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OBJECTIVE: To report the obstetrical outcomes in women with recurrent pregnancy loss (RPL) or recurrent implantation failure (RIF) diagnosed with chronic endometritis (CE).

DESIGN: Prospective study from 2014-2017 in a university setting.

MATERIALS AND METHODS: After IRB approval, 88 patients undergoing RPL or RIF workup were enrolled. A hysteroscopy and endometrial biopsy (EMB) were performed on all patients. Diagnosis of CE was confirmed with immunochemistry stains for CD138 (>5 plasma cells per HPF[1]). Diagnosed patients were treated with a course of antibiotics followed by a repeat EMB to confirm response to treatment. Pregnancy rates (PR), live birth rates (LBR) and mean time to pregnancy (TTP) were observed.

RESULTS: The overall incidence of CE was 45.5% (40/88). After a first course of antibiotics, the CE incidence was significantly reduced to 13.6% ($P = 0.00000817$). In the RIF and RPL groups, CE was present in 45.2% (14/31) and 46.6% (28/60) respectively. In the RIF group, PR were similar in the treated CE group compared to those with normal biopsies (85.7% (12/14) vs 64.7% (11/17); $P = 0.1834$). However, in the RPL group, there was a statistically significant difference in PR between patients with treated CE and normal biopsies (60.7% (17/28) vs. 84.4% (27/32); $P = 0.038$). There was also a trend towards higher LBR in the RPL group with normal biopsies compared to those with treated CE (46.9% (15/32) vs 25.5% (7/28), $P = 0.0793$). Mean TTP overall was 7.33 months in the treated CE group compared to 7.92 months for patients with a normal initial biopsy. Within the RPL group, the mean TTP was higher in women with treated CE compared to women with initial normal biopsies (8.30 vs 7.13, P=0.512). However, within the RIF group, the mean TTP was lower in women with treated CE compared to women with initial normal biopsies (6.57 vs 9.24, P=0.352).

CONCLUSIONS: This report suggests that CE may influence pregnancy rates in patients with RPL. Furthermore, not only was CE associated with a trend towards lower LBR in RPL patients, it also seems to extend the mean TTP in patients with RPL. Further research with a higher sample size would be necessary to corroborate these findings.

Reference:

1. Bouet et all. Chronic endometritis in women with recurrent pregnancy loss and recurrent implantation failure: prevalence and role of office hysteroscopy and immunohistochemistry in diagnosis. Fertil Steril 2016 105:106-110.

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RAC1 SIGNALING PATHWAY IS CRUCIAL FOR ETIOLOGY OF REPEATED IMPLANTATION FAILURE (RIF). E. Bastu,[a] T. Gunel,[b] O. U. Sezerman,[c] I. Demiral,[d] E. Gumusoglu,[b] E. Ulgen,[e] M. K. Hosseini,[b] F. Buyru,[f] J. Yeh.[g] [a]Department of Obstetrics and Gynecology, Istanbul University School of Medicine, Istanbul, Turkey; [b]Istanbul University Faculty of Science, Istanbul, Turkey; [c]Department of Obstetrics and Gynecology, Acibadem University School of Medicine, Istanbul, Turkey; [d]Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA; [e]Department of Biostatistics and Medical Informatics, Acibadem University School of Medicine, Istanbul, Turkey; [f]Istanbul University School of Medicine, Istanbul, Turkey; [g]Massachusetts General Hospital, Boston, MA.

OBJECTIVE: To evaluate if transcriptomic variations in the endometrium between women with of RIF and fertile control during window of implantation reveal insight to the etiology of RIF.

DESIGN: In this prospective cohort study, mRNA fractions were extracted from 45 endometrial biopsies obtained from women with RIF (n=24) or fertile controls (n=21) during the window of implantation (LH+7 to LH+10). Endometrial biopsies were collected using a Pipelle. Total RNA and protein were isolated from endometrium tissue samples.

MATERIALS AND METHODS: mRNA extracted from 45 endometrial biopsies obtained from women with RIF (age $\leq$38 years and BMI $\leq$28) (n=24) or fertile controls (age and BMI matched) (n=21) during the window of implantation (LH+7 to LH+10) and analyzed using Agilent/SurePrint G3 Human GE2 8x60k microarrays. The data was preprocessed and analyzed with the R package limma. RIF patients had a history of implantation failure from at least three consecutive IVF attempts in which 2-3 embryos of high grade quality were transferred in every cycle. Fertile controls had a history of at least one live birth.

RESULTS: In this study, we have applied a genome-wide transcript-level changes approach using oligo microarrays representing 37,600 genes to define the transcriptomic profile of RIF patients in comparison to fertile controls.The differentially-expressed genes (DEGs) that met the criteria $|\log_2(\text{Fold Change})| \geq 1$ and adjusted p-value ≤ 0.05 were accepted as statistically significant DEGs. The resulting 641 DEGs that met the criteria were then used for further selection with a feature selection wrapper algorithm that helps in identifying aspects the most relevant to the distinction between patients and controls. Feature selection was performed 100 times and DEGs that were chosen in all runs were accepted to be relevant DEGs. Functional enrichment analysis was carried out with 93 DEGs that were accepted as relevant. The BIOCARTA pathway "RAC1 cell motility signaling pathway" as well as related pathways were found to be enriched.

CONCLUSIONS: It is becoming evident that endometrial cells are inherently invasive and probably contribute to the processes at the implantation site. In this study, RAC1 was shown to be involved in endometrial stromal cell migration, which affects embryo implantation. Local growth factors such as PDGF-BB and HB-EGF may be utilized to enhance migration at the implantation site of patients with RIF.

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ENDOMETRIAL MIRNOME DURING THE IMPLANTATION WINDOWS CAN PREDICT EARLY MISCARRIAGE OR LIVE BIRTH AFTER FRESH OR FROZEN EMBRYO TRANSFER. L. Drissennek,[a] F. Entezami,[b] A. Gala,[c] C. Vincens,[d] D. Haouzi,[e] S. Hamamah.[f] [a]INSERM U1203, CHU Montpellier, Montpellier, France; [b]IVF Laboratory Eylau-UNILABS, Clinique de La Muette-Ramsay GDS, Paris, France; [c]CHU Montpellier, Montpellier, France; [d]CHU ADV, Montpellier, France; [e]U1203 - IRMB - CHRU Montpellier, Montpellier, France; [f]ART/PGD Department, Montpellier, France.

OBJECTIVE: The rates of miscarriages within the framework of the replacement of fresh or frozen-thawed embryos in patients under hormone replacement therapy remain a major problem in IVF/ICSI. By comparing the miRNome using the *Affymetrix miRNA Array, we previously identified miRNAs signature during the implantation window in pregnant patients after embryo replacement achieving live birth versus a miscarriage.* The aim of this study was to evaluate the miRNA expression profile in the prediction of early miscarriage or live birth after either fresh or frozen embryo replacement.

DESIGN: Endometrial biopsies were collected during the implantation windows from patients under hormone replacement therapy (HRT). RNAs were extracted from biopsies and miRNAs quantification was performed using the Taqman miRNA assays experiments. Then, miRNA expression was analyzed according to the IVF/ICSI outcomes (early embryo miscarriage versus live birth) after fresh or frozen embryos transfer.

MATERIALS AND METHODS: Endometrial biopsies were obtained from patients (n=15) with repeated implantation failures ($\geq$ 3) during IVF/ICSI cycles. Then, we assessed whether the expression profile of five selected miRNA quantified by RTqPCR was retrospectively associated to the attempt outcome in term of early miscarriage (n=6) or live birth (n=9) after embryo replacement.

RESULTS: Analyses of the quantification of the five selected miRNAs demonstrated the same sense of variation than *miRNA Array* data. These five miRNAs were over-expressed in endometrium from patients with a miscarriage compared with a live birth by a factor 2, 1.3, 1.5, 2.2, 1.7 for the miR-1, miR-2, miR-3, miR-4 and the miR-5, respectively. However, only the miR-4 emerged with a p-value near the statistical significance (P value= 0.058). Interestingly, this miR-4 potentially targets 1496 predicted-transcripts that are involved in numerous biological functions including the 14-3-3-mediated Signaling, the actin cytoskeleton signaling and the angiopoietin signaling that play a role in embryonic and postnatal angiogenesis.

CONCLUSIONS: miRNAs in endometrial tissues during the implantation windows during a cycle preceding fresh or frozen embryo transfer cycle can predict the outcome attempt. This information is crucial leading to develop a prognostic tool of the attempt outcome, opening news perspectives in the patient care management.

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