Original Article: Effect of Enoxaparin's Ability to success and Neonatal out Come of In Vitro Fertilization

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ABSTRACT

Introduction: The analysis of a cohort of patients during the embryo transfer phase was the main focus of this study. The aim of the study was to examine the effects of thirteen adjuvant therapies on the success of embryo transfer, including the clinical pregnancy and live birth rates with enoxaparin. **Materials and Method:** A random number was applied to each transfer in order to ensure data independence, and it was then used to select a single transfer for each patient while erasing the other 90 duplicate cycles. Gonadotropin stimulation was either downregulated or gonadotrophin antagonist stimulation—with or without pre-treatment with the oral contraceptive pill—was used to stimulate. Vitrification was used to freeze the embryos. **Results:** 16 known seropositive IVF implantation failure patients had 25 additional transfers of 47 embryos, resulting in two clinical pregnancies (fetal heart implantation rate, 42%). These patients did not want to participate in the trial and did not receive heparin and aspirin from their treating physician. **Conclusion:** A large number of the interventions examined in this study fall short of demonstrating any effects on the success of embryo transfers. According to the findings of our analysis enoxaparin use has shown promising, possibly advantageous results.

Introduction

When it comes to overcoming the various barriers to conception, up to one in six couples turn to in vitro fertilization (IVF). However, couples find the continued infertility, despite the optimization of IVF procedures, to be very upsetting, and doctors face a challenging task as a result [1-3]. IVF procedures can help people with specific fertility issues(Fig 1)

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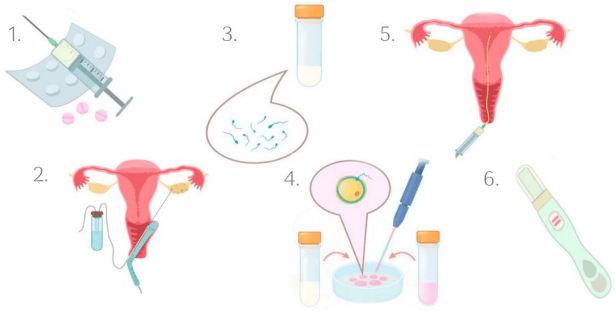

Figure 1: IVF sickle

The process is completed with embryo transfer after ovarian stimulation, oocyte collection, and fertilization have all been altered [4-6]. The success of an embryo transfer is significantly influenced by the endometrial receptivity and embryo quality. Oocyte quality, which affects embryo quality, depends on optimal folliculogenesis and oocyte maturation [7-9].

Therefore, therapies that would improve the follicular microenvironment for these processes are now being researched. Moreover, it's thought that only one-third of implantation attempts succeed due to inadequate endometrial receptivity [10-12]. Numerous interventions aimed at producing an "ideal" immune environment are being researched because it appears that decreased endometrial receptivity may have an immunological cause.

IVF adjuvant therapies come in a variety of shapes and sizes, each with a special mode of operation [13-15]. This study examined thirteen IVF adjuvants in an effort to clarify any ambiguity regarding their use. By enhancing the quality or implantation of the embryo through follicular development, oocyte maturation, and/or endometrial receptivity, these treatments seek to increase the viability of embryo transfer. It has been proven that the soy bean oil, egg phospholipid, and glycerine-based fat emulsion intralipid suppresses immune function [16-18].

Additionally, it has been discovered that glucocorticoids have immune-regulatory qualities and affect the activity of natural killer cells. An antioxidant called melatonin plays a role in the development of follicles, the maturation of oocytes, and ovulation. Another antioxidant, coenzyme Q10, is essential for energy metabolism and protecting cell membranes from oxidative damage [18-20].

Granulocyte colony-stimulating factor (G-CSF) analogs, such as filgrastim, are used in in vitro fertilization (IVF) because it is believed that natural G-CSF is crucial for oocyte maturation.

Androgens like testosterone and DHEA are necessary for both the early stages of oocyte growth and the quality of the developing oocyte. Growth hormone modulates the effect of FSH on granulosa cells by up-regulating the synthesis of insulin-like growth factor 1, which is important in follicular development and oocyte maturation; Antibiotics have been proposed to improve endometrial receptivity by reducing the negative effects of microbial colonization;

Patients and doctors alike pay attention to these adjuvant therapies, which makes sense, but there is frequently little conclusive evidence for them and little is known about how they affect embryo transfer, subsequent pregnancy rates, and live birth rates [21-23]. Although there isn't much evidence that these treatments work, it's still possible that they could theoretically lead to better IVF results [24-26].

The analysis of a cohort of patients during the embryo transfer phase was the main focus of this study. The aim of the study was to examine the effects of thirteen adjuvant therapies on the success of embryo transfer, including the clinical

pregnancy and live birth rates, including intralipid, steroids, melatonin, coenzyme Q10, filgrastim, testosterone, DHEA, growth hormone, antibiotics, hCG infusion, aspirin, enoxaparin/heparin, and dopamine agonists [27].

Material and Methods

Based on a private, multi-site IVF clinic's standardized database, a retrospective cohort study was carried out. The embryo transfers that took place between January 2019 and April 2020, with a total of 90 transfers, were collected (n=90), as this covered the time when adjuvant usage was highest. When there was a lack of information or additional adjuvants were used and there were fewer than 20 cases, the cycles were excluded (n=12), leaving 90 embryo transfers.

A random number was applied to each transfer in order to ensure data independence, and it was then used to select a single transfer for each patient while erasing the other 90 duplicate cycles. Gonadotropin stimulation was either downregulated or gonadotrophin antagonist stimulation—with or without pre-treatment with the oral contraceptive pill—was used to stimulate. Vitrification was used to freeze the embryos. Comparing proportions was done statistically using the Chi-square test with Mantel-Haenszel correction or, if a value was present, the Fisher exact 2 tailed test.

Ethical Considerations: This study has been approved by the committee of Alborz University of Medical Sciences(Ethic No: IR.ABZUMS.REC.1401.258)

Results

including four women's five GIFT cycles with three eggs. There were 184 thaw transfers (328 embryos) and 116 fresh transfers (227 embryos). Ten biochemical pregnancies, three ectopic pregnancies, six fetal heart miscarriages, 23 live births of singletons, and six live births of twins were recorded. The percentages of combined positive pregnancy tests per transfer (14 percent and 17 percent, respectively), fetal heart implantation rates per embryo (6 percent and 8 percent), and live birth rates per embryo did not differ significantly between treatment and placebo cycles. Generalized estimating equation analyses of the primary endpoints revealed that significant covariates for positive hCG and live-birth pregnancy rates included average cell number in the transferred embryos, diagnosis of ovulatory disorder, single vs. Smoking history, endometriosis diagnosis, multiple embryo transfers, and the quantity of antibodies that are positive.

The procedure for difficult embryo transfer had a significant detrimental impact on the percentage of live births. When using heparin and aspirin, the relative pregnancy rates per transfer rates were compared to each other.

The placebo was 0.65 for positive pregnancy tests and 0.60 for live birth in these models that included the statistically significant covariates. The unadjusted relative pregnancy rates were 0.80 and 0.82, respectively. The average cell number, ovulatory disorder diagnosis, current smoker status, number of antibodies positive, and difficult transfer were significant covariates for fetal heart implantation rates and live birth rates per embryo transferred.

Significantly lowering the rate of live births per transferred embryo were the female age and transfer cycles 4–7 in the trial. The number of positive antibodies did not significantly interact with the treatment. The relative costs of treating patients with heparin and aspirin vs.

Both 0.64 and 0.77 were used as the placebo treatment in these models. The fetal heart implant and live birth rates were unaffected by GIFT, embryo grade, fresh vs. Thawed embryos, endometrial thickness, luteal phase support type, specific antibody positivity, including ANA-alone positivity, parity, gravidity, number of prior cycles or embryo transfers prior to the

trial, BMI, and transfer doctor or clinic are some other factors to consider(Figure 2).

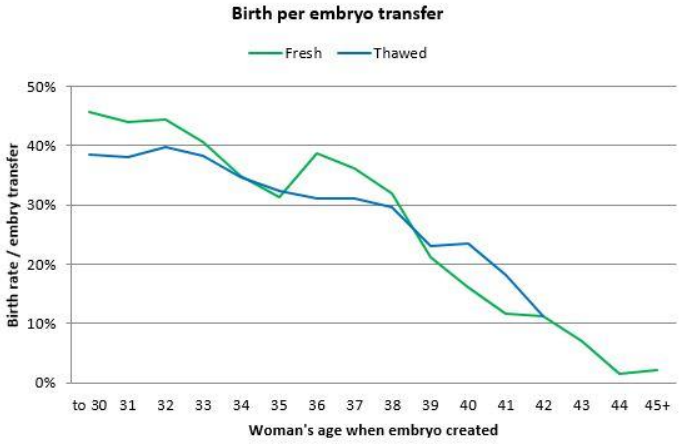

Figure 2: Birth per embryo

The fetal heart implantation rate for trial participants was significantly higher than the 4 point 5 percent (147 fetal hearts per 3,237 transferred embryos) for 1,447 IVF implantation failure patients who were not enrolled in the trial but had 1,788 embryo transfers during the same time period. Regarding infertility diagnoses, embryo grade, and cell number in particular, the traits of the trial participants were comparable to those of the other IVF implantation failure patients.

Additionally, 16 known seropositive IVF implantation failure patients had 25 additional transfers of 47 embryos, resulting in two clinical pregnancies (fetal heart implantation rate, 42%). These patients did not want to participate in the trial and did not receive heparin and aspirin from their treating physician(Figure 3).

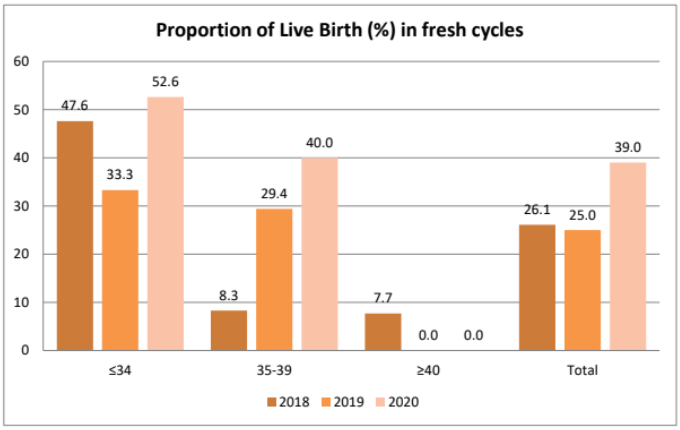

Figure 3: Neonatal rate after intervention

Discussion

Although our study shows that many interventions fail to show any statistically significant improvements to embryo transfer success, many of the adjuvant therapies examined have theoretically positive effects. Negative effects are observed on the univariate analyses of a variety of therapies, which is not surprising given our population [28-30]. As can be seen from table 2's demographics, women who have previously experienced IVF failure are frequently those who use adjuvant therapies,

rarely meeting ideal embryo age goals and/or having the opportunity for embryo freezing. These negative effects for all treatments except melatonin became non-significant after allowing for confounders and using logistic regression to control for glaring differences between our cases and controls [31-33].

Our study's use of melatonin had an unexpectedly negative effect on embryo transfers. The reduction in live birth rates found in our analysis is the first one to reach statistical significance [34-36]. Melatonin has potential applications in the IVF cycle, according to theory. Studies have shown that melatonin receptors are present on granulosa cells and that pre-ovulatory follicular fluid contains high concentrations of melatonin [37-39].

Melatonin has been used as an adjuvant therapy due to its known antioxidant properties and demonstrated safety because oxidative stress is a potential cause of poor oocyte quality and decreased fertilization rates [40-42].

Studies have shown a strong correlation between its effectiveness and an improvement in oocyte quality, but there is little information specifically assessing its impact on pregnancy outcomes [43-45]. Melatonin's effectiveness in IVF has been the subject of conflicting findings in the literature that has evaluated pregnancy outcomes, but outcomes have generally been either non-significant or favorable [46-48].

In the two randomized controlled trials that Showell's Cochrane review of antioxidant use included, there was no correlation between higher pregnancy rates in women receiving melatonin and the use of antioxidants [49-51]. 70 of the 145 patients in the included trials received melatonin out of the total 145 patients. Since 341 patients were included in our study, we were able to measure the effects of melatonin on embryo transfer and implantation success at a nearly five-fold higher rate than that found in Showell's Cochrane review [52-55]. Despite not being random, our larger sample size gives us the chance to show a difference that perhaps smaller randomized controlled trials would not be able to [56-58].

Because melatonin's theoretical advantages have an earlier impact during the IVF cycle, our results show a negative impact that is different from what is currently known. It is crucial that the detrimental impact on implantation and subsequent live birth rates that has been observed is thoroughly investigated, and that the use of melatonin in IVF is reevaluated in high-quality study designs with sufficient sample sizes [59-61]. The use of testosterone had no discernible effects on embryo transfers, according to our analysis. Nagel et al. and our findings are in agreement's 2015 Cochrane review found that there were no statistically significant differences when testosterone use was taken into account after performance bias was reduced [62-64].

The univariate analysis of our study's data, however, indicates that testosterone negatively affects pregnancy and live birth rates, contrary to Nagel's unadjusted data, which seemed promising. Our findings may differ from Nagel's because our research focuses on the success of embryo transfer while Nagel's review included studies looking at the entire IVF cycle. The negative shift revealed by testosterone in our study is unexpected and calls for further investigation with high-quality studies [65-67].

On the other hand, the theoretical advantages of testosterone and other androgens are proposed to include modulation of the decidualization process and decidual-trophoblast interactions, which are regarded as "the critical processes that control embryo implantation". Similar negative effects on the success of embryo transfers were seen by our study's use of growth hormone on univariate data, but these effects were not statistically significant once confounders were taken into account.

The effects of growth hormone use in IVF have only been studied in a few small-sample studies

to date, but results have been either non-significant or encouraging . Studies showing growth hormone's modulation of FSH effects on granulosa cells through up-regulation of insulin-like growth factor 1 synthesis have led to the proposed use of growth hormone as an adjuvant therapy in IVF. A better oocyte quality was predicted to result in a higher success rate for embryo transfer because these processes are crucial for follicular development and oocyte maturation.

Our univariate results contradicted this, with a focus on success after embryo transfer, and instead suggested that growth hormone may have negative effects on endometrial receptivity, despite its potential positive effects on earlier IVF cycle processes like oocyte quality and production. With the use of an hCG infusion, there were no discernible differences in the outcomes of embryo transfer.

Through a number of mechanisms, including angiogenesis, increased endometrial cell receptivity, and a decrease in natural killer cells, hCG promotes immunological tolerance of the embryo and may have favorable effects on implantation. Our information on hCG has already been published, but the results are slightly different because of the different study design.

While Craciunas et al.'s findings are similar, the effectiveness of hCG infusions as an adjuvant to IVF therapy has produced conflicting results. Our results do not support its use in IVF cycles because no meaningful beneficial effect can be shown in the Cochrane review . In our study, coenzyme Q10 use had no discernible effect on how successfully embryo transfers went.

Coenzyme Q10 supplementation may enhance mitochondrial function, scavenge free radicals, and prevent oxidative damage in oocytes, according to studies . Ben-Meir et al. in an aged animal model. (32) showed that adding coenzyme Q10 to a diet "delayed ovarian reserve depletion, restored oocyte mitochondrial gene expression, and improved mitochondrial activity.". Turi et al. Coenzyme Q10 in follicular fluid was first shown to exist in by's study (12). It has been hypothesized that this will increase implantation rates. In our study, this theory could not be significantly supported or refuted.

Conclusion

A large number of the interventions examined in this study fall short of demonstrating any effects on the success of embryo transfers. According to the findings of our analysis enoxaparin use has shown promising, possibly advantageous results.

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