ORIGINAL ARTICLE: ENDOMETRIOSIS

Endometriosis does not impact live-birth rates in frozen embryo transfers of euploid blastocysts

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Objective: To determine whether subfertility in patients with endometriosis is due to impaired endometrial receptivity by comparing pregnancy and live-birth outcomes in women with endometriosis versus two control groups without suspected endometrial factors: noninfertile patients who underwent assisted reproduction to test embryos for a single-gene disorder and couples with isolated male factor infertility.
Design: Retrospective cohort.
Setting: Multicenter private practice.
Patient(s): All patients aged 24 to 44 years undergoing euploid frozen blastocysts transfer from January 2016 through March 2018.
Intervention(s): None.
Main Outcome Measure(s): Live birth, clinical pregnancies, pregnancy losses, and aneuploid rates in preimplantation genetic testing for aneuploidy cycles.
Result(s): The analysis included 459 euploid frozen embryo transfer cycles among 328 unique patients. There were no differences in clinical pregnancy, pregnancy loss, or live-birth rates in patients with endometriosis compared with both control groups. The aneuploidy rates were lowest in the preimplantation genetic testing for monogenic disorders cohort, and the endometriosis patients had aneuploidy rates similar to those of the male factor infertility patients.
Conclusion(s): It is unclear whether endometriosis primarily affects in vitro fertilization outcomes via oocyte quality or the endometrium. By controlling for embryo quality using euploid frozen embryo transfer cycles, we found no difference in pregnancy outcomes in patients with endometriosis compared with patients undergoing treatment for male factor infertility and noninfertile patients. (Fertil Steril® 2020;■:■–■. ©2020 by American Society for Reproductive Medicine.)
Key Words: Aneuploid rates, endometriosis, euploid blastocyst transfers

Endometriosis is a chronic inflammatory disease defined by the presence of ectopic endometrial tissue, most commonly in the ovaries, anteroposterior cul-de-sac, uterosacral and broad ligaments, and fallopian tubes (1, 2). The symptoms include dysmenorrhea, dyspareunia, and chronic pelvic pain, which are typically present during the reproductive years (3, 4). The prevalence of endometriosis in reproductive-age women is estimated to be 5% to 15%, and 30% to 50% in women with infertility (5–7). Assisted reproductive technology (ART) can be used to help women achieve pregnancy; however, some studies have suggested that women with endometriosis have worse laboratory and clinical outcomes compared with other patients undergoing in vitro fertilization (IVF) (8).

The proposed mechanisms include poor oocyte quality, alterations in the composition of follicular fluid, and impaired endometrial receptivity. Oxidative stress and increased free radicals may result in oocyte damage and impaired embryo development, potentially leading to poor reproductive outcomes (9, 10). In 2017 Juneau et al. (11) sought to determine whether embryo aneuploidy rates were higher in patients with endometriosis. When compared with their age-matched peers, IVF patients with endometriosis undergoing

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blastocyst biopsy and preimplantation genetic testing (PGT) had similar rates of aneuploidy.

Other investigators have attempted to uncover endometrial factors that could alter endometrial receptivity or disrupt estrogen and progesterone signaling to result in implantation failure among patients with endometriosis (12, 13). Lower implantation and clinical pregnancy rates in patients with endometriosis have been observed in several clinical studies, but the findings are conflicting (2, 4, 6, 14). Implantation and pregnancy outcomes among patients with endometriosis may also vary by the cycle type (i.e., fresh versus frozen embryo transfer). Although some studies have not found a difference in pregnancy outcomes in patients with endometriosis according to cycle type, others have demonstrated superior clinical pregnancy and live-birth rates when embryo transfer is deferred to a subsequent frozen cycle (3, 15–18). These studies have not controlled for embryo quality and have included both cleavage stage and blastocyst transfers of preimplantation genetic testing for aneuploidy (PGT-A) untested embryos.

We investigated whether subfertility in patients with endometriosis is due to impaired endometrial receptivity in euploid blastocyst frozen embryo transfers (FET). A secondary aim was to evaluate whether rates of aneuploidy are higher among patients with surgically confirmed endometriosis.

MATERIALS AND METHODS

This study was a retrospective cohort analysis of patients undergoing FET from January 2016 through March 2018 at a single large fertility center. Patients with surgically confirmed endometriosis were compared with two control groups without suspected endometrial factors. These two control groups were noninfertile patients who underwent ART to test embryos for a single gene disorder; and couples with isolated male factor (MF) infertility. Couples with multiple diagnoses were excluded from the analysis. Cycles using donor oocytes or a gestational carrier were also excluded. All FET cycles of vitrified, warmed PGT-A normal blastocyst(s) to patients meeting these criteria over this period were included in the analysis. The patients included ranged in age from 24 to 44 years. All euploid blastocysts were scored per the Gardner and Schoolcraft classification system as grade BB or better (19). This study was approved by the Schulman institutional review board under protocol 00027148.

Ovarian Stimulation and PGT-A

Before stimulation, the patients were treated with oral contraceptives for 2 to 3 weeks. Ovarian stimulation was achieved with follicle-stimulating hormone and human menopausal gonadotropin preparations. In gonadotropin-releasing hormone (GnRH) antagonist cycles, the antagonist was started when the lead follicle had reached 14 mm. For GnRH agonist cycles, leuprolide acetate was used for pituitary suppression. When two or more follicles measured >18 mm in diameter, 10,000 IU of human chorionic gonadotropin (hCG) or 4 mg of GnRH agonist was used for final oocyte maturation (20). Mature oocytes were inseminated using intracytoplasmic sperm injection and cultured to the blastocyst stage. Trophectoderm biopsy was performed on good-quality blastocysts on days 5 to 7. The PGT-A analysis was performed using array comparative genomic hybridization or next-generation sequencing.

In a subsequent cycle, patients with a euploid blastocysts available for transfer underwent ovarian suppression with oral contraceptive pills. Endometrial preparation was achieved with intramuscular, oral, vaginal, or transdermal estradiol per patient and physician preference, and 50 mg daily of intramuscular progesterone in oil was started when the endometrial thickness was at least 8 mm and estradiol level had reached 200 pg/mL (21). Embryo transfer was performed after the fifth dose of intramuscular progesterone.

The primary treatment outcome for analysis was live birth per embryo transfer. The secondary outcomes included pregnancy rate, defined as a positive serum hCG per transfer; clinical pregnancy rate (CPR), defined as a cycle with an ultrasound confirmed gestational sac; and clinical pregnancy loss, a miscarriage after a confirmed clinical pregnancy. Corresponding IVF cycles that resulted in available vitrified blastocyst(s) were also analyzed, and the outcomes of embryo culture, including fertilization rates and available blastocysts, were compared in the study group to the two controls. The PGT-A results, including the number and percentage of euploid blastocysts, were also analyzed. Blastocysts whose biopsy samples provided inadequate DNA for PGT-A result were excluded from this analysis.

Statistical Analysis

Descriptive statistics were used to demonstrate the mean and standard deviation for continuous variables. Statistical analysis of clinical outcomes among groups was performed using *t*-tests and chi-square tests. Analysis of variance was used to analyze the differences among the group means for continuous variables. The PGT-A outcomes were analyzed using both an adjusted and unadjusted model. A chi-square test was performed in the unadjusted model, and generalized estimating equations were used to account for repeated cycles in the same patient and were adjusted for female age at time of egg retrieval. $P<.05$ was considered statistically significant. The R statistical computing system (version 3.6.3) and the add-on R packages tableone (v. 0.11.1), gee (v. 4.13–20), geepack (v. 1.3–1), csv (v. 0.5.5), and tidyverse (v. 1.0.3) were used to perform data analyses and modeling.

RESULTS

A total of 459 FET cycles of PGT-A–normal blastocysts were performed between 2016 and 2018 in patients with a single infertility diagnosis of surgically confirmed endometriosis, in couples in treatment for MF infertility, or in couples without infertility who were undergoing PGT-A and preimplantation genetic testing for monogenic disorders (PGT-M) for single-gene disorders. These FET cycles were among 328 unique patients, and included 39 patients with endometriosis, 253 patients in treatment for MF infertility, and 36 noninfertile patients undergoing PGT-M. All FET cycles performed in these patients during the study period were included in the analysis: 54 cycle in patients with endometriosis, 355 cycles

in patients in treatment for MF infertility, and 50 cycles after PGT-M. The mean age of this patient population was 35.2 years, with an average body mass index (BMI) of 25.6 kg/m^2. Both age and BMI were similar between the groups. The number of embryos transferred per cycle were comparable between all groups: endometriosis 1.06; MF 1.09; and PGT-M 1.06 (Table 1).

Pregnancy Outcomes According to Infertility Diagnosis

The primary outcome of live birth did not differ between endometriosis patients when compared with either control group (Fig. 1). Patients with endometriosis had a live birth rate of 61.1%, not significantly different compared with patients in treatment for MF infertility (49.6%, P=.141) and patients undergoing PGT-M (52.1%, P=.346). No statistically significant differences were observed in any secondary clinical outcome between endometriosis patients and the control groups. Patients with endometriosis had high positive serum hCG (79.6%) and CPR (72.2%) per embryo transfer. This was similar to patients in treatment for MF infertility (positive hCG 73.8%, P=.454 and CPR 65.1%, P=.379), and noninfertile couples undergoing PGT-M (positive hCG 80.0%, P=1.0 and CPR 62.0%, P=.368). Once implantation occurred, patients with endometriosis did not have a higher risk of clinical pregnancy loss (11.1%) than patients in treatment for MF infertility (13.5%, P=.786) or those using PGT-M (8.0%, P=.838).

Stimulation and Embryo Culture Outcomes According to Infertility Diagnosis

We then analyzed stimulation parameters and embryo culture outcomes from each fresh cycle resulting in a blastocyst available for biopsy. Several patients underwent multiple fresh cycles for embryo banking or due to the lack of an available euploid embryo for transfer after PGT. Patients with endometriosis completed 49 fresh cycles, compared with 295 cycles in patients in treatment for MF infertility and 42 cycles for PGT-M. Similar to the time of embryo transfer, there was no difference in mean patient ages (35.2 years, P=.152) or BMI (25.4 kg/m^2, P=.293) at the time of retrieval (Table 2). Ovarian reserve did not differ in patients with endometriosis (= antimüllerian hormone [AMH] 2.75 ng/mL) compared with patients in treatment for MF (AMH 3.68) and patients using PGT-M (AMH 3.69, P=.289). Peak estradiol was similar among all study groups (P=.573).

Patients with endometriosis had similar oocytes retrieved (16.4) compared with patients in treatment for MF infertility (17.1, P=.178) and patients using PGT-M (17.9, P=.516). The number of mature oocytes (endometriosis 12.02, MF 13.3, P=.106; PGT-M 13.6, P=.430) was also similar in each group. The fertilization and blastulation rates were not impaired in patients with endometriosis compared with the control groups. The mean number of two-pronuclei in patients with endometriosis (10.1) was similar to that of patients in treatment for MF infertility (10.2, P=.334) and noninfertile patients using PGT-M (10.6, P=.932). There were no differences in the number of good-quality blastocysts available for biopsy in patients with endometriosis (5.5) compared with MF infertility patients (4.7, P=.415) and PGT-M patients (5.7, P=.537).

PGT-A Outcomes According to Infertility Diagnosis

A total of 1,873 good-quality blastocysts were biopsied for PGT, 261 from patients with endometriosis, 1,378 from patients in treatment for MF infertility, and 234 from noninfertile patients using PGT-M. Ploidy status was obtained in 250 blastocysts in the endometriosis cohort, 1,332 blastocysts in patients in treatment for MF infertility, and 225 noninfertile patients. Similar rates of aneuploidy were observed in patients with endometriosis—113 blastocysts (45.2%)—compared with patients in treatment for MF infertility (562 blastocysts [42.4%], P=.416) (Fig. 2). In the unadjusted model, noninfertile patients undergoing PGT-M had lower rates of aneuploidy (30.7%, P<.002), and this difference persisted after adjusted for age in the generalized estimating equation analysis (P<.001). Noninfertile patients using PGT-M also had lower rates of aneuploidy compared with patients in treatment for MF infertility (P=.001).

DISCUSSION

Endometriosis is a common cause of infertility, and ART can be used to help patients achieve pregnancy. Despite these interventions, some studies have demonstrated poor pregnancy outcomes in patients with endometriosis. Poor oocyte and embryo quality, and impaired endometrial receptivity have been proposed as potential mechanisms contributing to poor clinical outcomes. These data demonstrate that euploid blastocysts have similar pregnancy outcomes in women

TABLE 1

Patient characteristics in frozen embryo transfer cycles compared by infertility diagnosis.

Characteristic	Endometriosis	Male factor	PGT-M	*P* value
No. of patients	39	253	36	—
No. of FET cycles	54	355	50	—
Age (y)	35.4 ± 3.1	35.4 ± 3.5	34.3 ± 3.8	.086
BMI (kg/m^2)	23.9 ± 5.9	25.9 ± 5.2	25.2 ± 4.4	.061
No. of embryos transferred	1.06	1.09	1.06	.628

Note: Values are mean ± standard deviation, unless stated otherwise. BMI = body mass index; FET = frozen embryo transfer; PGT-M = preimplantation genetic testing for monogenic disorders.

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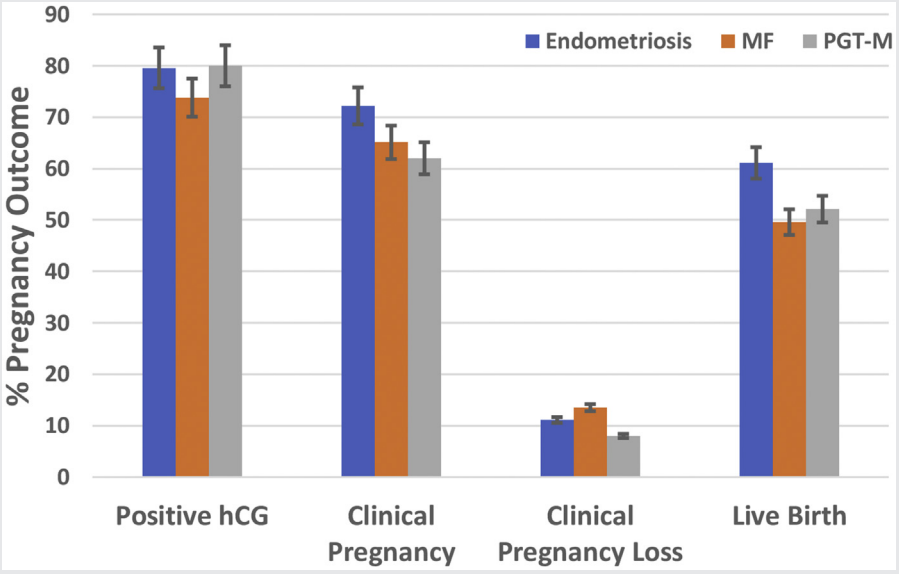
FIGURE 1



Pregnancy outcomes in patients with endometriosis compared with those of patients in treatment for male factor infertility and noninfertile patients undergoing preimplantation genetic testing for monogenic disorders (PGT-M).

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with endometriosis compared with women without female infertility in frozen embryo transfer cycles.

Using the theory of retrograde menstruation, the components of refluxed blood, including erythrocytes, macrophages, and cell debris, collect in the pelvis. Lysed erythrocytes release iron, and iron overload will result in oxidative damage and inflammation (9). Increased free radicals produced during the inflammatory response can directly damage oocytes and embryos, potentially leading to poor reproductive outcomes (10). When evaluating oocyte quality, Orazov et al. (22) found patients with endometriomas had fewer high-quality meiosis II oocytes obtained during retrieval and more structural changes such as displacement of the nucleus into the oocyte membrane and partial or complete absence of the nuclear envelope. Alteration in the meiotic spindle has also been proposed as a possible mechanism contributing to structural instability, resulting in aneuploidy (23).

Despite all of these possible mechanisms for poor embryo quality in patients with endometriosis, a large age-matched study showed no difference in aneuploid rate in patients undergoing blastocyst biopsy and PGT (11). Patient age was the only factor contributing to increased rates of aneuploidy in this study population. Our study demonstrated similar findings, with no statistically significant differences in aneuploid rate in blastocysts obtained from patients with endometriosis compared with patients in treatment for MF infertility. Patients undergoing PGT-M for a single-gene disorder had the lowest rates of aneuploidy compared with both groups, but this may be due to the small sample size in this cohort; we

TABLE 2

Fresh cycle characteristics with stimulation and culture outcomes.

Characteristic	Endometriosis	Male factor	PGT-M	*P* value
No. of fresh cycles	49	295	42	—
Age (y)	35.3 ± 2.7	35.4 ± 3.4	34.2 ± 3.7	.152
AMH (ng/mL)	2.75 ± 2.12	3.68 ± 2.96	3.69 ± 2.02	.289
Peak E_2 concentration (pg/mL)	3376 ± 1711	3613 ± 1444	3632 ± 1523	.573
Total no. oocytes retrieved	16.4 ± 7.7	17.1 ± 8.7	17.9 ± 11.2	.725
No. of MII oocytes	12.0 ± 5.9	13.3 ± 6.9	13.6 ± 9.0	.474
No. of 2PN	10.1 ± 5.5	10.2 ± 5.7	10.6 ± 7.3	.905
No. of blastocysts	5.5 ± 3.4	4.7 ± 3.3	5.7 ± 3.8	.081

Note: Values are mean ± standard deviation, unless stated otherwise. AMH = antimüllerian hormone; BMI = body mass index; E_2 = estradiol; FET = frozen embryo transfers; MII = metaphase 2; PGT-M = preimplantation genetic testing for monogenic disorders; 2PN = two pronuclei.

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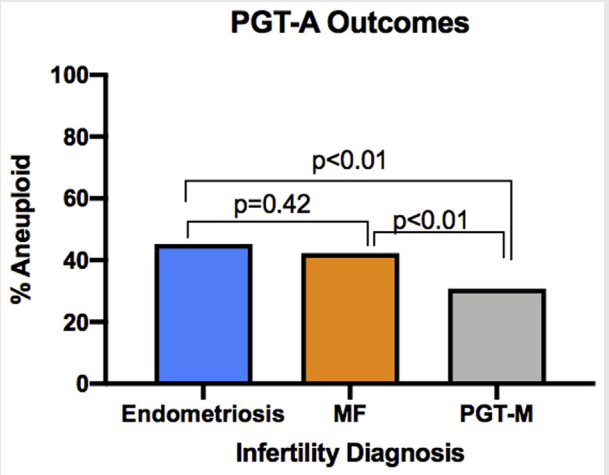
FIGURE 2



Preimplantation genetic testing for aneuploidy (PGT-A), outcomes according to infertility diagnosis.

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A potential limitation of this present study was its retrospective nature and the small sample size of both the endometriosis and the PGT-M cohort. The study was powered to detect a 20% difference in live birth, and it is possible that a smaller difference exists. Some studies have indicated the stage of endometriosis may impact implantation and live-birth rates, with worsening outcomes with increased stage (26). Although all patients in the endometriosis cohort had a surgical diagnosis, staging was not documented in all cases, so we were unable to assess the effect of stage on pregnancy outcomes. Also, patients in the MF and PGT-M cohorts had not undergone laparoscopy, so patients with mild endometriosis may have been included in this group.

To our knowledge, this is the largest study to assess the impact of surgically diagnosed endometriosis on live birth in euploid blastocysts vitrified embryo transfers. The high live-birth rate in endometriosis patients did not suggest a negative effect. Overall, the results from our study may provide reassurance regarding good prognosis for live birth when endometriosis patients have a euploid blastocyst available for transfer.

are not aware of data suggesting that infertility increases the risk of aneuploidy.

Further studies have attempted to identify alterations in the endometrium that may result in poor pregnancy outcomes in patients with endometriosis. Lessy et al. (12) aimed to identify endometrial biomarkers that could induce changes in gene expression and receptivity. They demonstrated expression of $\alpha v\beta 3$ integrin, which peaks at the onset of uterine receptivity, to be diminished or absent in patients with endometriosis. Other studies have suggested progesterone and estrogen signaling is disrupted in these patients, with endometrial tissue failing to respond properly to progesterone exposure (13). This imbalance may decrease endometrial receptivity by failing to counteract the estrogen-induced proliferation and subsequent decidualization.

In our study, only euploid blastocysts were transferred, allowing us to better assess the receptivity of the endometrium. All clinical outcomes including clinical pregnancy, pregnancy loss, and live birth were similar in patients with endometriosis compared with patients in treatment for MF and those undergoing PGT-M. There is evidence to suggest the eutopic endometrium in patients with endometriosis exhibits characteristics of progesterone resistance, aberrant cell signaling, and reduction of homeostatic proteins, which could result in a decrease in endometrial receptivity (24). Other studies have shown ovarian suppression with GnRH agonists or oral contraceptive pills can normalize alterations in the endometrium of patients with endometriosis by reducing angiogenesis, cell proliferation, vascular endothelial growth factor secretion, and aromatase production (25). The results of our study did not suggest decreased implantation or live birth in patients with endometriosis undergoing euploid embryo transfer. However, because the patients in our study were undergoing ovarian suppression, we cannot extrapolate these results to fresh embryo transfer cycles or natural conception.

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