study was appropriately powered to detect substantial differences between EnT types at trigger or ET day if each embryo was considered an independent trial, it lacked a sufficient number of patients in age groups D (41–43 years) and E (≥ 43 years) to do so. To confirm whether the observed negative effects of EnT on implantation rate were statistically significant, cohorts of up to approximately 20,000 patients would be needed.

Although an effect for EnP was fortuitously observed, it was not anticipated, because of the small number of patients with type 3 EnP, and consequently, the limited statistical power ($< 50\%$). This study lacked a sufficient number of patients to rule out an independent association between EnP and adverse implantation outcomes after controlling for P levels. Similarly, despite substantial evidence for the effects of stimulation protocols on the endometrium (74, 78, 79), the small number of patients undergoing down-regulation protocols limited the possibility of drawing any conclusions.

Several other factors besides EnT and EnP likely contribute to the variability in implantation rate in euploid transfers. Hormonal and secreted factors produced by both the embryo and the endometrium (41, 45, 74, 78–80), morphological differences (81–89), and genetic and epigenetic alterations not detected by preimplantation genetic screening all potentially represent implantation and survival barriers. A more comprehensive understanding of these barriers is not likely to be addressed by additional clinical studies of EnT or EnP alone.

Although this study cannot currently make any definitive clinical recommendations, no evidence was found of improved implantation rate or clinical outcomes with increasing EnT, or of improved outcomes in euploid embryos derived from younger oocytes. The findings from this study suggest that aggressive “optimization” of EnT is unlikely to lead to substantial clinical benefits. However, attempts should be made to trigger ovulation before the transformation to a type 3 EnP.

REFERENCES

1. La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. *Hum Reprod Update* 2014;20:124–40.
2. Polat M, Bozdogan G, Yerali H. Best protocol for controlled ovarian hyperstimulation in assisted reproductive technologies: fact or opinion? *Semin Reprod Med* 2014;32:262–71.
3. Chronopoulou E, Harper JC. IVF culture media: past, present and future. *Hum Reprod Update* 2015;21:39–55.

4. Schoolcraft WB, Surrey ES, Gardner DK. Embryo transfer: techniques and variables affecting success. *Fertil Steril* 2001;76:863–70.
5. Ghazzawi IM, Al-Hasani S, Karaki R, Sousa S. Transfer technique and catheter choice influence the incidence of transcervical embryo expulsion and the outcome of IVF. *Hum Reprod* 1999;14:677–82.
6. Friedman BE, Lathi RB, Henne MB, Fisher SL, Milki AA. The effect of air bubble position after blastocyst transfer on pregnancy rates in IVF cycles. *Fertil Steril* 2011;95:944–7.
7. Coroleu B, Barri PN, Carreras O, Martínez F, Parriego M, Hereter L, et al. The influence of the depth of embryo replacement into the uterine cavity on implantation rates after IVF: a controlled, ultrasound-guided study. *Hum Reprod* 2002;17:341–6.
8. Frankfurter D, Trimarchi JB, Silva CP, Keefe DL. Middle to lower uterine segment embryo transfer improves implantation and pregnancy rates compared with fundal embryo transfer. *Fertil Steril* 2004;81:1273–7.
9. Rovei V, Dalmaso P, Gennarelli G, Lantieri T, Basso G, Benedetto C, et al. IVF outcome is optimized when embryos are replaced between 5 and 15 mm from the fundal endometrial surface: a prospective analysis on 1184 IVF cycles. *Reprod Biol Endocrinol* 2013;11:114.
10. Wells D, Alfarawati S, Fragouli E. Use of comprehensive chromosomal screening for embryo assessment: microarrays and CGH. *Mol Hum Reprod* 2008;14:703–10.
11. Schoolcraft WB, Fragouli E, Stevens J, Munne S, Katz-Jaffe MG, Wells D. Clinical application of comprehensive chromosomal screening at the blastocyst stage. *Fertil Steril* 2010;94:1700–6.
12. Okada H, Tsuzuki T, Shindoh H, Nishigaki A, Yasuda K, Kanzaki H. Regulation of decidualization and angiogenesis in the human endometrium: mini review. *J Obstet Gynaecol Res* 2014;40:1180–7.
13. Lubahn DB, Moyer JS, Golding TS, Couse JF, Korach KS, Smithies O. Alteration of reproductive function but not prenatal sexual development after insertional disruption of the mouse estrogen receptor gene. *Proc Natl Acad Sci USA* 1993;90:11162–6.
14. Katzenellenbogen BS. Biology and receptor interactions of estradiol and estradiol derivatives in vitro and in vivo. *J Steroid Biochem* 1984;20:1033–7.
15. Harris HA. Estrogen receptor-beta: recent lessons from in vivo studies. *Mol Endocrinol* 2007;21:1–13.
16. Couse JF, Korach KS. Estrogen receptor null mice: what have we learned and where will they lead us? *Endocr Rev* 1999;20:358–417.
17. Hapangama DK, Kamal AM, Bulmer JN. Estrogen receptor β : the guardian of the endometrium. *Hum Reprod Update* 2015;21:174–93.
18. Wetendorf M, DeMayo FJ. The progesterone receptor regulates implantation, decidualization, and glandular development via a complex paracrine signaling network. *Mol Cell Endocrinol* 2012;357:108–18.
19. Dehbashi S, Parsanezhad ME, Alborzi S, Zarei A. Effect of clomiphene citrate on endometrium thickness and echogenic patterns. *Int J Gynecol Obstet* 2003;80:49–53.
20. Ruiz-Alonso M, Blesa D, Diaz-Gimeno P, Gómez E, Fernández-Sánchez M, Carranza F, et al. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. *Fertil Steril* 2013;100:818–24.
21. Garrido-Gómez T, Quiñero A, Antúnez O, Diaz-Gimeno P, Bellver J, Simón C, et al. Deciphering the proteomic signature of human endometrial receptivity. *Hum Reprod* 2014;29:1957–67.
22. Galliano D, Bellver J, Diaz-García C, Simón C, Pellicer A. ART and uterine pathology: how relevant is the maternal side for implantation? *Hum Reprod Update* 2015;21:13–38.
23. Revel A. Defective endometrial receptivity. *Fertil Steril* 2012;97:1028–32.
24. Grunfeld L, Walker B, Bergh PA, Sandler B, Hofmann G, Navot D. High-resolution endovaginal ultrasonography of the endometrium: a noninvasive test for endometrial adequacy. *Obstet Gynecol* 1991;78:200–4.
25. Yoshimitsu K, Nakamura G, Nakano H. Dating sonographic endometrial images in the normal ovulatory cycle. *Int J Gynaecol Obstet* 1989;28:33–9.
26. Noyes RW. Dating the endometrial biopsy. *Fertil Steril* 1950;1:23.
27. Kwan I, Bhattacharya S, Kang A, Woolner A. Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). *Cochrane Database Syst Rev* 2014; CD005289.
28. Teixeira DM, Dassunção LA, Vieira CV, Barbosa MA, Coelho Neto MA, Nastri CO, et al. Ultrasound guidance during embryo transfer: a systematic review and meta-analysis of randomized controlled trials. *Ultrasound Obstet Gynecol* 2015;45:139–48.
29. Al-Ghamdi A, Coskun S, Al-Hassan S, Al-Rejjal R, Awartani K. The correlation between endometrial thickness and outcome of in vitro fertilization and embryo transfer (IVF-ET) outcome. *Reprod Biol Endocrinol* 2008;6:37.
30. Kovacs P, Matyas S, Boda K, Kaali SG. The effect of endometrial thickness on IVF/ICSI outcome. *Hum Reprod* 2003;18:2337–41.
31. Noyes N, Liu HC, Sultan K, Schattman G, Rosenwaks Z. Endometrial thickness appears to be a significant factor in embryo implantation in in-vitro fertilization. *Hum Reprod* 1995;10:919–22.
32. Zhang X, Chen C-H, Confino E, Barnes R, Milad M, Kazer RR. Increased endometrial thickness is associated with improved treatment outcome for selected patients undergoing in vitro fertilization-embryo transfer. *Fertil Steril* 2005;83:336–40.
33. McWilliams GD, Frattarelli JL. Changes in measured endometrial thickness predict in vitro fertilization success. *Fertil Steril* 2007;88:74–81.
34. Richter KS, Bugge KR, Bromer JG, Levy MJ. Relationship between endometrial thickness and embryo implantation, based on 1,294 cycles of in vitro fertilization with transfer of two blastocyst-stage embryos. *Fertil Steril* 2007;87:53–9.
35. Aydin T, Kara M, Nuretlin T. Relationship between endometrial thickness and in vitro fertilization-intracytoplasmic sperm injection outcome. *Int J Fertil Steril* 2013;7:29–34.
36. Zhao J, Zhang Q, Li Y. The effect of endometrial thickness and pattern measured by ultrasonography on pregnancy outcomes during IVF-ET cycles. *Reprod Biol Endocrinol* 2012;10:100.
37. Dain L, Bider D, Levron J, Zinchenko V, Westler S, Dirnfeld M. Thin endometrium in donor oocyte recipients: enigma or obstacle for implantation? *Fertil Steril* 2013;100:1289–95.
38. Weissman A, Gotlieb L, Casper RF. The detrimental effect of increased endometrial thickness on implantation and pregnancy rates and outcome in an in vitro fertilization program. *Fertil Steril* 1999;71:147–9.
39. Noyes N, Hampton BS, Berkeley A, Licciardi F, Grifo J, Krey L. Factors useful in predicting the success of oocyte donation: a 3-year retrospective analysis. *Fertil Steril* 2001;76:92–7.
40. Dietterich C, Check JH, Choe JK, Nazari A, Lurie D. Increased endometrial thickness on the day of human chorionic gonadotropin injection does not adversely affect pregnancy or implantation rates following in vitro fertilization-embryo transfer. *Fertil Steril* 2002;77:781–6.
41. Yuval Y, Lipitz S, Dor J, Achiron R. The relationships between endometrial thickness, and blood flow and pregnancy rates in in-vitro fertilization. *Hum Reprod* 1999;14:1067–71.
42. Laasch C, Puscheck E. Cumulative embryo score, not endometrial thickness, is best for pregnancy prediction in IVF. *J Assist Reprod Genet* 2004;21:47–50.
43. Garcia-Velasco JA, Isaza V, Caligara C, Pellicer A, Remohí J, Simón C. Factors that determine discordant outcome from shared oocytes. *Fertil Steril* 2003;80:54–60.
44. Baruffi RL, Contart P, Mauri AL, Petersen C, Felipe V, Garbellini E, et al. A uterine ultrasonographic scoring system as a method for the prognosis of embryo implantation. *J Assist Reprod Genet* 2002;19:99–102.
45. Remohí J, Ardiles G, García-Velasco JA, Gaitán P, Simón C, Pellicer A. Endometrial thickness and serum oestradiol concentrations as predictors of outcome in oocyte donation. *Hum Reprod* 1997;12:2271–6.
46. Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC, et al. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20:530–41.
47. Rinaldi L, Lisi F, Floccari A, Lisi R, Pepe G, Fishel S. Endometrial thickness as a predictor of pregnancy after in-vitro fertilization but not after intracytoplasmic sperm injection. *Hum Reprod* 1996;11:1538–41.
48. Bodri D, Colodron M, Vidal R, Galindo A, Durban M, Coll O. Prognostic factors in oocyte donation: an analysis through egg-sharing recipient pairs showing a discordant outcome. *Fertil Steril* 2007;88:1548–53.
49. Sundström P. Establishment of a successful pregnancy following in-vitro fertilization with an endometrial thickness of no more than 4 mm. *Hum Reprod* 1998;13:1550–2.

50. De Geyter C, Schmitter M, De Geyter M, Nieschlag E, Holzgreve W, Schneider HP. Prospective evaluation of the ultrasound appearance of the endometrium in a cohort of 1,186 infertile women. *Fertil Steril* 2000;73:106–13.
51. Asante A, Coddington CC, Schenk L, Stewart EA. Thin endometrial stripe does not affect likelihood of achieving pregnancy in clomiphene citrate/intrauterine insemination cycles. *Fertil Steril* 2013;100:1610–4.e1.
52. Barker MA, Boehnlein LM, Kovacs P, Lindheim SR. Follicular and luteal phase endometrial thickness and echogenic pattern and pregnancy outcome in oocyte donation cycles. *J Assist Reprod Genet* 2009;26:243–9.
53. Lebovitz O, Orvieto R. Treating patients with “thin” endometrium—an ongoing challenge. *Gynecol Endocrinol* 2014;30:409–14.
54. Glujovsky D, Pesce R, Fiszbajn G, Sueldo C, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. *Cochrane Database Syst Rev* 2010:CD006359.
55. Cohen MJ, Rosenzweig TS, Revel A. Uterine abnormalities and embryo implantation: clinical opinion altered by peer debate. *Reprod Biomed Online* 2007;14:555–8.
56. Check JH, Dietterich C, Choe JK, Cohen R. Effect of triple line vs isoechogetic endometrial texture on pregnancy outcome following embryo transfer according to use of controlled ovarian stimulation (COH) or estrogen/progesterone replacement. *Clin Exp Obstet Gynecol* 2013;40:37–9.
57. Järvelä IY, Sladkevicius P, Kelly S, Ojha K, Campbell S, Nargund G. Evaluation of endometrial receptivity during in-vitro fertilization using three-dimensional power Doppler ultrasound. *Ultrasound Obstet Gynecol* 2005;26:765–9.
58. Zhao J, Zhang Q, Wang Y, Li Y. Endometrial pattern, thickness and growth in predicting pregnancy outcome following 3319 IVF cycle. *Reprod Biomed Online* 2014;29:291–8.
59. Hock DL, Bohrer MK, Ananth CV, Kemmann E. Sonographic assessment of endometrial pattern and thickness in patients treated with clomiphene citrate, human menopausal gonadotropins, and intrauterine insemination. *Fertil Steril* 1997;68:242–5.
60. Bohrer MK, Hock DL, Rhoads GG, Kemmann E. Sonographic assessment of endometrial pattern and thickness in patients treated with human menopausal gonadotropins. *Fertil Steril* 1996;66:244–7.
61. Rashidi BH, Sadeghi M, Jafarabadi M, Tehrani Nejad ES. Relationships between pregnancy rates following in vitro fertilization or intracytoplasmic sperm injection and endometrial thickness and pattern. *Eur J Obstet Gynecol Reprod Biol* 2005;120:179–84.
62. Chen S-L, Wu F-R, Luo C, Chen X, Shi X-Y, Zheng H-Y, et al. Combined analysis of endometrial thickness and pattern in predicting outcome of in vitro fertilization and embryo transfer: a retrospective cohort study. *Reprod Biol Endocrinol* 2010;8:30.
63. Puerto B, Creus M, Carmona F, Cívico S, Vanrell JA, Balasch J. Ultrasonography as a predictor of embryo implantation after in vitro fertilization: a controlled study. *Fertil Steril* 2003;79:1015–22.
64. Zácková T, Järvelä IY, Tapanainen JS, Feyereis J. Assessment of endometrial and ovarian characteristics using three dimensional power Doppler ultrasound to predict response in frozen embryo transfer cycles. *Reprod Biol Endocrinol* 2009;7:151.
65. Scott L. The biological basis of non-invasive strategies for selection of human oocytes and embryos. *Hum Reprod Update* 2003;9:237–49.
66. Fragouli E, Lenzi M, Ross R, Katz-Jaffe M, Schoolcraft WB, Wells D. Comprehensive molecular cytogenetic analysis of the human blastocyst stage. *Hum Reprod* 2008;23:2596–608.
67. Lathi RB, Westphal LM, Milki AA. Aneuploidy in the miscarriages of infertile women and the potential benefit of preimplantation genetic diagnosis. *Fertil Steril* 2008;89:353–7.
68. Luna M, Grunfeld L, Mukherjee T, Sandler B, Copperman AB. Moderately elevated levels of basal follicle-stimulating hormone in young patients predict low ovarian response, but should not be used to disqualify patients from attempting in vitro fertilization. *Fertil Steril* 2007;87:782–7.
69. Keltz MD, Stein DE, Berin I, Skorupski J. Elevated progesterone-to-estradiol ratio versus serum progesterone alone for predicting poor cycle outcome with in vitro fertilization. *J Reprod Med* 2012;57:9–12.
70. Papanikolaou EG, Pados G, Grimbizis G, Bili E, Kyriazi L, Polyzos NP, et al. GnRH-agonist versus GnRH-antagonist IVF cycles: Is the reproductive outcome affected by the incidence of progesterone elevation on the day of HCG triggering? A randomized prospective study. *Hum Reprod* 2012;27:1822–8.
71. Kyrrou D, Al-Azemi M, Papanikolaou EG, Donoso P, Tziomalos K, Devroey P, et al. The relationship of premature progesterone rise with serum estradiol levels and number of follicles in GnRH antagonist/recombinant FSH-stimulated cycles. *Eur J Obstet Gynecol Reprod Biol* 2012;162:165–8.
72. Fiorentino F, Bono S, Biricik A, Nuccitelli A, Cotroneo E, Cottone G, et al. Application of next-generation sequencing technology for comprehensive aneuploidy screening of blastocysts in clinical preimplantation genetic screening cycles. *Hum Reprod* 2014;29:2802–14.
73. Winand R, Hens K, Dondorp W, de Wert G, Moreau Y, Vermeesch JR, et al. In vitro screening of embryos by whole-genome sequencing: now, in the future or never? *Hum Reprod* 2014;29:842–51.
74. Fanchin R, Righini C, Olivennes F, Ferreira AL, de Ziegler D, Frydman R. Consequences of premature progesterone elevation on the outcome of in vitro fertilization: insights into a controversy. *Fertil Steril* 1997;68:799–805.
75. Sonigo C, Dray G, Roche C, Cédric-Durnerin I, Hugues J-N. Impact of high serum progesterone during the late follicular phase on IVF outcome. *Reprod Biomed Online* 2014;29:177–86.
76. Fanchin R, Righini C, Ayoubi JM, Olivennes F, de Ziegler D, Frydman R. New look at endometrial echogenicity: objective computer-assisted measurements predict endometrial receptivity in in vitro fertilization-embryo transfer. *Fertil Steril* 2000;74:274–81.
77. Ochsenkühn R, Arzberger A, von Schönfeldt V, Gallwas J, Rogenhofer N, Crispin A, et al. Subtle progesterone rise on the day of human chorionic gonadotropin administration is associated with lower live birth rates in women undergoing assisted reproductive technology: a retrospective study with 2,555 fresh embryo transfers. *Fertil Steril* 2012;98:347–54.
78. Paulson RJ, Sauer MV, Lobo RA. Embryo implantation after human in vitro fertilization: importance of endometrial receptivity. *Fertil Steril* 1990;53:870–4.
79. Tang B, Gurpide E. Direct effect of gonadotropins on decidualization of human endometrial stroma cells. *J Steroid Biochem Mol Biol* 1993;47:115–21.
80. Weimar CH, Post Uiterweer ED, Teklenburg G, Heijnen CJ, Macklon NS. In-vitro model systems for the study of human embryo-endometrium interactions. *Reprod Biomed Online* 2013;27:461–76.
81. Racowsky C, Stern JE, Gibbons WE, Behr B, Pomeroy KO, Biggers JD. National collection of embryo morphology data into Society for Assisted Reproductive Technology Clinic Outcomes Reporting System: associations among day 3 cell number, fragmentation and blastomere asymmetry, and live birth rate. *Fertil Steril* 2011;95:1985–9.
82. Cummins JM, Breen TM, Harrison KL, Shaw JM, Wilson LM, Hennessey JF. A formula for scoring human embryo growth rates in in vitro fertilization: its value in predicting pregnancy and in comparison with visual estimates of embryo quality. *J In Vitro Fert Embryo Transf* 1986;3:284–95.
83. Puissant F, Van Rysselberge M, Barlow P, Deweze J, Leroy F. Embryo scoring as a prognostic tool in IVF treatment. *Hum Reprod* 1987;2:705–8.
84. Dennis SJ, Thomas MA, Williams DB, Robins JC. Embryo morphology score on day 3 is predictive of implantation and live birth rates. *J Assist Reprod Genet* 2006;23:171–5.
85. Vernon M, Stern JE, Ball GD, Wininger D, Mayer J, Racowsky C. Utility of the national embryo morphology data collection by the Society for Assisted Reproductive Technologies (SART): correlation between day-3 morphology grade and live-birth outcome. *Fertil Steril* 2011;95:2761–3.
86. Tesarik J, Greco E. The probability of abnormal preimplantation development can be predicted by a single static observation on pronuclear stage morphology. *Hum Reprod* 1999;14:1318–23.
87. Balaban B, Yakin K, Urman B, Isiklar A, Tesarik J. Pronuclear morphology predicts embryo development and chromosome constitution. *Reprod Biomed Online* 2004;8:695–700.
88. Scott L, Alvero R, Leondires M, Miller B. The morphology of human pronuclear embryos is positively related to blastocyst development and implantation. *Hum Reprod* 2000;15:2394–403.
89. Berger DS, Zapantis A, Merhi Z, Younger J, Polotsky AJ, Jindal SK. Embryo quality but not pronuclear score is associated with clinical pregnancy following IVF. *J Assist Reprod Genet* 2014;31:279–83.

SUPPLEMENTAL TABLE 1

Study population characteristics.

Characteristic	Cycle type											
	Frozen					Total frozen	Fresh					Total fresh
Age group	A	B	C	D	E		A	B	C	D	E	
Cycles	70	48	50	8	4	180	60	51	47	16	2	176
Age (y)												
Mean	32.1	36.5	39.6	42.0	43.8		32.0	36.3	39.5	41.7	43.4	
SD	2.7	0.9	0.7	0.6	0.7		2.8	1.0	0.8	0.5	0.6	
Basal FSH (mIU/mL)												
Mean	6.1	5.3	6.5	6.6	6.0		5.6	5.5	6.0	5.7	6.2	
SD	3.0	2.7	3.6	1.6	2.9		2.6	2.7	3.5	3.1	5.2	
Peak E ₂ (pg/mL)												
Mean	3,458	3,087	3,167	2,596	2,864		3,373	3,486	3,066	3,001	2,918	
SD	1,463	1,494	1,620	1,410	768		1,225	1,425	1,621	1,198	1,302	
Eggs retrieved												
Mean	21.7	17.7	19.0	20.8	18.0		21.5	19.6	17.7	17.6	26.0	
SD	11.2	8.0	10.1	19.3	2.9		9.6	7.6	9.5	10.5	12.7	
MII eggs												
Mean	17.1	13.3	15.2	18.6	12.5		17.1	14.7	12.9	12.9	22.5	
SD	10.4	7.0	9.0	15.6	2.4		8.5	7.1	8.0	9.4	12.0	
Blastocyst count												
Mean	8.7	6.8	6.0	7.3	4.8		9.2	7.8	6.6	5.9	10.0	
SD	5.0	3.9	5.0	7.8	2.1		5.7	4.6	5.4	3.7	8.5	
Embryos transferred												
Mean	1.4	1.3	1.2	1.1	1.0		1.4	1.5	1.3	1.1	2.0	
SD	0.7	0.6	0.4	0.4	0.0		0.5	0.5	0.5	0.3	0.0	
Gestational sac												
Mean	0.7	0.8	0.5	0.9	0.8		0.6	0.7	0.6	0.7	1.0	
SD	0.6	0.5	0.5	0.6	0.5		0.7	0.8	0.6	0.6	1.4	
Antagonist cycles	60	39	40	6	4	149	45	42	39	12	2	140
Down-regulation cycles	5	2	4	0	0	11	6	3	2	1	0	12
Microflare cycles	5	7	6	2	0	20	9	6	6	3	0	24
EnT measured at trigger cycles	21	19	23	5	1	69	59	49	46	16	2	172
EnT at trigger (mm)												
Mean	9.6	8.7	9.4	8.2	8.0		9.8	10.4	9.5	9.3	9.5	
SD	1.9	1.6	1.4	1.1	NA		2.0	1.9	1.6	1.5	0.7	
Type 1 EnP at trigger cycles	6	6	10	0	0	22	19	24	11	3	0	57
Type 2 EnP at trigger cycles	13	12	12	4	1	42	34	22	26	12	2	96
Type 3 EnP at trigger cycles	2	0	0	1	0	3	5	3	8	1	0	17
EnT at transfer cycles	70	48	50	8	4	180	60	51	47	16	2	176
EnT at transfer (mm)												
Mean	9.1	8.7	9.5	8.7	8.9		9.7	10.5	9.1	8.9	9.4	
SD	2.2	1.5	2.4	1.4	0.9		2.1	2.6	1.6	1.6	1.5	
Type 1 EnP at ET cycles	0	0	0	0	0	0	1	0	0	0	0	1
Type 2 EnP at ET cycles	5	5	4	0	0	14	9	7	4	5	0	25
Type 3 EnP at ET cycles	65	43	46	8	4	166	50	44	43	11	2	150

Note: Values are n, unless otherwise indicated. Patients were divided by age group and cycle type, as detailed in the Materials and Methods section. The number of patients and their associated hormone levels, endometrial characteristics, and embryologic parameters were calculated for each group. EnT = endometrial thickness; EnP = endometrial pattern; ET = embryo transfer; NA = not applicable.

Gingold. Endometrium in euploid embryo transfers. *Fertil Steril* 2015.

SUPPLEMENTAL TABLE 2

Clinical outcomes by age group, cycle type, stimulation protocol, and P elevation.

Subset	Grouped by	Cycles (n)	Total ET	Total GS	Total pregs	Total CPs	IR (95% CI)	PR (95% CI)	CPR (95% CI)
All	Age group								
	A	130	184	82	91	69	0.45 (0.37–0.52)	0.70 (0.61–0.78)	0.53 (0.44–0.62)
	B	99	136	74	79	64	0.54 (0.46–0.63)	0.80 (0.71–0.87)	0.65 (0.54–0.74)
	C	97	121	55	59	50	0.45 (0.36–0.55)	0.61 (0.50–0.71)	0.52 (0.41–0.62)
	D	24	27	18	17	16	0.67 (0.46–0.83)	0.71 (0.49–0.87)	0.67 (0.45–0.84)
	E	6	8	5	5	3	0.63 (0.24–0.91)	0.83 (0.36–1.00)	0.50 (0.12–0.88)
Fresh	Age group								
	A	60	84	33	35	26	0.39 (0.29–0.51)	0.58 (0.45–0.71)	0.43 (0.31–0.57)
	B	51	74	37	38	28	0.50 (0.38–0.62)	0.75 (0.60–0.86)	0.55 (0.40–0.69)
	C	47	60	29	27	25	0.48 (0.35–0.62)	0.57 (0.42–0.72)	0.53 (0.38–0.68)
	D	16	18	11	11	10	0.61 (0.36–0.83)	0.69 (0.41–0.89)	0.63 (0.35–0.85)
	E	2	4	2	2	1	0.50 (0.07–0.93)	1.00 (0.16–1.00)	0.50 (0.01–0.99)
Frozen	Age group								
	A	70	100	49	56	43	0.49 (0.39–0.59)	0.80 (0.69–0.89)	0.61 (0.49–0.73)
	B	48	62	37	41	36	0.60 (0.46–0.72)	0.85 (0.72–0.94)	0.75 (0.60–0.86)
	C	50	61	26	32	25	0.43 (0.30–0.56)	0.64 (0.49–0.77)	0.50 (0.36–0.64)
	D	8	9	7	6	6	0.78 (0.40–0.97)	0.75 (0.35–0.97)	0.75 (0.35–0.97)
	E	4	4	3	3	2	0.75 (0.19–0.99)	0.75 (0.19–0.99)	0.50 (0.07–0.93)
Cycle type	FET	180	236	122	138	112	0.52 (0.45–0.58)	0.77 (0.70–0.83)	0.62 (0.55–0.69)
	Fresh ET	176	240	112	113	90	0.47 (0.40–0.53)	0.64 (0.57–0.71)	0.51 (0.44–0.59)
Stim type	Antagonist	289	378	179	195	156	0.47 (0.42–0.53)	0.67 (0.62–0.73)	0.54 (0.48–0.60)
	Downreg	23	34	19	19	16	0.56 (0.38–0.73)	0.83 (0.61–0.95)	0.70 (0.47–0.87)
	Microflare	44	64	36	37	30	0.56 (0.43–0.69)	0.84 (0.70–0.93)	0.68 (0.52–0.81)
Trigger P4 (ng/mL)	≤ 1.5	225	296	156	166	132	0.53 (0.47–0.59)	0.74 (0.68–0.79)	0.59 (0.52–0.65)
	> 1.5	129	178	76	83	68	0.43 (0.35–0.50)	0.64 (0.55–0.73)	0.53 (0.44–0.62)

Note: Patients were stratified by age group and further divided into fresh and frozen cycles; by cycle type; by stimulation protocol; and by presence of $P > 1.5$ ng/mL. For each category, GSs, pregnancies, and CPs were tallied, and IR, PR, and CPR were calculated; 95% CIs were calculated using the Clopper–Pearson method. CI = confidence interval; CP = clinical pregnancy; CPR = clinical pregnancy rate; downreg = down-regulation; ET = embryo transfer; FET = frozen embryo transfer; GS = gestational sac; IR = implantation rate; P4 = progesterone; pregs = pregnancies; PR = pregnancy rate; stim type = stimulation protocol type.

Gingold. Endometrium in euploid embryo transfers. *Fertil Steril* 2015.

SUPPLEMENTAL TABLE 3

Clinical outcomes separately divided by EnT and EnP.

Subset	Grouped by	Cycles (n)	Total ET	Total GS	Total pregs	Total CP	IR (95% CI)	PR (95% CI)	CPR (95% CI)	
All	EnT at trigger (mm)	≤7	23	28	12	13	12	0.43 (0.24–0.63)	0.57 (0.34–0.77)	0.52 (0.31–0.73)
		7–8	48	54	29	35	26	0.54 (0.40–0.67)	0.73 (0.58–0.85)	0.54 (0.39–0.69)
		8–9	53	73	40	39	30	0.55 (0.43–0.66)	0.74 (0.60–0.85)	0.57 (0.42–0.70)
		9–10	44	60	31	32	27	0.52 (0.38–0.65)	0.73 (0.57–0.85)	0.61 (0.45–0.76)
		10–11	34	46	21	22	19	0.46 (0.31–0.61)	0.65 (0.46–0.80)	0.56 (0.38–0.73)
		11–12	25	36	19	14	13	0.53 (0.35–0.70)	0.56 (0.35–0.76)	0.52 (0.31–0.72)
		>12	14	19	8	10	7	0.42 (0.20–0.67)	0.71 (0.42–0.92)	0.50 (0.23–0.77)
Fresh	EnT at transfer (mm)	≤7	12	17	6	7	5	0.35 (0.14–0.62)	0.58 (0.28–0.85)	0.42 (0.15–0.72)
		7–8	36	50	26	24	22	0.52 (0.37–0.66)	0.67 (0.49–0.81)	0.61 (0.43–0.77)
		8–9	38	48	23	23	17	0.48 (0.33–0.63)	0.61 (0.43–0.76)	0.45 (0.29–0.62)
		9–10	24	30	11	13	9	0.37 (0.20–0.56)	0.54 (0.33–0.74)	0.38 (0.19–0.59)
		10–11	25	36	11	14	10	0.31 (0.16–0.48)	0.56 (0.35–0.76)	0.40 (0.21–0.61)
		11–12	20	31	19	15	15	0.61 (0.42–0.78)	0.75 (0.51–0.91)	0.75 (0.51–0.91)
		>12	21	28	16	17	12	0.57 (0.37–0.76)	0.81 (0.58–0.95)	0.57 (0.34–0.78)
Frozen	EnT at transfer (mm)	≤7	17	24	12	13	12	0.50 (0.29–0.71)	0.76 (0.50–0.93)	0.71 (0.44–0.90)
		7–8	73	87	48	57	45	0.55 (0.44–0.66)	0.78 (0.67–0.87)	0.62 (0.50–0.73)
		8–9	27	38	19	20	16	0.50 (0.33–0.67)	0.74 (0.54–0.89)	0.59 (0.39–0.78)
		9–10	17	25	13	14	11	0.52 (0.31–0.72)	0.82 (0.57–0.96)	0.65 (0.38–0.86)
		10–11	20	23	13	16	12	0.57 (0.34–0.77)	0.80 (0.56–0.94)	0.60 (0.36–0.81)
		11–12	13	17	9	11	9	0.53 (0.28–0.77)	0.85 (0.55–0.98)	0.69 (0.39–0.91)
		>12	13	22	8	7	7	0.36 (0.17–0.59)	0.54 (0.25–0.81)	0.54 (0.25–0.81)
All	EnP at trigger	1	79	106	53	55	42	0.50 (0.40–0.60)	0.70 (0.58–0.79)	0.53 (0.42–0.64)
		2	138	179	97	97	82	0.54 (0.47–0.62)	0.70 (0.62–0.78)	0.59 (0.51–0.68)
		3	20	26	8	11	8	0.31 (0.14–0.52)	0.55 (0.32–0.77)	0.40 (0.19–0.64)
Fresh	EnP at transfer	1	1	1	0	0	0	0.00 (0.00–0.98)	0.00 (0.00–0.98)	0.00 (0.00–0.98)
		2	25	34	14	14	11	0.41 (0.25–0.59)	0.56 (0.35–0.76)	0.44 (0.24–0.65)
		3	150	205	98	99	79	0.48 (0.41–0.55)	0.66 (0.58–0.74)	0.53 (0.44–0.61)
Frozen	EnP at transfer	2	14	23	10	12	9	0.43 (0.23–0.66)	0.86 (0.57–0.98)	0.64 (0.35–0.87)
		3	166	213	112	126	103	0.53 (0.46–0.59)	0.76 (0.69–0.82)	0.62 (0.54–0.69)

Note: The EnT at either trigger or ET day, both fresh and frozen, was binned into thickness categories. EnP was binned as described in the Materials and Methods section. The number of patients in each bin, and the number of total ETs, was noted. For each category, GSs, pregnancies, and CPs were tallied, and IR, PR, and CPR were calculated; 95% CIs were calculated using the Clopper-Pearson method. CI = confidence interval; CP = clinical pregnancy; CPR = clinical pregnancy rate; downreg = down-regulation; EnP = endometrial pattern; EnT = endometrial thickness; ET = embryo transfer; FET = frozen embryo transfer; GS = gestational sac; IR = implantation rate; P4 = progesterone; pregs = pregnancies; PR = pregnancy rate; stim type = stimulation protocol type.

Gingold. Endometrium in euploid embryo transfers. Fertil Steril 2015.

SUPPLEMENTAL TABLE 4

Clinical outcomes divided by EnT and EnP in combination.

Subset	EnP	EnT	Cycles (n)	Total ET	Total GS	Total pregs	Total CP	IR (95% CI)	PR (95% CI)	CPR (95% CI)		
All	At trigger	1	≤8	19	22	10	15	9	0.45 (0.24–0.68)	0.79 (0.54–0.94)	0.47 (0.24–0.71)	
			>8	60	84	43	40	33	0.51 (0.40–0.62)	0.67 (0.53–0.78)	0.55 (0.42–0.68)	
	2	≤8	42	48	26	27	24	0.54 (0.39–0.69)	0.64 (0.48–0.78)	0.57 (0.41–0.72)		
		>8	96	131	71	70	58	0.54 (0.45–0.63)	0.73 (0.63–0.81)	0.60 (0.50–0.70)		
	3	≤8	8	9	4	5	4	0.44 (0.14–0.79)	0.63 (0.24–0.94)	0.50 (0.16–0.84)		
		>8	12	17	4	6	4	0.24 (0.07–0.50)	0.50 (0.21–0.79)	0.33 (0.10–0.65)		
Fresh	At transfer	2	≤8	3	4	1	1	1	0.25 (0.01–0.81)	0.33 (0.01–0.91)	0.33 (0.01–0.91)	
			>8	22	30	13	13	10	0.43 (0.25–0.63)	0.59 (0.36–0.79)	0.45 (0.24–0.68)	
	3	≤8	45	63	31	30	26	0.49 (0.36–0.62)	0.67 (0.51–0.80)	0.58 (0.42–0.72)		
		>8	105	142	67	69	53	0.47 (0.39–0.56)	0.66 (0.56–0.75)	0.50 (0.41–0.60)		
	Frozen	At transfer	2	≤8	5	7	4	4	4	0.57 (0.18–0.90)	0.80 (0.28–0.98)	0.80 (0.28–0.99)
				>8	9	16	6	8	5	0.38 (0.15–0.65)	0.89 (0.52–1.00)	0.56 (0.21–0.86)
3		≤8	85	104	56	66	53	0.54 (0.44–0.64)	0.78 (0.67–0.86)	0.62 (0.51–0.73)		
		>8	81	109	56	60	50	0.51 (0.42–0.61)	0.74 (0.63–0.83)	0.62 (0.50–0.72)		

Note: The EnT at either trigger or ET day, both fresh and frozen, was classified as thin (≤ 8 mm) or thick (> 8 mm). The EnP was binned as described in the Materials and Methods section. The number of patients in each bin and number of total ET was noted. For each category, GSs, pregnancies, and CPs were tallied, and IR, PR, and CPR were calculated; 95% CIs were calculated using the Clopper–Pearson method. CI = confidence interval; CP = clinical pregnancy; CPR = clinical pregnancy rate; downreg = down-regulation; EnP = endometrial pattern; EnT = endometrial thickness; ET = embryo transfer; FET = frozen embryo transfer; GS = gestational sac; IR = implantation rate; P4 = progesterone; pregs = pregnancies; PR = pregnancy rate; stim type = stimulation protocol type.

Gingold. Endometrium in euploid embryo transfers. *Fertil Steril* 2015.

SUPPLEMENTAL TABLE 5

Clinical outcomes divided by EnP and P4 at trigger in combination.

Trigger

EnP	P4	Cycles (n)	Total ET	Total GS	Total pregs	Total CP	IR (95% CI)	PR (95% CI)	CPR (95% CI)
1	>1.5	54	70	35	38	28	0.50 (0.38–0.62)	0.70 (0.56–0.82)	0.52 (0.38–0.66)
	≤1.5	24	35	17	16	13	0.49 (0.31–0.66)	0.67 (0.45–0.84)	0.54 (0.33–0.74)
2	>1.5	89	115	70	68	57	0.61 (0.51–0.70)	0.76 (0.66–0.85)	0.64 (0.53–0.74)
	≤1.5	49	64	27	29	25	0.42 (0.30–0.55)	0.59 (0.44–0.73)	0.51 (0.36–0.66)
3	>1.5	7	8	3	4	3	0.38 (0.09–0.76)	0.57 (0.18–0.90)	0.43 (0.10–0.82)
	≤1.5	13	18	5	7	5	0.28 (0.10–0.53)	0.54 (0.25–0.81)	0.38 (0.14–0.68)

Note: The EnP at trigger was binned as described in the Materials and Methods section. Progesterone at trigger was classified as nonelevated (≤ 1.5 ng/mL) or elevated (> 1.5 ng/mL). The number of patients in each bin, and the number of total ETs, was noted. For each category, GSs, pregnancies, and CPs were tallied, and IR, PR, and CPR were calculated; 95% CIs were calculated using the Clopper–Pearson method. CI = confidence interval; CP = clinical pregnancy; CPR = clinical pregnancy rate; EnP = endometrial pattern; ET = embryo transfer; GS = gestational sac; IR = implantation rate; P4 = progesterone; pregs = pregnancies; PR = pregnancy rate.

Gingold. Endometrium in euploid embryo transfers. *Fertil Steril* 2015.