B option

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Abstract title: if randomised, identify the trial as such in title → 25

New transcriptomic insight improves endometrial Recurrent Implantation Failure (RIF) diagnosis and distinguishes clearly between displaced and disrupted Window Of Implantation (WOI) (21)

Study question: A single sentence, limited to the primary objective of the study (do not include secondary questions) → 25

Endometrial Recurrent Implantation Failure: a matter of timing or an altered Window of implantation signature? Are we able to diagnose both of them? (23)

Summary answer: The main conclusion. A single sentence, this should be limited to the primary results of the study, without any discussion of their implications → 25

Transcriptomics stratifies WOI samples into distinct subgroups demonstrating that there are at least two RIF main causes, displaced and disrupted WOI, but we can only distinguish between them with the proposed transcriptomic analysis (33)

What is known already: One or two short sentences → 100

Endometrial transcriptomics prediction has been applied to human WOI in two main works: Simon (Diaz-Gimeno et al., 2011) and Macklon groups (Koot et al., 2016). Diaz-Gimeno considers endometrial RIF as a displacement and is not distinguishing a disrupted WOI signature. Nerveless, Koot considers endometrial RIF as a disrupted WOI removing the LH timing effect. Both of the models are considering LH as gold standard in the prediction design, however, Diaz-Gimeno signature clinical application have been demonstrated approximately 25% of RIF discrepancies between transcriptomics profile and LH in the expected WOI (LH+7)(Ruiz-Alonso, 2013). (94)

Study design, size, duration: Cross sectional – control versus treatment, longitudinal –time-course, age-course. Numbers
of treated/controls, treatment duration, sampling procedures → 75

Retrospective analysis comparing WOI endometrial transcriptomics and prediction in controls (n=72) versus RIF patients (n=43) in samples collected from LH+5 to LH+8. Raw data was downloaded from GEO database ((GSE58144) (Koot et al, 2016). In the same dataset we compared both predictor methodologies, Diaz-Gimeno and Koot, and we proposed a new transcriptomics insight to fill the gap between both studies and be able to detect and distinguish both types of RIF. (75)

Participants/materials, setting, methods: General approach used eg cell/tissue culture/transfection, animal treatments/models, transgenesis. Species, ages, gender, cell type. Methods and endpoints used – eg hormone, cytokine, growth factor measurements, cell numbers/proliferation, tissue morphology/composition, FACS, immunohistochemistry, Westerns, quantitative PCR, FISH → 75

Data was pre-processed and normalized using quantile method from limma R package. Different designs for SVM predictors using caret R package were performed: one considering RIF versus Controls removing and not removing LH variations, and the other

one stratifying samples by transcriptomics and predicting RIF displacement. The predictive value was compared between Diaz-Gimeno and Koot signatures and a new diagnostic algorithm that distinguish between both types of RIF is proposed in the same sample cohort (75).

Main results and the role of chance: P values, biological gradient, repeatability/robustness, mechanisms identified/involved →200

WOI samples were classified by unsupervised transcriptomic methods (K-means) in ER: Early Receptive, R: receptive and LR: Late-Receptive profiles. Comparing transcriptomics with LH as gold standard we found some discrepancies and displaced samples, but LH+5 were mostly in ER, LH+8 were mostly in LR, LH+6 were mainly in ER and LH+7 were many of them in R but some samples were displaced to ER and PR profiles. WOI displacement predictor supervised by transcriptomic profiles classified RIF samples in ER, R or PR for Koot signature with an ACC=0.90 and with Diaz-Gimeno with an ACC=0.98.

RIF samples that were not displaced could be detected using a second model called disrupted WOI which is supervised by control R and RIF R samples. With this design, Koot signature obtained an ACC=1 (Sp 1, S 1); and Diaz-Gimeno signature an ACC=0.789 (Sp 1, S 0.38).

With the predictor proposed by Macklon, removing LH variation without consider transcriptomic variability, koot signature obtained an ACC=0.97 and Diaz-Gimeno an ACC=0.896. The problem in this design is that the methodology is not able to distinguish RIF displacement from disrupted WOIs. (198)

Limitations, reasons for caution: Descriptive, only in vitro, cell transfection, shown only in one species, technical limitations and reasons for caution, cell/animal lethality in a knock-out, disease- or cell-specificity → **50**

This study has as main objective show both types of RIF causes to understand the gap between both hypotheses about endometrial RIF transcriptomics concept. Is not important the prediction parameters in an absolute value. By other hand, clinical relevance in terms of pregnancy of each transcriptomic profile should be checked. (50)

Wider implications of the findings: Agreement/disagreement with literature, resolution of previous disparity, new insights/mechanisms in disease(s), new therapeutic potential, cell-, species- gender-, or age-implications, relevance to other systems → **50**

Besides of understanding the gap between both works, the main insight of this study is how design prediction transcriptomics to distinguish clinically between the patient that could be personalised by embryo transfer day and the patient with a disrupted WOI that should be study for the development of new treatments. (50)

Study funding/competing interest(s): select option