Irritable Bowel Syndrome: Adverse Impact on Patients Undergoing Euploid Embryo Transfer

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Objective: *To evaluate the effect of irritable bowel syndrome (IBS) on pregnancy outcomes in patients undergoing single euploid embryo transfers.*

Methods: *This is a retrospective cohort study at a reproductive medicine center. The study included 59 patients with IBS matched with 1406 patients without IBS who underwent single euploid embryo transfer. Main outcomes included live birth rate, pregnancy loss rate, and clinical pregnancy rate.*

Results: *The positive pregnancy rate was 67.7% in the IBS group and 71.0% in the control group. The clinical pregnancy rate was 45.8% in the IBS group and 63.0% in the control group. The live birth rate was 40.8% in the IBS group and 56.3% in the control group. The pregnancy loss rate was 38.5% in the IBS group compared to 21.3% in the control group. The adjusted odds of clinical pregnancy were 52.1% lower in patients with IBS (OR 0.479, 95% CI: 0.27, 0.82). The adjusted odds of live birth were 47.8% lower in patients with IBS (OR 0.52, 95% CI: 0.30, 0.90). The adjusted odds of pregnancy loss were 2.32 times higher in patients with IBS (OR 2.32, 95% CI: 1.16, 6.45).*

Conclusion: *In patients who underwent single euploid embryo transfer, patients with IBS had a lower likelihood of clinical pregnancy and live birth when compared to patients without IBS. Patients with IBS also had a higher likelihood of pregnancy loss. With little currently known about the effect of IBS on pregnancy outcomes, this study provides insight and suggests that IBS may have an adverse effect on pregnancy outcomes.*

BACKGROUND

Irritable Bowel Syndrome (IBS) is one of the most common gastrointestinal disorders and is more prevalent in women.[1] The estimated prevalence is about 10-15% in Western countries; [2,3] however, the actual prevalence is likely greater as there is often a delay to diagnosis and only about 25% of patients seek medical care.[3]

While the pathophysiology of IBS is unclear, some suggested mechanisms include visceral hypersensitivity, psychological dysfunction, and immunoinflammatory disturbances, such as cytokine dysregulation.[1,4] It has been suggested that factors relating to disturbances in immune regulators may have an adverse effect on pregnancy outcomes. For example, Challis et al described that an abnormal balance of cytokines may initiate and intensify an inflammatory response resulting in adverse pregnancy outcomes, such as spontaneous abortion and preterm delivery (Challis et al).5 Given this potential adverse effect of inflammatory disturbances on pregnancy outcomes, it is thought that IBS, a pro-inflammatory disorder, may negatively impact pregnancy.

In a retrospective study, Khashan et al found that maternal IBS was associated with an increased risk of miscarriage and ectopic pregnancy.[1] Likewise, Alnoman et al found that women with IBS were more likely to have pregnancies complicated by hypertensive disorders, gestational diabetes and deep venous thromboses (DVTs). They also found

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that women with IBS were more likely to have had pregnancies via in vitro fertilization (IVF) (Alnoman et al).6 While these prior studies offer some insight, they are also limited by confounding factors such as maternal age and heterogeneity in the study population. There is an overall lack of literature surrounding IBS and pregnancy outcomes, especially in patients undergoing assisted reproductive technology (ART).

Given its large prevalence in women, there should be a greater understanding of IBS and its impact on pregnancy outcomes. ART offers the opportunity to study patients in an environment where components impacting implantation and pregnancy rates, such as aneuploidy or uterine factor infertility, are better controlled. In this study, we aim to evaluate the effect of IBS on pregnancy outcomes in patients undergoing single euploid embryo transfers.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

The institutional review board at Weill Cornell Medical College approved our study protocol. For this retrospective cohort study, all patients undergoing single euploid frozen embryo transfer at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine between January 2018 and December 2022 were assessed for potential inclusion. The study group included patients with a diagnosis of IBS, which had previously been recorded as part of the patients past medical histories. Patients with other inflammatory bowel disorders, uterine factor and severe male factor infertility were excluded. The control group included age-matched patients without IBS who underwent single euploid embryo transfer during the same time period.

Clinical and Laboratory Protocols

Ovarian stimulation, trigger for final oocyte maturation, oocyte retrieval, embryo culture, and embryo transfer (ET) were performed per our standard protocols.[7] Ovarian stimulation was carried out to maximize follicular response while minimizing the risk of ovarian hyperstimulation syndrome (OHSS). The initial gonadotropin dose was based on age, weight, antral follicle count, anti-mullerian hormone (AMH) and previous response to stimulation. Ovarian stimulation was carried out with a combination of gonadotropins (Follistim, Merck, Kenilworth, NJ, USA; Gonal-F, EMD-Serono, Geneva, Switzerland; and/or Menopur, Ferring Pharmaceuticals Inc, Parsippany, NJ, USA), with ovulation being suppressed with once daily 0.25 mg Ganirelix Acetate (Merck, Kenilworth, NJ, USA) or Cetrotide (EMD-Serono, Geneva, Switzerland) injections.[7]

Human chorionic gonadotropin (hCG) and GnRH agonist triggers were used either alone or combined as the ovulation triggers. Novarel (Ferring Pharmaceuticals Inc, Parsippany, NJ, USA) or Pregnyl (Merck, Kenilworth, NJ, USA) was administered according to a sliding scale (10000 IU for E2<1500 pg/mL, 5000 IU for E2 1501–2500 pg/mL, 4000 IU for E2 2501–3000 pg/mL, and 3300 IU for E2>3001 pg/mL) when given as the sole trigger (Huang et al).7 The trigger was given when the two lead follicles attained at least a mean diameter >17 mm. Oocyte retrieval was performed with transvaginal ultrasound guidance under conscious sedation approximately 35–36 hours after trigger administration. All retrieved oocytes were exposed to 40 IU recombinant hyaluronidase (Cumulase, Halozyme Therapeutics Inc., San Diego, CA, USA) to remove the cumulus-corona complex.[8,9]

Our center routinely performs intracytoplasmic sperm injection (ICSI) for patients undergoing IVF for preimplantation genetic testing for aneuploidy (PGT-A). Sperm injection was carried out based on previously described protocols.[8,9] The spermatozoon selected for injection was based on head morphology, midpiece and flagellar shape, and dynamic characteristics such as swimming patterns and progression.[8,9] Oocytes were examined 12–17 hours after ICSI for the presence of two distinct pronuclei (PN) and two clear polar bodies. All embryos were cultured using in-house culture media and were frozen and biopsied on day 5 or day 6 (blastocyst stage). PGT-A was performed based on previously described protocols.[10]

Patients underwent either natural cycle or programmed frozen embryo transfer (FET) based

on clinical history. For natural cycle FET, patients were monitored for ovulation. Embryo transfer was performed 5 days after the natural luteinizing hormone (LH) surge. Vaginal progesterone (P) suppositories 100mg were taken twice a day starting the morning after embryo transfer. For programmed FET cycles, patients underwent endometrial preparation based on previously described protocols.[11,12] Briefly, patients were prepped with leuprolide acetate in the luteal phase. Transdermal E2 patches (0.1 mg) were initiated on the second day of menses and serially increased up to a dose of 0.4 mg until an endometrial thickness of ≥7 mm was attained. Patients were then started on progesterone with a starting dose of 25 mg intramuscularly (IM) for one night and followed thereafter by 50 mg IM daily, and the E2 dose was decreased to 0.2 mg. E2 and P levels were measured after transfer to confirm the adequacy of the supplementation. Luteal support was continued until 10-12 weeks of gestation. All ETs were performed with Wallace catheters (Smiths Medical Inc., Norwell, MA, USA) at approximately 1-2 cm less than the uterine depth identified at prior trial transfer and under ultrasound guidance.

Study Variables

Demographic and baseline characteristics recorded for all recipients include age, body mass index (BMI) (kg/m2), gravidity, parity, peak endometrial thickness (mm), type of transfer cycle (programmed vs. natural). All clinical pregnancies were confirmed using transvaginal ultrasonography, noting the number of gestational sacs and fetuses with cardiac activity.

The primary outcome was live birth rate. Secondary outcomes included positive pregnancy rate, clinical pregnancy rate and pregnancy loss rate. Positive pregnancy rate was defined as the presence of a positive hCG level on CD 29 (serum level >5 mIU/mL).

Clinical pregnancy rate was defined as the presence of an intrauterine gestational sac. Any birth prior to 24 weeks was considered a pregnancy loss. Any birth after 24 weeks of gestation was considered a live birth.

Statistical Analyses

Descriptive statistics were used to characterize the study sample with respect to demographic and clinical factors of interest. Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as n (%). Where appropriate, the paired t-test were used to examine the association between demographic/clinical variables of interest. Mixed-effects logistic regression models were used to evaluate the independent effect of IBS on pregnancy, implantation, and live birth rates. All p-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in Stata BE 17.0 (StataCorp LLC).

RESULTS

There were 59 patients with a confirmed history of IBS who underwent single euploid embryo transfer during the study period. There were 1406 patients in the control group. The average maternal age was 35.36 in the IBS group and 35.25 in the control group (p = 0.79). There were more patients in the control group who had previously been pregnant (69% vs. 47%, p 0.002) and given birth (37% vs. 15%, p< 0.001). The groups were similar for BMI, type of transfer cycle (programmed vs. natural), and peak endometrial stripe thickness Table 1.

Pregnancy outcomes are displayed in Table 2. In the initial analysis, the live birth rate was significantly lower in the IBS group compared to the control group (40.8% vs 56.3%, p = 0.01). The clinical pregnancy rate was significantly lower in the IBS group compared to the control group (45.8% vs 63.0%, p = 0.01). The positive pregnancy rate was similar between the IBS and control groups (67.7% vs. 71.0%, p = 0.60). The pregnancy loss rate was significantly higher in the IBS group (38.5% vs. 21.3%, p = 0.02).

Mixed effects logistic regression was performed to account for confounding variables Table 2. The adjusted odds of clinical pregnancy were 52.1% lower in patients with IBS (OR 0.479, 95% CI: 0.27, 0.82). The adjusted odds of live birth were 47.8% lower in patients with IBS (OR 0.52, 95% CI: 0.30, 0.90). The adjusted odds of pregnancy loss were

Table 1. Baseline Demographics.

	IBS (n = 59)	Control (n = 1406)	p-value
Maternal age	35.36	35.25	0.79
Gravid	28 (47%)	974 (69%)	0.002
Parity	9 (15%)	524 (37%)	<0.001
BMI	20.93	22.38	0.068
Type of transfer cycle			0.76
Programmed	26 (44%)	490 (35%)	
Natural	33 (56%)	916 (65%)	
Peak endometrial stripe thickness (mm)	9.02	9.15	0.6

Note: Values are average or number (percentage)
BMI = body mass index

Table 2. Pregnancy Outcomes

	IBS	Control	P-value*	Adjusted Odds Ratio**
Positive pregnancy rate	67.70%	71.00%	0.6	0.79, 95% CI [0.44, 1.40]
Clinical pregnancy rate	45.80%	63.90%	**0.01**	0.48, 95%CI [0.27,0.82]
Pregnancy loss rate	38.50%	21.30%	**0.02**	2.32, 95%CI [1.16, 6.45]
Live birth rate	40.80%	56.30%	**0.01**	0.52, 95% CI [0.30, 0.90]

* p-value determined by paired t test
** Odds ratio comparing IBS patients to controls adjusted by maternal age, type of transfer cycle (programmed vs. natural), BMI, gravidity, parity, peak endometrial strip thickness.

2.32 times higher in patients with IBS (OR 2.32, 95% CI: 1.16, 6.45). There was no difference in the positive pregnancy rate (OR 0.79, 95% CI: 0.44, 1.40).

DISCUSSION

In this retrospective study, we found that despite having a similar likelihood of a positive pregnancy test, patients with IBS had a lower likelihood of clinical pregnancy and live birth compared to patients without IBS. We also found that patients with IBS had a higher likelihood of pregnancy loss. There is limited data evaluating pregnancy outcomes in patients with IBS. To our knowledge, there has been no prior study comparing pregnancy outcomes in patients with IBS undergoing IVF. The current studies involving IBS and ART focus on patient symptoms during IVF treatment.[13] By evaluating single euploid embryo transfers, we are controlling for aneuploidy, which is a major factor that can affect pregnancy outcomes. We also only evaluated patients without uterine factor or male factor infertility. While we evaluated both natural and programmed transfer cycles, there was no difference in type of transfer cycle between the IBS and control groups. Peak endometrial thickness was also similar between the two groups. Additionally mixed effects logistic regression was performed to account for other confounding variables, such as gravidity and parity.

IBS is estimated to affect 10-15% of the United States population and is two times more common in women than in men, particularly in women of childbearing age.2,14 While the pathophysiology is not completely understood, abnormalities in the mucosal enteroendocrine system and systemic

immune responses, including increase immune activation, have been suggested to participate in the brain-gut dysfunction found in IBS.[15]

The immune system plays a critical role in pregnancy, as it is both a pro-inflammatory and anti-inflammatory condition.[16] Maternal and placental hormones likely affect inflammatory pathways and changes in this system could therefore affect pregnancy outcomes. For example, hypoxia and the innate immune response are two mechanisms by which humans respond to disruptions in organ function, which in theory could lead to miscarriage, intrauterine growth restriction, preeclampsia, and preterm delivery.[5] Various inflammatory conditions, such as endometriosis, have already been shown to be associated with higher rates of infertility and adverse pregnancy outcomes. It is therefore easy to suggest that IBS, another pro-inflammatory disorder, could have a negative impact on pregnancy.

There are very few studies that look at pregnancy outcomes in patients with IBS. A large population-based retrospective by Alnoman et al found increased rates of pregnancy induced hypertension, gestational diabetes and DVTs in patients with IBS.

They did not find a difference in pregnancy outcomes such preterm delivery, placenta abruption, or preterm premature rupture of membranes.[6] This study however did not look at the effect of IBS on miscarriage rates or live birth rates. Another earlier study by Khashan et al found that patients with IBS had higher miscarriage and ectopic pregnancy rates, however similar rates of preeclampsia and still birth compared to patients without IBS.[1] Our study also found that women with IBS have higher rates of pregnancy loss. More specifically, women with IBS were 2.3 times more likely to have a pregnancy loss and also approximately 50% less likely to have a live birth compared to patients without IBS. Unlike the study by Khashan et al, we were able to adjust for various confounding variables that can affect implantation, such as aneuploidy or uterine abnormalities, by evaluating only patients who underwent euploid embryo transfer with confirmed normal uterine cavities

There is also a possible association between IBS and infertility. In a review article by Anton et al, the authors propose that oxidative stress might lead to infertility in IBS patients, although there is overall a lack in evidence (Anton et al).[17] In our study, compared to patients with IBS, we found that the control group was more likely to have previously been pregnant and given birth. While more research is needed, our findings suggest that patients with IBS may have higher rates of infertility. Limitations of the study include a small sample size. As a retrospective study based on chart review, the study is limited in access to data dependent on provider documentation and patient follow up. Given that an IBS diagnosis was dependent on physician documentation, this may contribute to the small number of patients seen in the study group. Additionally, the diagnosis of IBS is difficult and patients may be misdiagnosed. We were also unable to account for severity of disease or if patients were on medications. Although the BMI among study participants was normal, we were also unable to fully assess the nutritional status of these patients. Future research should prospectively evaluate pregnancy outcomes in patients undergoing IVF with IBS, taking into consideration severity of disease. It would also be interesting to prospectively evaluate how IBS related symptoms change during IVF and pregnancy.

CONCLUSIONS

In patients who underwent single euploid embryo transfer, our study found that patients with IBS had a lower likelihood of clinical pregnancy and live birth when compared to patients without IBS. Patients with IBS also had a higher likelihood of pregnancy loss. With little currently known about the effect of IBS on pregnancy outcomes, this study provides insight and suggests that IBS has an adverse effect on pregnancy outcomes.

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