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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-β (TGF-B) family are identified as the major active factors in mouse seminal plasma (14). Seminal TGF-B 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-1β, IL-6 and leukaemia 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 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 TGFβ and prostaglandin E_2 (PGE_2) 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, uptaking 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-1β, 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 of randomized control trials suggest that intercourse around the time of embryo transfer improve IVF implantation rates and increase 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.

5. References

[1] Rogers PAW, Murphy CR. Uterine receptivity for implantation: human studies. In: Yoshinaga K , editors . Blastocyst implantation. Norwell , MA: Serono Symposia Press. 1989; 231 – 280

[2] Finn CA, Martin L. The control of implantation. J Reprod Fertil. 1974; 39(1): 195-206.

[3] Robertson SA, Mau VJ, Hudson SA, et al. Cytokine-leukocyte networks and the establishment of pregnancy. Am J Reprod Immunol 1997;37:438-442.

[4] Mann T. The Biochemistry of Semen and the Male Reproductive Tract. John Wiley and Sons, Inc., New York; 1964

[5] Aumuller G, Riva A. Morphology and functions of the human seminal vesicle. Andrologia 1992;24:183-196.
[6] Robertson SA. Seminal plasma and male factor signalling in the female reproductive tract. Cell Tissue Res 2005;322:43-52.
[7] Robertson SA, Mayrhofer G, Seamark RF. Uterine epithelial cells synthesize granulocyte-macrophage colony-stimulating factor and interleukin-6 in pregnant and nonpregnant mice. Biol Reprod 1992;46:1069-1079.
[8] Robertson SA, Mau VJ, Tremellen KP, et al. Role of high molecular weight seminal vesicle proteins in eliciting the uterine inflammatory response to semen in mice. J Reprod Fertil 1996;107:265-277.
[9] O'Leary S, Jasper MJ, Warnes GM, et al. Seminal plasma regulates endometrial cytokine expression, leukocyte recruitment and embryo development in the pig. Reproduction 2004;128:237-247.
[10] Phillips DM, Mahler S. Migration of leukocytes and phagocytosis in rabbit vagina. J Cell Biol 1975;67:334a.
[11] McMaster MT, Newton RC, Dey SK, et al. Activation and distribution of inflammatory cells in the mouse uterus during the preimplantation period. J Immunol 1992;148:1699-1705.
[12] Mattner PE. Phagocytosis of spermatozoa by leucocytes in bovine cervical mucus in vitro. J Reprod Fertil 1969;20:133-134.
[13] Roldan ER, Gomendio M, Vitullo AD. The evolution of eutherian spermatozoa underlying selective forces: female selection sperm competition. Biol Rev Camb Philos Soc 1992;67:551-593.
[14] Tremellen KP, Seamark RF, Robertson SA. Seminal transforming growth factor beta1 stimulates granulocyte-macrophage colony-stimulating factor production and inflammatory cell recruitment in the murine uterus. Biol Reprod 1998;58:1217-1225.
[15] Pandya IJ, Cohen J. The leukocytic reaction of the human uterine cervix to spermatozoa. Fertil Steril 1985;43:417-421.
[16] Thompson LA, Barratt CL, Bolton AE, et al. The leukocytic reaction of the human uterine cervix. Am J Reprod Immunol 1992;28:85-89.
[17] Denison FC, Grant VE, Calder AA, et al. Seminal plasma components stimulate interleukin-8 and interleukin-10 release. Mol Hum Reprod 1999;5:220-226.
[18] Gutsche S, von Wolff M, Strowitzki T, et al. Seminal plasma induces mRNA expression of IL-1beta, IL-6 and LIF in endometrial epithelial cells in vitro. Mol Hum Reprod 2003;9:785-791.
[19] Tremellen KP, Valbuena D, Landeras J, Ballesteros A, Martinez J, Mendoza S,et all. The effect of inter course on pregnancy rates during assisted human reproduction. Hum Reprod.2000;15(12):2653-2658.
[20] Aflatoonian A., Ghandi S., Tabibnejad N. The effect of entercourse around Embryo Transfer on Pregnancy Rate in Assisted Reproductive Technology Cycles. IJFS 2009;2: 169-172
[21] Bellinge BS, Copeland CM , Thomas TD, et al. The influence of patient insemination on the implantation rate in an in vitro fertilization and embryo transfer program. Fertil Steril 1986; 46: 252 – 6.
[22] Fishel S, Webster J, Jackson P, Faratian B. Evaluating of high vaginal insemination at oocyte recovery in patients undergoing *in vitro* fertilization. Fertil Steril. 1989;51:135-138.
[23] Von Wolff M, Rosner S, Thone C, et al. Intravaginal and intracervical application of seminal plasma in in vitro fertilization or intracytoplasmic sperm injection treatment

cycles – a double blind , placebo – controlled , randomized pilot study . Fertil Steril 2009 ; 91:167 – 72

[24] Tucker MJ, Wong CJ, Chan YM, Leong MK, Leong CK. Post-operative artificial insemination –does it improve GIFT outcome? Hum Reprod. 1990;5(2):189-192.

[25] Qasim SM, Trias A, Karacan M, Shelden R, Kemmann E. Does the absence or presence of seminal fluid matter in patients undergoing ovulation induction with intrauterine insemination? Hum Reprod. 1996; 11(5):1008-1010.

[26] Coulam C.B and Stern, J.J. Effect of seminal plasma on implantation rates. Early pregnancy: Biol. Med, 1995;1: 33 – 36.

[27] Stern, J.J, Coulam, C.B, Wagenknecht, D.R, Peters AJ, et al. Seminal plasma treatment of recurrent spontaneous abortion. Am J Reprod Immunol, 1992;27,50.

[28] Naeye RL. Coitus and associated amniotic-fluid infection. N Engl J Med. 1979;29;301(22):1198-200.

[29] Fanchin R, Harmas A, Benaoudia F. Microbial flora of the cervix assessed at the time of embryo transfer adversely affects *in vitro* fertilization outcome. Fertil Steril. 1998;70(5):866-870.

[30] Sharkey DJ, Macpherson Am, Tremellen KP, Robertson SA. Seminal plasma differentially regulates inflammatory cytokine gene expression in human cervical and vaginal epithelial cells. Mol Hum Reprod. 2007 Jul;13(7):491-501.

[31] Fox CA, Wolff HS, Baker JA. Measurement of intra-vaginal and intra-uterine pressures during human coitus by rodio-telemetery. J Reprod Fertill. 1970;22(2)243-251.

[32] Fanchin R , Righini C , Olivennes F . Uterine contractions at the time of embryo transfer alter pregnancy rates after in vitro fertilization . Hum Reprod . 1998 ; 13(7):1968 – 1974

[33] Fanchin R , Righini C , Ayoubi JM, Olivennes F , de Ziegler D . Uterine contractions at the time of embryo transfer : a hindrance to implantration ? Contracept Fertil Sex . 1998 jul – Aug : 26(7 – 8): 498 – 505

[34] Barker JN, Mitra RS, Griffiths CE, et al. Keratinocytes as initiators of inflammation. Lancet 1991;337:211-214

[35] Quayle AJ. The innate and early immune response to pathogen challenge in the female genital tract and the pivotal role of epithelial cells. J Reprod Immunol 2002;57:61-79.

[36] Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony- stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. J Exp Med 1994;179:1109-1118.

[37] Burnham K, Robb L, Scott CL, et al. Effect of granulocyte-macrophage colony-stimulating factor on the generation of epidermal Langerhans cells. J Interferon Cytokine Res 2000;20:1071-1076.

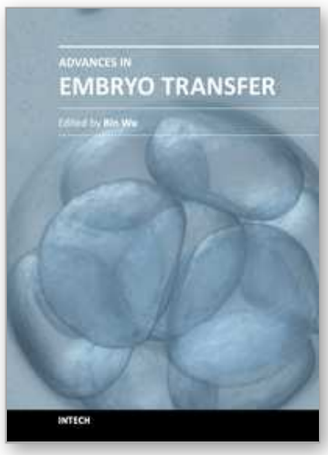
[38] Diehl S, Rincon M. The two faces of IL-6 on Th1/Th2 differentiation. Mol Immunol 2002;39:531-536.

[39] Thompson LA, Barratt CL, Bolton AE, et al. The leukocytic reaction of the human uterine cervix. Am J Reprod Immunol 1992;28:85-89.

[40] Lim KJ, Odukoya OA, Ajjan RA, et al. The role of T-helper cytokines in human reproduction. Fertil Steril 2000;73:136-142.

[41] Jasper MJ, Tremellen KP, Robertson SA.Reduced expression of IL-6 and IL-1alpha mRNAs in secretory phase endometrium of women with recurrent miscarriage. J Reprod Immunol 2007;73:74-84.

[42] Kunz G, Leyendecker G. Uterine peristaltic activity during the menstrual cycle: characterization regulation function dysfunction. Reprod Biomed Online 2002;4 Suppl 3:5-9.



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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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