UNEXPLAINED EUPLOID EMBRYO TRANSFER FAILURE: TESTING AND TREATMENT OPTIONS

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Background

Endometriosis affects 5-10% of women of reproductive age and up to 50% of these women experience infertility (1). Despite advances in Assisted Reproductive Technology (ART), the overall mean success rate for IVF rarely exceeds 70%, even with preimplantation genetic testing (PGT-A) (2) (Fig. 1). Endometriosis has been identified as an underlying cause of unexplained euploid embryo transfer failure (UEETF) (3,4). Additional studies show that medical suppression of the hypothalamic/pituitary/gonadal axis with lowering of estrogen is a therapeutic option to improve outcomes for those with UEETF (3,4).

If there are reversible factors contributing to implantation failure, than treatment of presumed or confirmed endometriosis might be expected to improve outcomes compared to “no treatment” before the next transfer.

Objective

The purpose of this study was to compare success rates among first time IVF patients using preimplantation genetic tested (PGT-A) embryos, women with UEETF who underwent 2 months of ovulation suppression with GnRH agonist (GnRHa) or controls receiving no treatment (NoTx). A subset of UEETF subjects underwent endometrial biopsy and testing for endometriosis biomarkers, BCL6 and SIRT1 (3,5) (Fig 2).

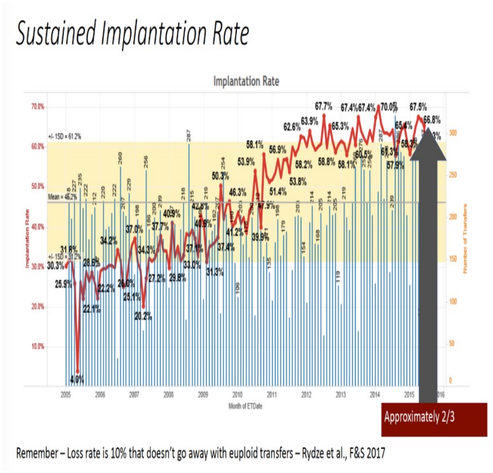

Figure 1: Over time, implantation rates for a single embryo transfer has reached a plateau of < 70%. *Courtesy Richard Scott*

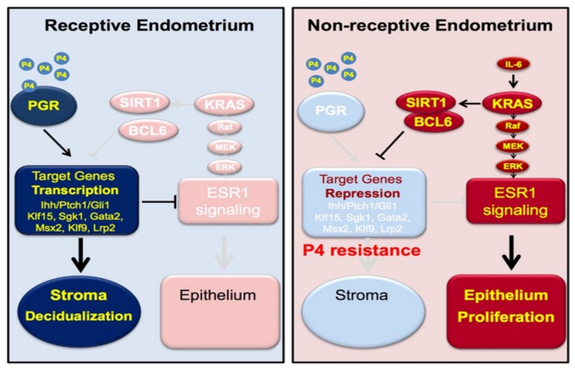

Figure 2. Non-receptive endometrium (right panel) is associated with inflammation often caused by endometriosis. BCL6/SIRT1 biomarker expression in the luteal phase are indicators of P-resistance, and likely contribute to euploid embryo transfer failure.

Materials and Methods

Electronic records of 205 frozen embryo transfer (FET) cycles using euploid embryos between 2019 and 2023 were examined. A total of 127 first IVF attempt (FirstPGTA) were evaluated and compared to 61 transfers in women with prior UEETF. We compared 47 of those who were treated with GnRHa (Lupron) suppression for 2 months (GnRHa) and 14 received no treatment (NoTx) prior to the next euploid embryo FET. Pregnancy success was defined as live birth or ongoing pregnancy (heartbeat after 12 weeks).

We performed endometrial biopsies on 48 women with prior UEETF, using standard immunohistochemistry (IHC) staining for BCL-6 and SIRT1. Hscore was assigned as part of IHC analysis, by a blinded observer. A cut-off of 1.4 and 2.0 (out of 4.0) was considered positive for BCL-6 and SIRT1, respectively. Pregnancy success rates are reported as a 95%CI and compared using *chi*-squared for trend testing.

Results

There were significantly lower ongoing pregnancy rates in women with prior UEETF who did not receive treatment prior to their next transfer (34%) compared to those that were treated with GnRHa suppression for 2 months (68%). Pregnancy success was higher in first time transfers (FirstPGTA), and GnRHa groups compared to NoTx (Chi square for trend, p=0.02) (Fig 3).

HSCOREs for BCL6 testing were positive in 42 of 48 cases (87.5%), while HSCOREs for SIRT1 were positive in 39 of 45 cases (88.8%). These results suggest that endometriosis is present in a majority of women with UEETF.

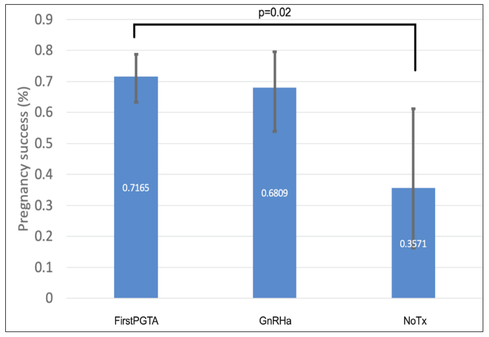

Figure 3. Pregnancy success rates (live birth/ongoing pregnancy) in first attempt PGT-A (FirstPGTA) compared to those with prior failure treated with GnRH agonist suppression (GnRHa) or no further treatment (NoTx).

Conclusions

Unexplained failure after euploid embryo transfer is unfortunately still common and there are no formal recommendations for treatment other than simply repeating another transfer with available embryos. This study suggests that no treatment prior to the next transfer is inferior to medical treatment for presumed endometriosis. Biomarkers for endometriosis (BCL6 and SIRT1) were positive for a majority of subjects tested with UEETF. Endometrial suppression for 2 months with GnRHa was superior to *no treatment*, providing similar outcomes to overall first time PGT-A FET success rates, while “no treatment” resulted in inferior outcomes.

References

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