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## Intercourse and ART Success Rates

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### 1. Introduction

Embryo implantation is critically dependent on a supportive uterine environment. Uterine receptivity is the culmination of a cellular and molecular transformation mediated locally by paracrine signals under the governance of ovarian steroid hormones, with cells and cytokines of the immune system playing integral roles in this process (1,2). The implantation rates and subsequent pregnancy rates in In Vitro Fertilization (IVF) programs are lower than the normal fertile population. During IVF treatment regimens, intercourse is not allowed and artificial insemination is excluded. There is a substantial body of evidence supporting the need for exposure of the female reproductive tract to semen / seminal plasma around the time of embryo implantation in order to maximize reproductive efficiency (3). The aim of this chapter is to examine the available evidences suggesting why intercourse is beneficial or harmful to assisted reproductive techniques outcome.

In the reproductive process, seminal plasma is viewed primarily as a transport medium for spermatozoa traversing the female cervix and uterus after coitus (4, 5). However, studies in animal species show that seminal plasma also delivers to the female an array of signaling molecules that interact with epithelial cells lining the female reproductive tract. This interaction triggers local cellular and molecular changes that resemble an inflammatory response (6). In mouse and pig experiments, seminal fluid activates expression of several pro-inflammatory cytokines and chemokines in uterine epithelial cells (7-9). In turn, these factors amplify the actions of seminal fluid chemotactic agents resulting in vascular changes and recruitment and activation of macrophages, granulocytes and dendritic cells. These cells accumulate in the uterine endometrial tissue subjacent to the epithelial surface, and migrate between epithelial cells into the luminal cavity (9-11). The infiltrating leukocytes are implicated in clearance of seminal debris from the female tissues and potentially selection of fertilizing sperm (12,13). The infiltrating leukocytes may also influence the female immune response to seminal antigens and evoke tissue remodelling changes to condition the endometrial environment in preparation for pregnancy (3,6).

In mice and pigs, the epithelial cells of the uterine endometrium are the primary site of seminal fluid interaction and, the induced key cytokines are GM-CSF and IL-6, as well as the chemokines KC (mouse IL-8 homologue) and MCP-1 (7-9). Experiments with male mice by vasectomy or surgical removal of the seminal vesicle gland show that the active signaling

moieties (signaling molecules) are contained within the seminal plasma fraction of the ejaculate and are derived from the seminal vesicle (8). Cytokines of the transforming growth factor- $\beta$  (TGF- $\beta$ ) family are identified as the major active factors in mouse seminal plasma (14). Seminal TGF- $\beta$  is synthesized in the latent form in the seminal vesicle gland and is activated in the female tract upon deposition at mating (14).

However, how seminal fluid activates inflammatory cytokine synthesis or leukocyte infiltration in any compartment of the human female tract is unclear. Two previous *in vivo* studies in women have shown neutrophil exocytosis in the cervical tissues following either sexual intercourse or artificial insemination and they reported that sperm, but not seminal plasma, is required to elicit this "leukocytic reaction" (15,16). There are preliminary indications that signaling activity is also associated with the cell-free, plasma fraction of semen. *In vitro* studies demonstrate that human female reproductive tract cells can respond to seminal plasma, with increased IL-8 and secretory leukocyte protease inhibitor (SLPI) secretion from cervical explants (17). Endometrial epithelial cells are reported to show elevated synthesis of IL-1 $\beta$ , IL-6 and leukemia inhibitory factor (LIF) after culture with seminal plasma (18). Seminal fluid might also target infiltrating leukocytes directly, since IL-10 production in human monocyte U937 cells can be induced in response to seminal fluid constituents (17). Transmission of seminal factors in the female reproductive tract organizes molecular and cellular changes in the endometrium to facilitate embryo development and implantation.

## 2. Clinical studies

The available literature on the potential benefit of intercourse in patients undergoing assisted reproduction techniques is not extensive. To date; only two studies have examined the effect of intercourse around the time of embryo transfer on ART cycles (19, 20), while several studies have looked at the effect of artificial insemination with whole semen or seminal plasma (21-23). In a multicenter randomized study, patients undergoing fresh (400 cycles) and thawed (200 cycles) embryo transfer were randomized either to abstain or to engage in vaginal intercourse around the time of embryo transfer. There were no significant difference in pregnancy rates between the intercourse and abstinence groups but viability of transferred embryos at 6 - 8 weeks was significantly higher in the exposed semen group than abstained group. The authors' result indicates that exposure to semen around the time of embryo transfer increases the likelihood of successful early embryo implantation and development (19). In another study, 390 women were randomly divided into intercourse and abstinence groups during embryo transfer period and results indicated that intercourse did not significantly increase the pregnancy and implantation rates in ART cycles (20). Clinical pregnancy rates were not significantly different in two groups. In a prospective trial, Bellinge demonstrated an improved implantation rate with high vaginal deposition of a portion of their partners' semen samples compared with controls (21). However, in a subsequent prospective trial, Fishel found no significant effect of the use of high vaginal insemination at the time of oocyte recovery in patients undergoing IVF (22). Neither of these two reports utilized true randomization methods to assign treatment - control protocols. The final randomized control trial allocated patients to high vaginal insemination with either their partners' seminal plasma or a saline placebo at the time of oocyte retrieval (23). This study of 168 patients reported a 45% relative increase in implantation rates in the seminal plasma exposed group, but it did not reach statistical significance. In one retrospective study, postoperative intrauterine and intracervical insemination was performed in gamete intrafallopian transfer (GIFT) program

and the result showed that clinical pregnancy rates were higher in patients with additional postoperative insemination (24). In one randomized, double blind study, the absence or presence of seminal fluid in patients undergoing ovulation induction with intrauterine insemination was investigated. Intercourse was restricted. A comparison of clinical pregnancy rates between two groups showed no significant difference. Further in non-participants with unregulated intercourse, the pregnancy rates were not significantly different (25). Coulam and Stern suggested that higher implantation rates were obtained in a group of women experiencing infertility and/or recurrent spontaneous abortion who received vaginal capsules of seminal plasma versus placebo, however this difference was not significant (26). The same group reported that in women experiencing a history of recurrent spontaneous abortion, seminal plasma enhanced the probability of live birth by 21% (27). Therefore the vast majority of evidence suggests that exposure of the female reproductive tract to sperm/seminal plasma through either artificial insemination or intercourse does not have negative impact on outcome.

### 3. Discussion

Theoretically, intercourse can impair implantation by these mechanisms:

- i. the introduction of infection,
- ii. initiation of uterine contractions (at orgasm),
- iii. pressure created by penile contact with the cervix may dislodge the embryos, furthermore intercourse may produce painful rupture of ovarian follicles.

Intercourse has been linked with ascending uterine infection during late pregnancy (28), and subclinical infection of the upper reproductive tract is associated with poor IVF embryo transfer outcome (29). During an IVF cycle the uterine cavity is vulnerable to intercourse related infection since the cervical mucus barrier that prevents ascending infection is disrupted by passage of the embryo transfer catheter. On the other hand, Sharkey et al investigated seminal plasma induction of inflammatory cytokines and chemokines gene regulation in human cervical vaginal epithelial cells in vitro. These experiments show that seminal plasma can elicit expression of a range of inflammatory cytokines and chemokines in reproductive epithelia, and implicate the ectocervix as the primary site of responsiveness. Seminal factor regulation of inflammatory cytokines in the cervical epithelium is implicated in controlling the immune response to seminal antigens. This inflammatory cytokines also is responsible for defense against infectious agents introduced at intercourse (30). Intercourse increases uterine myometrial activity during female orgasm (31) and these contractions may interfere implantation of early embryo since high levels of spontaneous uterine activity are associated with poor IVF outcome (32, 33). On the positive side, intercourse may act to assist implantation. Seminal plasma induction of the pro - inflammatory and chemotactic cytokines supports the interpretation because one function of seminal fluid is to activate an inflammatory cascade after deposition in the human female reproductive tract at intercourse, analogous to the consequences of mating in mice (6) and in pigs (8). Since each of these factors also regulates leukocyte recruitment and activation in humans, it is likely that elevated production of the pro - inflammatory and chemotactic cytokines in the cervix elicits changes in local leukocytes, which manifest as the post - coital leukocytic reaction in women (15, 16). Epithelial cell regulation of this response is consistent with the notion that epithelial cytokines control accumulation and functional behavior of local dendritic cell, macrophage and

granulocyte populations in other epithelia (34). However, since the effects of seminal fluid on leukocytes have not been examined, the possibility of direct seminal fluid signaling in these cells contributing to the response, cannot be excluded. Active synthesis of a wider range of cytokines in the cervix after intercourse would facilitate optimal competence in protecting the higher reproductive tract from pathogen invasion and in reinforcing the defensive barrier function of this epithelial surface (35).

Induction of GM-CSF and IL-6 in the cervical tissues would influence the activation status of local antigen-presenting cells, programming phenotypes that impact the ensuing response to antigens processed by those cells (36-39). The significance of these two cytokines being preferentially expressed in the ectocervix is consistent with this tissue being the primary site for female 'sampling' of paternal antigens. Their presence together with the action of the immune-deviating agents TGF $\beta$  and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in seminal fluid would be expected to ensure that the outcome of any antigen-specific immune response did not adversely affect female tolerance of any future exposure to semen. Similarly, uptake and processing of male antigens in semen may provide an opportunity for priming the maternal immune response in preparation for an ensuing pregnancy fathered by the same male, since the conceptus shares many of the same paternal antigens (13, 39). IL-6, together with LIF and IL-1 $\beta$ , can also be induced in uterine endometrial cells by seminal factors *in vitro* (18), where it appears to be a key determinant of uterine receptivity at embryo implantation (40,41). This suggests that the action of seminal fluid in regulating the quality of female tract immune responses may extend higher into the female tract, after transport of active seminal constituents by uterine peristaltic contractions which transport macromolecular material as high as the fallopian tube (42). Whether GM-CSF, IL-8 and IL-6 can also be induced in endometrial cells or not needs to be examined.

#### 4. Conclusion and recommendations

A large number of randomized control trials suggest that intercourse around the time of embryo transfer improves IVF implantation rates and increases pregnancy rates in ART cycle, but some studies thought that intercourse did not significantly increase pregnancy rate. While this mechanism of intercourse improving pregnancy rate is not fully understood, it seems that semen/seminal plasma could induce immune reactions in female reproductive tract that augments embryo development and endometrial receptivity. On the negative side, hyperstimulated ovaries are vulnerable to rupture during intercourse. Therefore, we suggest that intercourse around the time of embryo transfer should be encouraged, except in the small subgroup of women with large hyperstimulated ovaries.

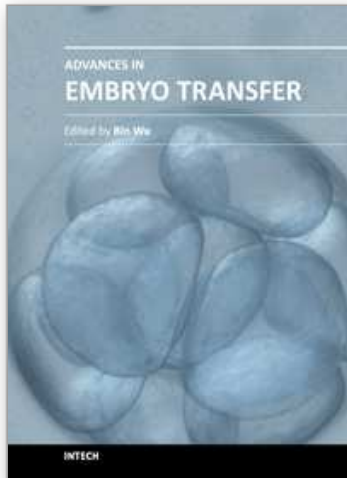
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Embryo transfer has become one of the prominent high businesses worldwide. This book updates and reviews some new developed theories and technologies in the human embryo transfer and mainly focus on discussing some encountered problems during embryo transfer, which gives some examples how to improve pregnancy rate by innovated techniques so that readers, especially embryologists and physicians for human IVF programs, may acquire some new and usable information as well as some key practice techniques. Major contents include the optimal stimulation scheme for ovaries, advance in insemination technology, improved embryo transfer technology and endometrial receptivity and embryo implantation mechanism. Thus, this book will greatly add new information for readers to improve human embryo transfer pregnancy rate.

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