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Frozen-thawed transfer increases birth weight of female babies only, but not male babies from our analyses of 2578 neonates in a solo practice

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### Study question:

What causes the neonates born after frozen-thawed embryo transfers (FET) heavier than fresh embryo transfers (fresh ET). Is there any difference between female and male babies?

#### Summary answer:

The factors to increase birth weight after FET on each gender were different.Female babies by the process of FET, but male babies by other factors.

#### What is known already:

The previous studies have shown birth weight of babies born after FET is heavier than fresh ET. However, there are no reports to investigate what caused babies born after FET are heavier than fresh ET. Birth weight also is correlated with gestational age and maternal age. Therefore, in the present study, the influence of FET was investigated between male and female neonates to determine if there is any causative factor to increase birth weight in each gender with reference to multivariate analyses adjusted for those parameters.

# Study design, size, duration:

A total of 2,578 full term neonates (37–41 weeks of gestation) born after FET (n=1959) and fresh ET (n=619) from 2008 to 2016 were investigated. All analyses were carried out both in male (n=1276) and female (n=1302) newborns.

#### Participants/materials, setting, methods:

Birth weight (g), gestational age (weeks) and maternal age (years) were compared between singletons born after FET and fresh ET using student's t-test. Multiple regression analyses were performed to reveal the variables relevant to birth weight among gestational age, maternal age, type of IVF (IVF or ICSI) and type of ET (FET or fresh ET).

## Main results and the role of chance:

Birth weight, gestational age and maternal age of male babies born after fresh ET vs FET were  $3089.0 \pm 386.2$  vs  $3153.6 \pm 390.5$  (p<0.05),  $38.8 \pm 1.1$  vs  $39.0 \pm 1.3$  (p<0.01),  $35.4 \pm 4.0$  vs  $35.7 \pm 3.6$ 

(ns), respectively. In addition, birth weight (g), gestational age (weeks) and maternal age (years) of female babies born after fresh ET and FET were 2971.2  $\pm$ 363.4vs 3056.1  $\pm$ 389.8 (p<0.01), 39.1  $\pm$ 1.2vs 39.1  $\pm$ 1.3 (ns), 35.1 $\pm$ 3.7vs 35.8  $\pm$ 4.1 (p<0.01), respectively. Multiple linear regression identified only gestational age (p<0.01, $\beta$ =0.42, 95%CI=116.91-148.57) as a parameter associated with male birth weight. Gestational age (p<0.01,  $\beta$ =0.41, 95%CI=105.76-135.53), maternal age (p<0.05,  $\beta$ =0.07, 95%CI=1.45- 11.02) and type of ET (p<0.01,  $\beta$ =0.08, 95%CI=29.91-119.08) were independently associated with female birth weight. The present study showed that cryopreservation was not associated with male birth weight.

### Limitations, reasons for caution:

Several factors such as BMI, smoking and birth order were not included as potential confounders in the present study.

### Wider implications of the findings:

It was revealed that the relevance of cryopreservation and maternal age to neonatal birth weight is unequivocal in females compared with males. Though the mechanisms in which those parameters influence baby development are still unclear, it is suggested that female embryos are more susceptible to those factors than males.

## **Trial registration number:**

not applicable

Keywords: Birth weight IVF outcome Frozen–thawed embryo transfer Sex difference IVF singletons