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Seminal plasma cytokines: what role do they play in human female reproduction?

The success of artificial insemination with washed sperm and of embryo transfer has demonstrated that pregnancy is achievable without contact with seminal plasma (SP). However, it has become increasingly evident that the physiological changes at implantation are associated with immunoregulatory interactions between the female reproductive tract and SP. The human SP contains a number of cytokines including transforming growth factor-β (TGF-β), which is produced by seminal vesicles and the prostate. The concentration of TGF-β in the SP is extraordinarily high, approximately five-fold higher than in the blood serum. Previous studies have shown that seminal TGF-β1 is a key factor in the development of maternal tolerance to paternal antigens. For this reason SP has been used in clinical practice in an effort to increase the success rate of assisted reproductive techniques. However, studies examining SP exposure during *in vitro* fertilization (IVF) or IVF with intracytoplasmic sperm injection (ICSI) procedures have generated conflicting results.

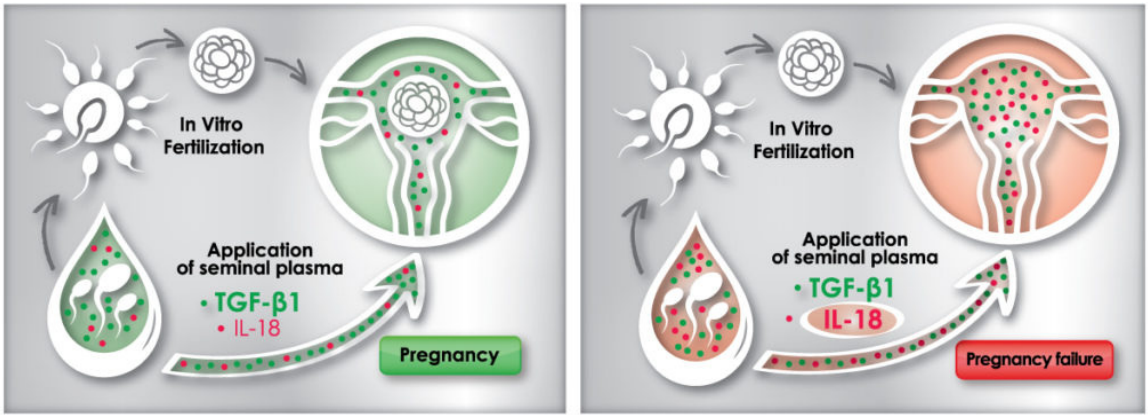

Fig. 1. Association between the reproductive success in patients exposed to sexual partner's seminal plasma during IVF/ICSI treatment and the levels of TGF-β1 and IL-18 in seminal plasma.

It should be noted that along with a favorable effect an adverse effect of SP on fertility and pregnancy may occur if the SP were to provide an insufficient, excessive or altered signal to the female reproductive system. Some cytokines may antagonize the synthesis or the effects of other cytokines. In this context, it was shown that TGF-β1 and interleukin (IL)-18 might serve opposite roles in immune regulation. Therefore, we have hypothesized that seminal IL-18 may thwart the beneficial effect of TGF-β1 during the early stages of pregnancy, potentially causing implantation failure.

In this study we have explored whether seminal TGF-β1 and IL-18 activity is associated with the reproductive outcome in patients exposed to SP during IVF/ICSI treatment. Patients (n=71) diagnosed with tubal factor infertility, who were undergoing IVF/ICSI treatment cycles, were recruited into the study. Patients had unprotected sexual relations until the 3-5th day prior the planned day of ovum pick-up (Day-OPU) and afterward not to have intercourse until the pregnancy results were known. The study group was

treated according to a fixed multi-dose gonadotropin-releasing hormone antagonist protocol. Just after oocyte pick-up, 0.5 ml fresh SP was injected into the vaginal vault of patients.

Quantitative measurements of total TGF-β1 (active plus latent) as well as IL-18 were determined by FlowCytomix™ technology. Comparison of the levels of the two cytokines in SP between pregnant and non-pregnant groups revealed that pregnancy is correlated with a lower concentration of IL-18 and lower content per ejaculate of IL-18 and TGF-β1. The TGF-β1/IL-18 ratio was significantly higher in pregnant group compared to non-pregnant group. Receiver operating characteristics analysis showed that IL-18 content per ejaculate is the most important predictor of IVF/ICSI success. The patient group defined by ≥1432.4 pg of IL-18 per ejaculate was found to have a low pregnancy rate (9.1%), whilst that defined by <1432.4 pg of IL-18 per ejaculate had a high pregnancy rate (61.2%). The content of TGF-β1 and IL-18 per ejaculate appears to be an essential factor determining the effect of unprotected intercourse before Day-OPU on the female immune response to embryo implantation.

In conclusion, this study shows for the first time that the levels of cytokines in SP are associated with reproductive success in patients exposed to SP during IVF/ICSI treatment. It also shows that determining the seminal fluid cytokine profile might be a useful tool for optimizing fertility treatments, in particular, assisted reproductive technologies. Further research is required to confirm the clinical importance of our findings.

Marina Nikolaeva, Gennady Sukhikh
The Federal State Budget Institution "Research Center for Obstetrics, Gynecology and Perinatology" of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

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