Examining the Impact of the Uterine Microbiome on Reproductive Outcomes

Quetrell Heyward, MD, MBA [a,b,c], Denis Vaughan, MD [a,b,c], Brittany Morse, MSc [a], Daniel Duvall Jr. [a], Denny Sakkas, PhD [a], Alexandra Huttler, MD [a,b,c], Karishma Patel, MD [a,b,c], and Alan Penzias, MD [a,b,c]

[a] Boston IVF-IVIRMA Global Research Alliance, Waltham, MA,
[b] Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA,
[c] Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Boston, MA

BACKGROUND AND OBJECTIVE

- Though the clinical significance of the uterine microbiome is poorly understood, it has been suggested that an imbalance of microorganisms within the reproductive tract can have an impact on reproductive outcomes[1-3]
- The Endometrial Microbiome Metagenomic Analysis/Analysis of Infectious Chronic Endometritis (EMMA/ALICE) test was recently developed to determine 1) the extent of the naturally-occurring bacteria *Lactobacilli* that promote implantation and pregnancy as well as 2) the presence of pathogenic bacteria that can impede favorable outcomes[4-5]
- The purpose of this study was to compare the reproductive outcomes of patients following an endometrial biopsy and EMMA/ALICE assessment of the uterine microbiome

METHODS

- All single, autologous, euploid frozen embryo transfers succeeding an endometrial biopsy with screening from Jan 1, 2021 to Dec 31, 2023 within a fertility network were included
- Cycles were stratified based on whether patients had a negative test, or a positive result (deficient *Lactobacilli* and/or positive pathogenic bacteria) with subsequent intervention (probiotics and/or antibiotics)
- Patient demographics and cycle data (Table 1.) were collected
- The primary outcome was the live birth rate per embryo transfer while secondary outcomes included positive beta HCG, clinical pregnancy, and miscarriage rates per embryo transfer
- Generalized estimating equation (GEE) models were used to compare the outcomes of the reference group (cycles with a negative screen) to the comparator group (cycles with a positive screen and subsequent treatment)

RESULTS

- There were a total of 66 and 90 single, autologous, euploid frozen embryo transfers following a negative and positive endometrial biopsy, respectively, that were included in the analysis
- Demographics and cycle characteristics were generally similar between the two groups (Table 1.)
- LBRs were also similar between the two groups (Table 2.), with 27 (40.91%) live births documented following a negative screen versus 36 (40.00%) live births recorded after a positive screen and intervention
- In the adjusted model (Table 2.), the risk of live birth was not statistically different (RR=1.01, 95% CI: 0.51-1.97), nor were there any significant differences in positive beta HCG, miscarriage, or clinical pregnancy rates between those with a negative or positive EMMA/ALICE screen (and consequential treatment)

Table 1. Demographics and Cycle Characteristics	Cycles following negative screen N=66	Cycles following positive screen N=90
Number of previous frozen embryo transfer cycles	1.71	2.27
Number of previous euploid frozen embryo transfer cycles	1.44	1.63
Age (years) at the time of biopsy	35.92	36.23
Anti-Müllerian hormone (ng/mL) at the time of biopsy	2.84	3.59
Body mass index (kg/m^2) at the time of biopsy	26.76	26.69
Gravidity at the time of biopsy	1.09	1.47
Parity at the time of biopsy	0.20	0.26
Frozen embryo transfer cycle preparation		
Programmed/medicated	43	59
Natural/modified natural	23	31
Peak Estradiol (pg/mL)	320.97	406.76
Dominant follicle size (mm)	20.40	20.50
Endometrial thickness (mm)	8.72	8.70

Table 2. Reproductive Outcomes	N (%)	Unadjusted	Adjusted*
Positive beta HCG			
Cycles following negative screen	41 (62.12%)	Ref	Ref
Cycles following positive screen	56 (62.22%)	1.05 (0.54, 2.03)	1.03 (0.51, 2.05)
Clinical pregnancy			
Cycles following negative screen	32 (48.48%)	Ref	Ref
Cycles following positive screen	45 (50.00%)	1.25 (0.66, 2.34)	1.30 (0.67, 2.50)
Miscarriage			
Cycles following negative screen	5 (7.58%)	Ref	Ref
Cycles following positive screen	9 (10.00%)	1.41 (0.40, 4.89)	1.35 (0.40, 4.62)
Live birth			
Cycles following negative screen	27 (40.91%)	Ref	Ref
Cycles following positive screen	36 (40.00%)	0.97 (0.50, 1.87)	1.01 (0.51, 1.97)

CONCLUSION

- Reproductive outcomes following treatment of uterine microbiome abnormalities were similar to patients with no initial evidence of microbiological imbalance
- While this may support the use of endometrial testing for naturally-occurring and pathogenic bacteria when faced with recurrent implantation failure or pregnancy loss, these results should be interpreted with caution given that 1) no test of cure was completed to confirm resolution, and 2) outcomes cannot be predicted if patients with a positive screen did not undergo treatment

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