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ORIGINAL ARTICLE

Infertile patients with inflammatory bowel disease have comparable in vitro fertilization clinical outcomes to the general infertile population

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ABSTRACT

To assess clinical outcomes of females diagnosed with Inflammatory Bowel Disease (IBD) and infertility, which underwent in vitro fertilization (IVF) with preimplantation genetic testing for aneuploidy. (PGT-A). Retrospective cohort study comparing clinical outcomes of patients with Inflammatory bowel disease who underwent IVF with PGT-A with a subsequent euploid single embryo transfer (SET) against a matched control group. Thirty-eight patients with an IBD diagnosis were compared to 114 controls. There was no significant difference in cycle outcomes among IBD and Control cohorts [implantation rate (71.0% vs. 78.0% ($p = .68$)], clinical pregnancy rate [50.0% vs. 60.5% ($p = .68$)], live birth [62.9% vs. 73.0% ($p = .06$)] multiple pregnancy rate [0% vs. 1.1% ($p = .25$)] and clinical pregnancy loss rate [10.5% vs. 5.7% ($p = .54$)]. An IBD diagnosis was not found to significantly modify the odds of implantation [adjusted OR = 0.6 (95% CI −1.2 to 0.8)]. Additionally, the odds of implantation in patients with IBD were not altered by having ulcerative colitis or Crohn's disease diagnosis. (OR = 0.4 95% CI 0.1–1.9). Patients diagnosed with IBD who undergo a SET have clinical outcomes comparable to the general infertile population. Patients and physicians can be reassured that an IBD diagnosis does not impair IVF treatment outcomes.

SYNOPSIS

Infertile patients with inflammatory bowel disease who utilized a single, euploid blastocyst transfer had IVF success rates comparable to the general infertile population.

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Introduction

Inflammatory bowel disease (IBD) is a disease that involves chronic inflammation of the digestive tract. IBD is common among adults between 15 and 40 years of age and affects more than 1 million people in the US [1]. Active IBD throughout a women's reproductive years may decrease fertility and fecundity [2].

IBD patients treated by surgery are at risk of tissue scarring and adhesion formation on the pelvic cavity that could lead to tubal infertility factor [3]. Even without surgical intervention, IBD can cause inflammation in the fallopian tubes or ovaries. The reduction in IVF success of IBD patients has been associated to the dysregulated immune response triggered by unknown environmental stimuli and is especially apparent in genetically susceptible individuals [4]. Classically, the adaptive immune response has been considered to play a major role in the pathogenesis of the disease and physiological processes such as embryo implantation [5,6]. The immune response mediated by T-cells may play an important regulatory role in the establishment of fetal tolerance during early pregnancy, development of placental trophoblasts to create the maternal/fetal interface, and promotion of embryo implantation [7,8].

Currently, there is limited data assessing endometrial receptivity and implantation rates in IBD patients who undergo IVF with PGT-A treatment. This study aims to assess cycle outcomes of IBD patients who undergo ART treatment that controls for embryonic ploidy, embryo transfer count, and endometrial environment.

Material and methods

Study design and patient populations

A single center, retrospective, cohort analysis of infertility patients who completed an IVF cycle with preimplantation genetic testing for aneuploidy (PGT-A); followed by a synthetic endometrial preparation and single-euploid embryo transfer (SET) cycle from January 2012 to January 2018.

Natural language processing and artificial intelligence algorithms were used to parse the study site's electronic medical records and identified women with an inflammatory bowel disease diagnosis [Crohn's disease (CD) and ulcerative colitis (UC)]. Diagnosis was manually confirmed from the review of patient self-reported records, referral letters, and clinical records.

A matched 3:1 cohort of control subjects were identified using a propensity-score matching algorithm based on clinical parameters including: oocyte age at retrieval, BMI, and ovarian reserve markers [anti-Müllerian hormone (AMH); basal antral follicle count (BAFC)]. Cases involving fresh transfer and/or multiple

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embryos were excluded. Also, uterine factor infertility diagnosis, ovum donation recipients, recurrent pregnancy loss, recurrent implantation failure, active hydrosalpinges, and severe male factor infertility were excluded from the analysis.

Stimulation protocol

Patients underwent conventional controlled ovarian stimulation for IVF [9,10]. Follicular development was measured transvaginally. When ≥2 mature follicles reached 18 mm, final oocyte maturation was induced with human chorionic gonadotropin (hCG) (10,000 IU, Novarel, Ferring Pharmaceuticals, Parsippany, NJ), recombinant human Chorionic Gonadotropin 250 µg (Ovidrel, EMD Serono, Rockland, MA), or Dual trigger with 2 mg of leuprolide acetate (Lupron, AbbVie Laboratories Chicago, IL) combined with 1000 IU hCG. Patients underwent vaginal oocyte retrieval under transvaginal ultrasound guidance 36 h after oocyte maturation was triggered.

Laboratory procedures

All metaphase II oocytes were fertilized with intracytoplasmic sperm injection (ICSI). Embryos were cultured to the blastocyst stage [9]. Trophectoderm biopsies were performed on day 5 or 6 of embryo development, contingent on embryo expansion and reaching a grade of ≥4BC (modified Gardner morphological score) [10]. Chromosome copy number analysis was performed with quantitative real time polymerase chain reaction (qPCR), and/or next-generation sequencing-based analysis (Next-Gen seq.). Biopsied embryos received a genetic interpretation of euploid, aneuploid or other [11].

Blastocysts were vitrified and cryopreserved immediately after trophectoderm biopsy (Cryotop method – Kitazato Corp., Shizuoka, Japan), and rewarmed [9,11].

Endometrial preparation and embryo transfer

Embryo transfers were performed under a synthetically prepared endometrium [9,10]. The uterine cavity was prepared with micronized oral estradiol (Estrace, Teva Pharmaceuticals, Fairfield, NJ) 2 mg twice daily for 4 days, then 2 mg three times daily. Serial transvaginal ultrasounds assessed endometrial lining. A thickness of ≥7 mm prompted a daily 50 mg intramuscular injection of oil-based progesterone (Watson Pharma Inc, Parsippanyu, NJ). Embryo rewarming and transfer occurred on the sixth day of progesterone supplementation. Transfer selection was based on embryo PGT results and morphology grading [10].

Statistical methods

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) Descriptive data was compared by unpaired two-sided Student's t test and Chi squared test. Results were expressed as means and standard deviations (DE) with Clopper-Pearson binomial 95% confidence intervals (95% CI). Adjusted odds ratios (OR) with 95% CI were calculated using univariate and multivariate logistic regression analyses to assess IBD diagnosis effect on the odds of implantation, clinical pregnancy, pregnancy loss, live birth, and multiple pregnancy. The logistic and linear regression models were fitted with generalized estimating equations (GEE) to account for patients who underwent multiple frozen-thawed embryo transfer (FET) cycles. Clinically relevant variables were included as covariates in the model. p values are two sided with significance set at $p < .05$.

Power analysis

To examine the effect of IBD diagnosis on embryo transfer outcomes, the study sample size provided an 80% power to detect a 25% difference in implantation rates ($\alpha = 0.05$).

Regulatory approval

The study was approved by an Institutional Review Board.

Results

A total of 3,274 single, euploid embryo transfer cycles were performed in 2,437 patients. A 1.1% ($n = 38$) IBD prevalence was observed in this population. Of these 38 FET cycles, 50% ($n = 19$) had ulcerative colitis (UC) and 50% ($n = 19$) had Crohn's disease (CD). A propensity score matched population of 114 control patients was included in the analysis.

A comparison analysis showed no statistical differences in gravidity, age, BMI, day 3 FSH, LH, AMH, antral follicle count, endometrial thickness, and endometrial pattern at embryo transfer ($p \geq .05$). Further demographics are listed on Table 1.

When comparing IBD patients versus controls, no significant differences were found in implantation: 71% ($n = 21$) vs. 78% ($n = 89$), ($p = .37$, OR 0.68 95% CI = 0.3–1.5); clinical pregnancy: 50% ($n = 19$) vs. 60.5% ($n = 69$), ($p = .44$, OR 0.68 95% CI = 0.2–1.8); clinical pregnancy loss: 10.5% ($n = 2$) vs. 5.7% ($n = 4$), ($p = .54$, OR 1.7 95% CI =0.29–9.8), live birth: 62.9% ($n = 17$) vs. 73.0% ($n = 65$), ($p = .60$, OR 0.80 Ci95% = 0.03–20.54)

Table 1. Demographic characteristics of patients with inflammatory bowel disease (IBD) and control group.

	Inflammatory bowel disease group	NO IBD group	
	$N = 38$	$N = 114$	p Value
Oocyte age	34.5 (4.3)	34.6 (3.8)	.9
Body mass index	22.6 (3.1)	23.5 (3.9)	.2
Baseline FSH (IU mL^{-1})	6.1 (2.3)	5.6 (2.9)	.4
Baseline LH (mIU mL^{-1})	4.1 (2.1)	3.6 (2.5)	.3
Anti Müllerian hormone (ng mL^{-1})	3.23 (2.8)	4.5 (5.4)	.1
Basal antral follicle count	12.2 (8.4)	11.4 (7.5)	.6
Endometrial thickness (mm)	9.4 (1.7)	9.1 (1.8)	.3
Previous oocyte retrievals	1.63 (1.28)	1.5 (1.03)	.7
Gravida	1.0 (1.4)	1.2 (1.4)	.5
Parity	0.3 (0.5)	0.5 (0.8)	.09

Results are expressed as mean ± standard deviations. Significance established at $p < .05$.

and multiple pregnancy rates: 0% vs. 1.1% ($n = 1$), ($p = .58$, OR1.07 95% CI = 0.3–0.5) (Table 2).

An IBD diagnosis was not associated with the odds of implantation ($\beta = -0.23$, adjusted OR = 0.79 [95% CI −1.2 to 0.8] $p = .66$) during the multivariate logistic regression analysis that utilized a GEE model and adjusted for age, AMH, BMI, endometrial thickness, and pattern at transfer.

A sub analysis compared the effect on implantation rates in patients with CD or UC. A significant difference in BAFC (CD: 15.7 ± 9.2 vs. UC: 9.11 ± 6.2, $p = .02$) was observed between IBD types. No other significant difference in patient demographics was found (Table 3). In an unadjusted comparison of CD and UC, similar implantation (63% vs. 78%), clinical pregnancy (58% vs. 80%), live birth (50% vs. 73.3%) and clinical pregnancy loss rates (14.2% vs. 8.3%) were observed. No multiple pregnancies were observed (Table 3). When adjusting for age, BMI, AMH, BAFC and endometrial thickness at ET, the odds of implantation were not altered by IBD patients having either a CD [63% ($n = 12$)] or UC diagnosis [78% ($n = 15$)] (OR = 0.4, 95% CI = 0.1–1.9, $p = .29$).

Discussion

IVF is a safe and effective approach for IBD patients. It appears IBD patients and the general infertility populations have comparable IVF success rates.

To date, this study assessed the largest cohort of SET in patients with IBD. The 1.1% prevalence of IBD found in this study population is consistent with US reports of 1.3% issued by the Center for Disease Control and Prevention [12].

Our study results are comparable to a study published by Pabby et al., which demonstrated patients with UC who underwent IVF had live birth rates (LBR) of 64%, compared to 71% in a UC nonsurgery group, and a 53% in a control group [13]. Additionally, it has been suggested that women who experience infertility and IBD can expect implantation rates of 60%, which is a similar rate experienced by women without IBD [14]. This study demonstrated higher implantation rates (71%) and live birth rates (73%) in IBD patients, which could be attributed to advances in embryo screening techniques. Our study model eliminates former confounders [15–17] by controlling for embryonic and endometrial factors, crucial drivers for implantation.

Furthermore, this study controlled for baseline and demographic characteristics, eliminating potential confounders. When using a logistic regression analysis, an IBD diagnosis did not impair implantation potential (Adjusted OR = 0.79 [95% CI −1.2 to 0.8] $p = .66$). When IBD patients were segregated by disease type (CD vs. UC), a statistically significant difference in BAFC (CD: 15.7 ± 9.2; UC: 9.11 ± 6.2, $p = .02$) was observed. However, this finding did not affect implantation, clinical pregnancy, live birth rate, and pregnancy loss. This study's findings must be taken with caution as the sub analysis was underpowered to detect small differences for these outcomes. Still, when using a complex regression analysis that controlled for age, BMI, AMH, BAFC, endometrial thickness at ET, and previous IVF cycles; no significant association was observed between IBD disease type and implantation potential (OR = 0.4 95% CI 0.1–1.9).

Study limitations exist within our analysis. As a retrospective study there are increased chances of selection bias, however we minimized this risk by utilizing machine learning processes with a large dataset to narrow our study population. Also, our statistical analyses controlled for age, BMI, ovarian reserve markers, type of inflammatory bowel disease, and other clinical variables of importance.

Heterogeneity of treatments was found throughout the study population. The observational nature of this study did not allow for a comprehensive assessment of the prior surgery or prescribed medications prior to IBD patient ART treatment. Thus, prior clinical intervention on IVF success rates was unable to be assessed. However, published comparative analyses have found no differences between specific types of surgery and the ability for IBD patients to conceive or achieve IVF success [13,14,18,19].

Another study limitation is measuring IBD severity or disease activity. IBD assessment is not comprehensively evaluated. Thus, there are multiple tools for disease's severity assessments such as the Truelove and Witts Index, the Powell Tuck index, the retrospective partial Mayo Score index for UC, and the Clinical Disease Activity Index (CDAI) for CD [20]. None of these

Table 2. Clinical outcomes of IBD patients versus control group using a euploid SET-FET model.

Outcome rate	IBD ($N = 38$)	No IBD ($n = 114$)	p Value	OR (95% CI)
Implantation	27 (71%)	89 (78%)	.37	0.68 (0.3–1.5)
Clinical pregnancy	19 (50%)	69 (60.5%)	.44	0.68 (0.2–1.8)
Clinical Pregnancy loss	2 (10.5%)	4 (5.7%)	.54	1.7 (0.29–9.8)
Multiple pregnancy	0	1 (1.1%)	.58	1.07 (0.3–0.5)
Live birth	17 (62.9%)	65 (73.03%)	.60	0.80 (0.03–20.54)

Data presented as n (%), unless specified otherwise. Binomial confidence intervals for all reported proportions. Adjusted odds ratios (OR) and their 95% confidence intervals (CI).

Table 3. Demographic characteristics of patients with inflammatory bowel disease (IBD) and clinical outcomes of IBD patients by specific type of disease (Crohn's disease versus ulcerative colitis) using a euploid SET-FET model.

	Crohn's disease		Ulcerative colitis		
	$n = 19$		$n = 19$		p Value
Patient age	33.32482	4.258029	35.76214	4.113343	.08
Body mass index	22.86229	3.537119	22.46418	2.781947	.72
Baseline FSH (IU mL^{-1})	6.0825	1.887621	6.2264	2.687292	.87
Baseline LH (mIU mL^{-1})	4.743333	2.470073	3.749	1.88473	.24
Anti Müllerian hormone (ng mL^{-1})	3.7797	3.933598	2.9355	2.166992	.54
Basal antral follicle count	15.73333	9.284908	9.117647	6.283733	.02*
Endometrial thickness at FET (mm)	9.752632	2.099304	9.185263	1.176055	.31
History of colon surgery (%)	21%	4\19	36.80%	7\19	.28
Implantation rate	63%	12/19	78%	15/19	.28
Clinical pregnancy rate	58%	7/12	80%	12/15	.22
Clinical pregnancy loss rate	14.2%	1/12	8.3%	1/15	.87
Multiple pregnancy rate	0%	$N = 0$	0%	$N = 0$	–
Live Birth rate	50%	6/12	73.3%	11/15	.10

Data presented as n (%), unless specified otherwise. Binomial confidence intervals for all reported proportions. Significance established at $p < .05$ FET = frozen euploid embryo transfer; IVF = in vitro fertilization.

assessments were incorporated during IVF stimulation or endometrial preparation cycles because of limited clinical, serological and hystopathological data of IBD activity within patient medical records. Nevertheless, based on previously published practices, patients included in the analysis were categorized to be under clinical remission and medically cleared before starting ART treatment [21,22].

The study was unable to measure the correlation of serum or endometrial inflammatory markers during stimulation or during frozen embryo transfer cycles. Future studies would benefit to include this measurement to improve the reproductive medical community's knowledge about the relationship between molecular pro-inflammatory markers and endometrial receptivity [23]. Last, this study did not have the ability to track and report perinatal outcomes other than live birth, as patients were discharged to various obstetrical practices after the successful clinical pregnancy state was diagnosed.

Our study has several strengths. We use clinically validated PGT-A techniques to assess the rates of embryonic ploidy for all embryos transferred [24,25]. Additionally, our methodology and application of a multilevel modeling framework by utilizing a GEE algorithm to account for repeated measures within our patient cohorts gives strength to our study results.

Patients can be reassured that although tubal disease is common, IBD is not associated with compromised endometrial receptivity or embryonic implantation potential. Although the inflammatory pathways differ in CD and UC, IBD type did not alter the potential for IVF success. IBD patients and the general infertile population have comparable IVF cycle outcomes when employing a single, euploid frozen embryo transfer.

Further investigation with randomized clinical trials with adequate power, long-term follow up, and a cohesive IBD population undergoing assisted reproduction techniques should be performed in order to find more accurate information about the effect of this disease on IVF outcomes and offspring development.

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Disclosure statement

The authors report no conflict of interest.

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