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High serum IGF-1 levels are associated with pregnancy loss following frozen-thawed euploid embryo transfer cycles

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ABSTRACT

An elevated level of insulin growth factor (IGF-1) in rat uterine fluid has been shown to exert detrimental effects of embryo development possibly leading to an increase in pregnancy loss. Interestingly, the administration of somatostatin to rats undergoing superovulation reduced IGF-1 levels in uterine luminal fluid and thus reversed its deleterious effects on embryo development and increased the number of normal embryos. Therefore, we investigated whether serum levels of IGF-1 correlate with the incidence of pregnancy loss following IVF. To account for aneuploidy and the effect of hormonal supplementation on serum IGF levels, we only included natural frozen-thawed euploid embryo transfer (N-FET) cycles. Sera collected in the follicular phase (cycle day 10) were tested for levels of IGF-1, IGF-2, and IGF-binding protein 1 (IGFBP-1) using quantitative ELISA. A total of 156 N-FET cycles were included: 120 resulted in a live birth whereas 36 led to a first trimester pregnancy loss. Women with a pregnancy loss had significantly higher serum IGF-1 levels compared to those who achieved a live birth (18.0 ± 1.1 vs. 14.6 ± 0.7 ng/mL, respectively). The two groups had comparable serum IGF-2 and IGFBP-1 levels. There was no significant difference in maternal age, body mass index, gravidity, parity, number of prior miscarriages, peak endometrial thickness, or infertility diagnosis between the two groups. In conclusion, women undergoing euploid blastocyst transfer with elevated serum IGF-1 concentrations may be at increased risk of pregnancy loss. This may constitute a novel molecular explanation of pregnancy loss of euploid conceptus.

1. Introduction

The major underlying etiology for an age-related reproductive decline is the exponential increase in the rates of chromosome mis-segregation in the oocyte and subsequently embryo aneuploidy (Franasiak et al., 2014; Hassold and Hunt, 2001; Leridon, 2004). However, euploid embryos can also have an abnormal implantation and pregnancy loss (Irani et al., 2017). Possible etiologies include abnormal uterine anatomy, anti-phospholipid antibody syndrome, infections, hormonal imbalances and metabolic disorders (Practice Committee of The American Society For Reproductive, 2012). A considerable proportion of miscarriages still have an unknown etiology.

Pre-implantation embryo development is controlled by cytokine and growth factors such as the insulin-like growth factor (IGF) system. IGF-1 is a 70-amino acid polypeptide that is predominantly synthesized by the liver (Arany et al., 1994). Through its autocrine and/or paracrine effects, IGF-1 plays several roles in follicular and embryo development (Guzeloglu-Kayisli et al., 2009; Adashi et al., 1985). Indeed, supplementation of culture medium with IGF-1 was shown to increase the blastocyst formation rates of porcine embryos and the number of cells in the inner cell mass (ICM) (Kim et al., 2005). Similarly, the blastocyst formation rate of human embryos increased by 25%, and the number of cells in the ICM increased by 59% after the addition of IGF-1 to the culture medium (Lighten et al., 1998).

Conversely, elevated IGF-1 levels have been shown to be embryotoxic (Katagiri et al., 1996). This has been attributed to the down-regulation of embryonic IGF-1 receptors leading to lower insulin-stimulated glucose uptake and higher apoptosis in the ICM following the exposure to high IGF-1 concentrations (Chi et al., 2000). Interestingly, the blockage of IGF-1 receptors also re-created a significant apoptosis in the ICM, thus robustly suggesting that the induction of apoptosis by high IGF-1 concentrations occur through decreasing IGF-1 receptor signaling (Chi et al., 2000). It has also been speculated that the detrimental embryotoxic effects of high IGF-1 levels observed in women

Abbreviations: IGF-1, insulin growth factor; IGFBP-1, IGF-binding protein 1; ICM, inner cell mass; N-FET, natural frozen-thawed euploid embryo transfer; BMI, body mass index

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with polycystic ovary syndrome might explain the increased rate of pregnancy in these women (Chi et al., 2000). With this in mind, we aimed to determine whether serum IGF-1 levels are different between women who achieve a live birth and those who have a pregnancy loss following the transfer of a euploid embryo.

2. Materials and methods

2.1. Subjects

The institutional review board at Weill Cornell Medical College approved this study. To account for aneuploidy, which is the most common cause of miscarriage, we have included only cycles in which euploid embryo(s) were transferred. None of the included women had abnormal uterine anatomy, anti-phospholipid antibody syndrome, diabetes, or hypothyroidism. Given that hormonal supplementation may affect serum IGF-1 levels, we have selected only natural frozen-thawed euploid embryo transfer (N-FET) cycles. Sera from 156 women were collected on cycle day 10 of N-FET cycles and frozen at −80 °C until assayed. The subjects underwent N-FET cycles between January 2015 and June 2016. Serum levels of IGF-1, IGF-2, and IGF-binding protein 1 (IGFBP-1) were compared between women who achieved a live birth and those who had a pregnancy loss.

2.2. Clinical protocol

During N-FET cycles, transvaginal ultrasonography was performed starting on cycle day 10 to assess follicle development and endometrial thickness/pattern. Ultrasounds were repeated until a trilaminar lining reached or exceeded 7 mm. We carefully monitored serum estradiol, LH, and progesterone levels until detection of the LH surge. Blastocyst transfer was performed 5 days following the LH surge using Wallace catheters (Smiths Medical Inc, Norwell, MA). Serum β-hCG levels were measured 9 days after the transfer to assess the cycle outcome.

2.3. IGF system assays

We used the commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN) to measure serum IGF-1, IGF-2, and IGFBP-1 levels. All analyses were conducted simultaneously and were assayed in duplicate. Individuals performing the assay were blinded to all clinical data. Inter-assay and intra-assay variability was < 10%.

2.4. Statistical analysis

Data were tested for normality. All values were expressed as mean ± standard error of the mean. Unpaired *t*-test was used as appropriate. A *P* value of < 0.05 was considered statistically significant. All data analyses were performed with SPSS statistics (IBM Corp, Armonk, NY).

3. Results

A total 156 sera from women with N-FET cycles of euploid blastocysts were included: 120 resulted in a live birth whereas 36 ended with a first trimester pregnancy loss. The demographic characteristics of patients in both groups are summarized in Table 1. The two groups had comparable maternal ages, gravidity, parity, number of prior miscarriages, body mass index (BMI), time interval between the measurement of serum IGF-1 level and embryo transfer, and peak endometrial thickness ($P > 0.05$). The infertility diagnosis (polycystic ovary syndrome, diminished ovarian reserve, advanced maternal age, tubal factor, male factor, and others) did not differ between the two groups ($P > 0.05$). The majority of pregnancy losses occurred early in the first trimester (6.1 ± 0.2 weeks' gestation).

Table 1
The demographic characteristics of patients who underwent natural frozen-thawed euploid blastocyst transfer resulting in a live birth or a pregnancy loss. BMI: Body mass index; NS: Not significant; IGF: insulin-like growth factor.

Parameter	Live birth (n = 120)	Pregnancy loss (n = 36)	*P* value
Age (years)	37.2 ± 0.4	37.1 ± 0.8	NS
BMI (Kg/m^2)	23.3 ± 0.3	25.0 ± 1.0	NS
Gravidity	1.8 ± 0.1	2.0 ± 0.2	NS
Parity	0.5 ± 0.1	0.5 ± 0.1	NS
# prior miscarriages	0.8 ± 0.1	0.8 ± 0.2	NS
Peak endometrial thickness (mm)	9.0 ± 0.2	8.3 ± 0.3	NS
Time between the measurement of IGF-1 level and embryo transfer (days)	11.2 ± 2.7	10.8 ± 2.8	NS

Table 2
Correlation between serum levels of IGF components in the follicular phase and both age and body mass index (BMI). IGF: insulin-like growth factor; IGFBP-1: IGF-binding protein 1; NS: not significant.

IGF component	Parameter	Pearson r	*P* value
	Age		
IGF-1		−0.03	NS
IGF-2		−0.02	NS
IGFBP-1		−0.02	NS
	BMI		
IGF-1		0.14	NS
IGF-2		0.11	NS
IGFBP-1		−0.21	0.01

BMI was negatively correlated with serum IGFBP-1 levels (r = −0.21; $P = 0.01$). However, serum IGF-1 and IGF-2 concentrations were not correlated with BMI (Table 2). There was no significant difference in serum levels of IGF-1, IGF-2, or IGFBP-1 between patients of different infertility diagnosis ($P > 0.05$). Furthermore, IGF components were not correlated with age (Table 2).

Serum IGF-1 levels measured on cycle day 10 of N-FET cycles were significantly higher in patients who had a pregnancy loss compared to those who achieved a live birth (18.0 ± 1.1 vs. 14.6 ± 0.7 ng/mL; $P = 0.03$) (Fig. 1). On the other hand, serum IGF-2 levels were comparable between the two groups (452.5 ± 13.2 vs. 471.1 ± 11.3 ng/mL; $P > 0.05$). In addition, there was no significant difference in serum IGFBP-1 levels between women who had a pregnancy loss and those who achieved a live birth (28.6 ± 2.7 vs. 26.1 ± 1.4 ng/mL; $P > 0.05$).

4. Discussion

The present study aimed to investigate the potential role of IGF

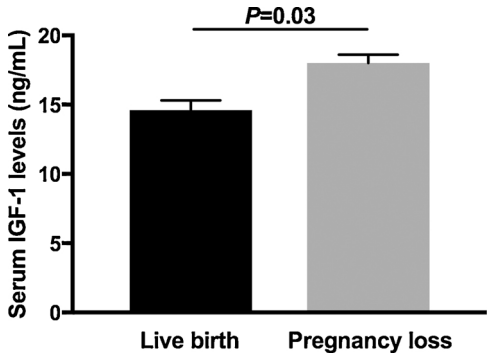

Fig. 1. The association between serum insulin-like growth factor (IGF)-1 concentrations measured in the follicular phase and the outcomes of natural frozen-thawed euploid blastocyst transfer cycles.

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