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THE HYPOTHESIS OF PREFERENTIAL LOSS OF FEMALE EMBRYOS: EMBRYONIC SEX IS NOT ASSOCIATED WITH INCREASED ODDS OF EARLY PREGNANCY LOSS

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OBJECTIVE:

The human sex ratio has long interested developmental biologists, statisticians, and other scientists. Primary Sex Ratio (PSR) in humans has been thought to be male-biased. Previously published studies about PSR have suggested this bias is due to a preferential loss of female conceptuses during the earliest stages of pregnancy^{1,2}. To date, the dynamics of PSR from conception to birth are poorly understood. Literature about PSR is currently based on subjective estimates, extrapolations from large historical cohorts, or based on data sourced from natural conceptions³. Yet, the use of data from patients who undergo ART treatment presents an opportunity to observe embryonic sex prior to transfer through the application of PGT. This study aims to analyze whether the selection of female embryos prior to frozen embryo transfer (FET) are at higher risk of suffering early pregnancy loss as compared to the selection of male embryos.

MATERIALS AND METHODS:

The study included patients who underwent a single euploid FET cycle from 2016-2021. Gender selection for family balancing cases were excluded from the analysis. PGT-A with NGS was performed for all cases. Cohorts were segregated into groups based on embryonic sex prior to transfer selection. Only top morphology embryos with a grade $\geq 4AA$ (Modified Gardner's) were included in the study. Patient demographics and IVF cycle outcomes were recorded. Biochemical pregnancy loss (BPL) was defined as detectable serum β -hCG and embryonic arrest prior to the development of a clinical pregnancy. Clinical pregnancy loss (CPL) was defined as the loss of a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs. Comparative statistics and an adjusted mixed model with a GEE were utilized for statistical analyses. A sample size of 906 single, euploid FETs per cohort was calculated to ensure an 80% power to detect a difference of 5% on clinical pregnancy loss rates ($\alpha=0.05$).

RESULTS:

1,363 male were compared to 1,045 female FETs. No differences were found in patient's age, BMI, AMH, endometrial thickness and other demographic variables between cohorts. Also, no differences were found in implantation, clinical pregnancy, ongoing pregnancy, BPL and CPL. After adjusting for age, BMI, AMH, day of biopsy and endometrial thickness, no association was found between embryo sex and increased odds of BPL (OR 0.50 CI95% 0.11-2.27, $p=0.37$); or CPL (OR 0.28 CI95% 0.07-1.16, $p=0.08$).

CONCLUSIONS:

By analyzing a large cohort of single euploid embryo transfers, we can observe the proportion of pregnancy losses that are not associated with aneuploidy, thus assessing the differences on early pregnancy loss rates based on embryonic sex while adjusting for other important covariates. For patients who undergo IVF with subsequent PGT-A and FET, there does not appear to be increased odds of pregnancy loss in selecting a single, euploid female embryo compared to male embryo counterparts.



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IMPACT STATEMENT:

Our study findings suggest that the male-biased sex ratio described in the literature might be product of biased analysis, and not of selective increased pregnancy loss of female embryos.

REFERENCES:

- 1 Mulley, J. F. Greater loss of female embryos during human pregnancy: a novel mechanism. *BioEssays* 41, e1900063 (2019).
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- 3 Orzack, S. H. et al. The human sex ratio from conception to birth. *Natl Acad Sci. USA*. **112**, E2102–E2111 (2015).