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**Key Words:** Inflammatory Bowel Disease (IBD); Embryo Implantation; pre-implantation genetic testing (PGT); in vitro fertilization (IVF); frozen embryo transfer (FET)

**Category:** Clinical Science // Female (in) fertility

**Title: PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD) HAVE SIMILAR REPRODUCTIVE OUTCOME COMPARED TO THE GENERAL INFERTILE POPULATION.**

**Study Question: 25:** Is reproductive outcome compromised in patients with IBD who undergo IVF with transfer of single euploid blastocyst?

**Summary Answer: 25:** IBD Patients who pursue a single euploid embryo transfer have similar odds of implantation, clinical pregnancy and pregnancy loss compared to the general infertile population.

**What is known already: 100:** Often, women with IBD experience challenges to family building throughout the course of their reproductive years. Patients may encounter decreased fertility and fecundity associated with pelvic adhesive disease from surgery and/or by the disease itself. IBD has been postulated to cause infertility due to an adverse autoimmune influence on embryo quality and/or endometrial receptivity. Currently, there is limited data assessing the implantation rate in IBD patients following IVF. This study aims to evaluate embryo transfer outcome in IBD patients who undergo transfer of screened embryos.

**Study design, size, and duration: 75:** This was a retrospective cohort study of patients who underwent IVF with preimplantation genetic testing and subsequent euploid single embryo transfer (SET) of a vitrified-warmed blastocyst in a synthetically prepared endometrial cavity from Jan 2012 to January 2018. Trophectoderm biopsies (Day 5-6) were analyzed by Next-Generation Sequencing or quantitative

Polymerase Chain Reaction (qPCR). A sample size of 36 patients per group was needed to detect a 25% difference in implantation rates with 80% power ( =0.05).

**Participants/materials, setting, and methods: 75**: Natural language processing was used to identify from the electronic medical records a cohort of women with the diagnosis of IBD. A matched 3:1 ratio cohort of control subjects were identified using a propensity-score matching algorithm based on oocyte age, BMI, and ovarian reserve markers. Cases involving the transfer of fresh and/or multiple embryos were excluded. Also, uterine factor infertility, ovum donation, recurrent pregnancy loss, recurrent implantation failure and severe male factor infertility were excluded.

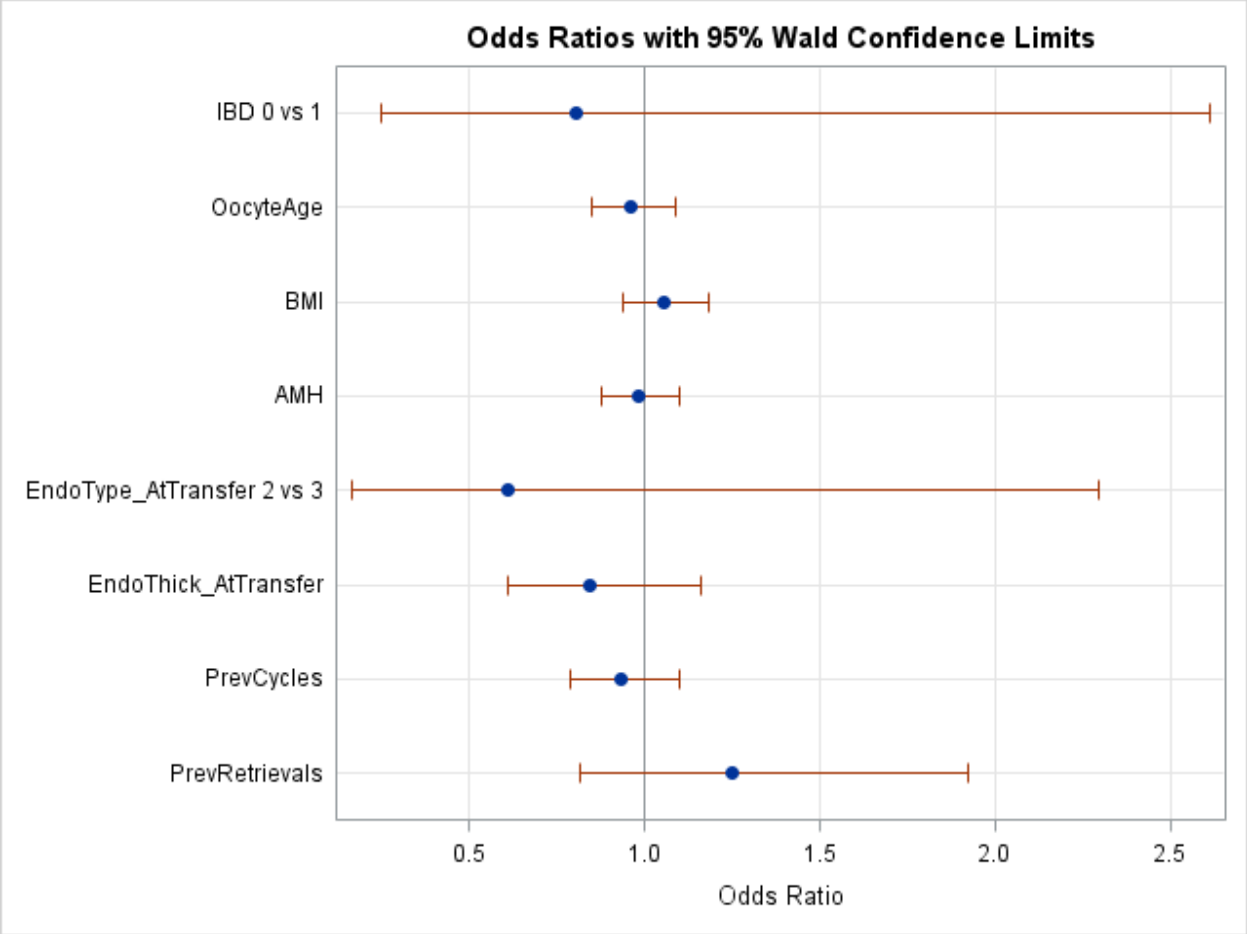
**Main results and the role of chance 200:** Of 3274 euploid, single, vitrified-thawed blastocyst transfers included, 38 patients with an IBD diagnosis were compared to 114 control patients. IBD and control patients had a similar implantation rate (71.0% vs. 78.0% (p=0.68)), clinical pregnancy rate (50.0% vs 60.5% (p=0.68)) and pregnancy loss rate (37% vs 25.8% (p=0.25)) respectively. An IBD diagnosis was not found to significantly modify the odds of implantation (adjusted OR= 0.6 [CI 95% -1.2–0.8]) after the data was evaluated using a GEE model that accounted for patients who underwent multiple cycles and controlled for oocyte age, body mass index , anti-müllerian hormone, basal antral follicle count and endometrial thickness at embryo transfer. Additionally, the odds of implantation were not altered by IBD patients having an ulcerative colitis or Crohn's disease diagnosis. (OR=0.4 CI95% 0.1 – 1.9).

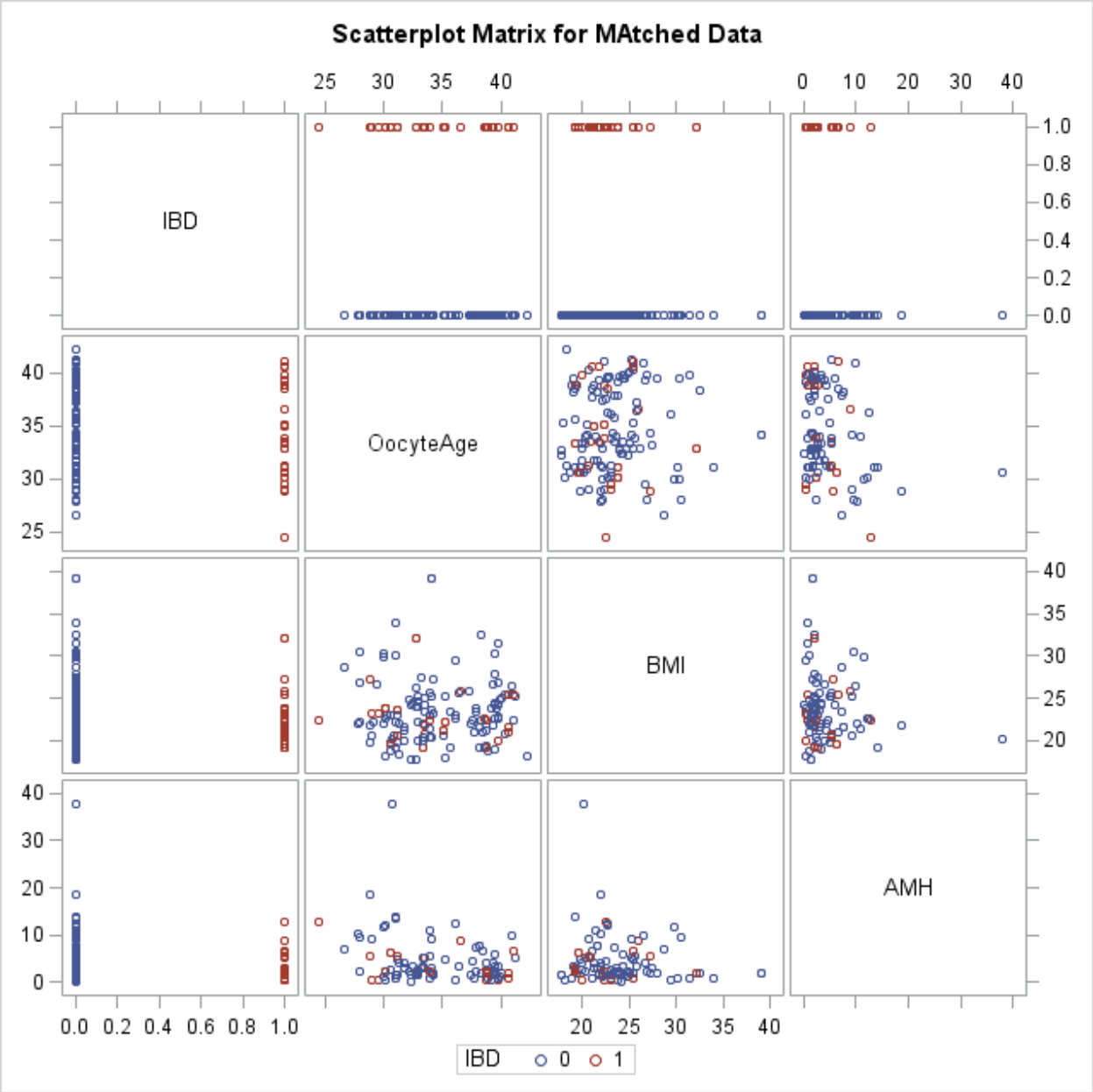
**Limitations, reasons for caution: 50:** We acknowledge the potential weakness of this study. The retrospective nature of the study creates a possible selection bias. The study's current results must therefore be considered with some caution. Larger, well-controlled studies are needed to verify the study's findings.

**Wider implications of the findings**: **50:** Patients who suffer from IBD have comparable embryo transfer outcomes to the general infertile population when pursuing a euploid, single, cryo-thawed embryo transfer. Patients and physicians can be reassured that an IBD diagnosis does not appear to adversely impact embryo quality and endometrial receptivity.

**Study funding/ competing interests:** Not applicable.

**Trial registration number:** This study was approved by the Western Institutional Review Board (Study Number: 1167398).


Odds Ratios with 95% Wald Confidence Limits
IBD 0 vs 1
OocyteAge
BMI
AMH
EndoType_AtTransfer 2 vs 3
EndoThick_AtTransfer
PrevCycles
PrevRetrievals
0.5
1.0
1.5
2.0
2.5
Odds Ratio




| | IBD | NO IBD | p value |
|---|---|---|---|
| | N= 38 | N= 114 | |
| Oocyte age | 34.5 (4.3) | 34.6 (3.8) | 0.9 |
| BMI | 22.6 (3.1) | 23.5 (3.9) | 0.2 |
| D3 FSH | 6.1 (2.3) | 5.6 (2.9) | 0.4 |
| D3 LH | 4.1 (2.1) | 3.6 (2.5) | 0.3 |
| AMH | 3.23 (2.8) | 4.5 (5.4) | 0.1 |
| BAFC | 12.2 (8.4) | 11.4 (7.5) | 0.6 |
| Endo Thinckness | 9.4 (1.7) | 9.1 (1.8) | 0.3 |
| Endo Type | 3 | 3 | 0.53 |

| | | | |
|---|---|---|---|
| Prev IVF cycles | 1.63 (1.28) | 1.5 (1.03) | 0.7 |
| Gravida | 1.0 (1.4) | 1.2(1.4) | 0.5 |
| Para | 0.3 (0.5) | 0.5 (0.8) | 0.09 |

| Outcome | IBD (N=38) | No IBD (n=114) | P value | OR (95% CI) | |
|---|---|---|---|---|---|
| Implantation rate | 27 (71%) | 89 (78%) | 0.37 | 0.68 (0.3 - 1.5) | |
| Clinical pregnancy | 19 (50%) | 69 (60.5%) | 0.44 | 0.68 (0.2 - 1.8) | |
| Early pregnancy loss | 10 (37%) | 23 (25.8%) | 0.25 | 1.68 (0.6 - 4.2) | |
| Multiple pregnancy | 0 | 1 (1.1%) | 0.58 | 1.07 (0.3 - 0.5) | |
| Ongoing pregnancy | 17 (62.9%) | 66 (74.1%) | 0.25 | 0.59 (0.2 - 1.4) | |

| **Analysis Of GEE Parameter Estimates** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Empirical Standard Error Estimates** | | | | | | | |
| **Parameter** | | **Estimate** | **Standard Error** | **95% Confidence Limits** | | **Z** | **Pr > \|Z\|** |
| **Intercept** | | 0.0432 | 2.1762 | -4.2221 | 4.3085 | 0.02 | 0.9841 |
| **IBD** | 1 | -0.2375 | 0.5403 | -1.2965 | 0.8215 | -0.44 | 0.6602 |
| **IBD** | 0 | 0 | 0 | 0 | 0 | . | . |
| **OocyteAge** | | 0.0293 | 0.0532 | -0.075 | 0.1336 | 0.55 | 0.5822 |
| **AMH** | | 0.0482 | 0.0656 | -0.0804 | 0.1768 | 0.74 | 0.4621 |
| **BMI** | | -0.0643 | 0.0453 | -0.1532 | 0.0246 | -1.42 | 0.1561 |
| **EndoType_AtTransfer** | 2 | 0.3703 | 0.5987 | -0.8031 | 1.5436 | 0.62 | 0.5362 |
| **EndoType_AtTransfer** | 3 | 0 | 0 | 0 | 0 | . | . |
| **EndoThick_AtTransfer** | | 0.158 | 0.13 | -0.0968 | 0.4128 | 1.22 | 0.2242 |

| Subanalysis with Crohn=1, UC=0. For implantation rates. | | | | | | |
|---|---|---|---|---|---|---|
| **Analysis of Maximum Likelihood Estimates** | | | | | | |
| **Parameter** | | **DF** | **Estimate** | **Standard Error** | **Wald Chi-Square** | **Pr > ChiSq** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Intercept** | | 1 | -121.3 | 225.6 | 0.2893 | 0.5907 |
| **IBDtypeC** | **0** | 1 | 52.541 | 50.4446 | 1.0848 | 0.2976 |
| **OocyteAge** | | 1 | -12.915 | 12.7252 | 1.03 | 0.3101 |
| **BMI** | | 1 | 14.7323 | 19.8828 | 0.549 | 0.4587 |
| **AMH** | | 1 | -17.515 | 13.7881 | 1.6137 | 0.204 |
| **EndoType_AtTransfer** | **2** | 1 | -74.272 | 80.9551 | 0.8417 | 0.3589 |
| **EndoThick_AtTransfer** | | 1 | 17.2638 | 32.8521 | 0.2762 | 0.5992 |
| **PrevCycles** | | 1 | 3.7408 | 12.0376 | 0.0966 | 0.756 |
| **PrevRetrievals** | | 1 | 21.5409 | 24.9808 | 0.7436 | 0.3885 |