Local and systemic factors and implantation: what is the evidence?

Chelsea Fox, M.D.,[a] Scott Morin, M.D.,[b,c] Jae-Wook Jeong, Ph.D.,[d] Richard T. Scott Jr., M.D.,[b,c] and Bruce A. Lessey, M.D., Ph.D.[a]

[a] Department of Obstetrics and Gynecology, Greenville Health System, Greenville, South Carolina; [b] Reproductive Medicine Associates of New Jersey, Basking Ridge, New Jersey; [c] Division of Reproductive Endocrinology, Department of Obstetrics, Gynecology, and Reproductive Sciences, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey; and [d] Department of Obstetrics, Gynecology and Reproductive Biology, Michigan State University, Grand Rapids, Michigan

Significant progress has been made in the understanding of embryonic competence and endometrial receptivity since the inception of assisted reproductive technology. The endometrium is a highly dynamic tissue that plays a crucial role in the establishment and maintenance of normal pregnancy. In response to steroid sex hormones, the endometrium undergoes marked changes during the menstrual cycle that are critical for acceptance of the nascent embryo. There is also a wide body of literature on systemic factors that impact assisted reproductive technology outcomes. Patient prognosis is impacted by an array of factors that tip the scales in her favor or against success. Recognizing the local and systemic factors will allow clinicians to better understand and optimize the maternal environment at the time of implantation. This review will address the current literature on endometrial and systemic factors related to impaired implantation and highlight recent advances in this area of reproductive medicine. (Fertil Steril® 2016;105:873–84. ©2016 by American Society for Reproductive Medicine.)

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This review will address the current literature on endometrial and systemic factors related to impaired implantation and highlight recent advances in this area of reproductive medicine. The review will be divided into two major parts: the first section will address endometrial factors; the second part, systemic factors.

IMPAIRED EXPRESSION OF ENDOMETRIAL FACTORS CORRELATES WITH REDUCED IMPLANTATION

Introduction

The human endometrium is a hormone-responsive mucosa that lines the uterine cavity and undergoes cyclic proliferation and differentiation to support embryo implantation (1). During the proliferative phase the endometrium grows in response to estrogen (E), arising from the remaining basalis layer that remains after menstruation. A dynamic transition from proliferation to a secretory morphology occurs after ovulation (2), orchestrated directly and indirectly by the sex steroids E and P (1), and is further mediated by a complex array of secondary autocrine and paracrine factors, including cytokines and chemokines and their receptors and second messengers (3, 4).

Endometrial development after ovulation normally culminates with a defined period of endometrial receptivity. The secretory phase is divided into three recognized stages. The early secretory phase, from postovulatory days 1 to 5, is characterized histologically by initiation of secretory products and characterized by the presence of subnuclear vacuoles that traverse the cells by postovulatory day 6 (5). The mid-secretory phase, representing the window of implantation and time of maximal endometrial receptivity, occurs from postovulatory day 6 to 10. During this period stromal cells are undergoing pseudo-decidualization reactions, and epithelial cells develop specialized structures known as pinopodes (6) and cell adhesion molecules (7–9). The third phase in nonconception cycles represents the late luteal phase (postovulatory days 11–14), during which preparation for menstruation occurs. In the absence of the nidatory hCG signal from the embryo, endometrial breakdown occurs, associated with apoptosis and an orchestrated inflammatory response that leads to an orderly and

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Reprint Requests: Bruce A. Lessey, M.D., Ph.D., Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Greenville Health System, 890 W. Faris Road, Ste. 470, Greenville, South Carolina 29605 (E-mail: blessey@ghs.org).

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brief episode of menstrual shedding in anticipation of the next cycle (10). When pregnancy occurs, decidualization of the endometrial stroma transforms into a specialized epithelialized mesenchymal structure, essential for pregnancy (11, 12).

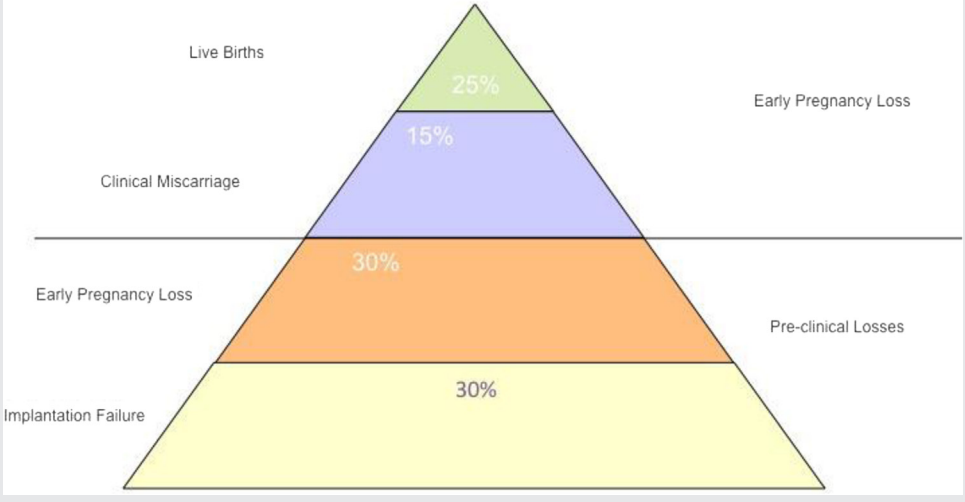
The mid-secretory phase coincides with the entry into the uterine cavity of the preimplantation blastocyst, with the differentiation of trophectoderm by postovulatory day 5. A defined period of endometrial receptivity during the mid-secretory phase also corresponds well to prime responsiveness of the corpus luteum (CL) to hCG (13, 14). In fact, evidence from the 1999 Wilcox study shows that late-implanting embryos are at higher risk for miscarriage than those that implant during the window of implantation (WOI), between postovulatory days 6 and 10 (15). One interpretation for these interesting findings is that a sustained rescue of the corpus luteum occurs best at the time of normal implantation. This hypothesis is supported by early studies that examined CL rescue in response to early or late administration of hCG (13). The CL has a more robust response to hCG administered on postovulatory days 8–10 compared with postovulatory days 11–14, and P may fall more quickly in early losses or implantation failure than after pregnancy is established (16). Our intention in this review, however, will be to focus not on the CL but rather on uterine factors that contribute to a delay in implantation that then contributes to both pregnancy loss and implantation failure.

The efficiency of human reproduction is relatively low compared with other mammalian species. As summarized by Macklon et al. (17) (Fig. 1), there are many more implantation failures and early clinical and preclinical losses than successful pregnancies. Although this is obvious to the clinician who treats infertility, our understanding of the basis for defects in endometrial receptivity has remained fragmented. A failed pregnancy can be the result of many diverse factors, including chromosomal defects in the nascent embryo, mechanical causes in the reproductive tract, or inflammatory changes associated with disease. Assigning cause and effect in terms of the embryo or endometrial defects has been problematic. In this era of preimplantation genetic screening, answers may be forthcoming. In a report on a large series of euploid blastocysts, the proportion of euploid embryos failing to implant was approximately 40% (18). For those who study endometrial receptivity defects, those data may be a "smoking gun" regarding the importance of the endometrium.

Do Endometrial Receptivity Defects Exist?

Historically, Georgianna Seegar Jones might have been the first investigator to show that defects in the endometrial histology could be associated with infertility (19). Using the then newly identified morphologic changes in the secretory phase endometrium (5), she noted for the first time that women with infertility could have a lag in predicted endometrial histologic development, a term she coined as "luteal phase deficiency." It is worth noting that the existence and impact of luteal phase deficiency has come under question (20, 21). Nevertheless, the concept of a shifting WOI has been shown to have continued importance. In a landmark study by Wilcox et al. in 1999 (15), it was noted that women who implant beyond the normal window had an increasing chance for pregnancy loss. Biochemical defects have also been described that support a concept of a delayed WOI and retarded histology, including the use of placenta protein-14 (also knows as glycodelin), integrins, MUC-1, pinopods, leukemia inhibitory factor, and many others (22–26). In addition, cycles without histologic lag have been described that display defects in key biomarkers of endometrial receptivity as well (27, 28).

FIGURE 1



The hidden impact of implantation failure. Adapted from Macklon et al. (17).

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