Endometrial function: facts, urban legends, and an eye to the future

Diana Valbuena, M.D., Ph.D.,[a] Cecilia T. Valdes, M.D.,[b] and Carlos Simon, M.D., Ph.D.[a,b,c,d]

[a] Igenomix, Parc Cientific Valencia University, Valencia, Spain; [b] Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas; [c] Department of Obstetrics and Gynecology, Valencia University and INCLIVA, Valencia, Spain; and [d] Department of Obstetrics and Gynecology, Stanford University, Stanford, California

The embryo alone, though very important, is not sufficient to explain successful or failed implantation. Human embryonic implantation is less efficient than in nonmenstruating species. The main difference lies in the decidual control of early implantation events and the subsequent course of pregnancy versus embryo control in nonmenstruating species. In this article, we introduce the facts behind the low efficiency of this crucial process, address urban legends routinely considered without high clinical quality evidence, and provide a vision of how the endometrial field will develop in the near future. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)

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"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less." (Marie Curie, 1867–1934)

When a morphologically and/or chromosomally normal embryo is transferred into an otherwise normal uterus and the patient has her menstruation in due course, there has been an unexplained event. How is this possible when I transferred a wonderful blastocyst into a normal uterus: What happened? In the absence of clear evidence, clinicians often begin to "believe" in a particular treatment or explanation of observed outcomes based on anecdotal evidence. For example, unable to explain failure of implantation of a euploid embryo in a seemingly normal endometrium, we become illogical and begin to search for, and apply, unproven tests and cures based on single cases and inevitably biased information.

When success or failure relies on collaboration between two partners, the functionality and synchronization of both are necessary. Therefore, the obvious answer is that the embryo alone, although very important, is not sufficient for implantation. Let us start from the beginning.

THE FACTS: WHY HUMAN EMBRYONIC IMPLANTATION IS LESS EFFICIENT THAN IN NONMENSTRUATING SPECIES

This issue is certainly fundamental but has not received all the attention it deserves. Women menstruate in a continuously resetting process from menarche to menopause to synchronize the arrival of a blastocyst to the uterine cavity during the endometrial window of implantation (WOI), allowing blastocyst adhesion followed by completion of decidualization of the endometrial stroma, which then controls trophoblast invasion and subsequent placentation.

Progesterone withdrawal is the "trigger" for menstruation in women and primates in nonpregnancy cycles. Clinically, we discuss "secretory transformation" of the endometrium that is classically seen histologically in the epithelium and indicates evidence of progesterone effect. On closer inspection, the prerequisite for menses to occur in women seems to be progesterone-induced endometrial transformation of the entire endometrium, epithelium, and stroma. In its broadest sense, decidualization is the postovulatory process of endometrial remodeling in preparation for pregnancy, which includes secretory transformation of the uterine glands, influx of specialized immune cells, and vascular remodeling. But of crucial relevance is the so-called decidualization process, which involves specifically the morphologic and biochemical reprogramming of the endometrial stromal compartment (1). The formation of the decidua is a conceptus-independent progressive process that involves hormonally regulated differentiation of maternal endometrial

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Reprint requests: Carlos Simon, M.D., Ph.D., Igenomix, Department of Obstetrics and Gynecology, Parc Cientific Valencia University, Paterna, Valencia 46980, Spain (E-mail: carlos.simon@igenomix.com).

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fibroblast-like stromal cells (2). This transformation begins in the midsecretory phase of the menstrual cycle around uterine spiral arterioles, immediately after the plasma membrane transformation that occurs in the luminal epithelium that is mandatory for the acquisition of endometrial receptivity (3).

Decidualization is driven by the postovulatory or endogenous rise in progesterone levels, increasing local cyclic adenosine monophosphate production (4–6), which stimulates synthesis of a complex network of intracellular and secreted proteins (7). Morphologically, this process is characterized by the transformation of elongated fibroblast-like stromal cells (ESCs) into enlarged polygonal/round cells shaped by a complex intracellular cytoskeleton rearrangement (8, 9). Decidualized ESCs secrete specific biomarkers, such as prolactin and insulin-like growth factor binding protein 1, both known to play an important role in endometrial differentiation and control of placental cytotrophoblast invasion (10, 11).

When decidualization is blocked, women don't menstruate. Progesterone receptor (PR) ligands, such as selective progesterone receptor modulators (SPRMs), consistently produce amenorrhea via preventing endometrial stromal decidualization; in fact, PR expression in stroma and epithelium is impressively reversed in women exposed to SPRMs (12). In nonmenstruating species, such as rodents, tissue breakdown and bleeding do not occur in response to progesterone withdrawal. Instead of shedding, considerable remodeling and reabsorption of the endometrium takes place. The endometrium of nonmenstruating mammals only decidualizes if there is contact between the embryo and endometrium, i.e., in implantation or if induced by oil or injury.

This takes us to the core issue: the low efficiency of human embryo implantation with euploid embryos, with rates of 50%–65% in various types of endometrial thickness and patterns (13) compared with other mammals (rodents 95%, rabbits 96%). The main difference between humans and rodents lies in the decidual control of human implantation and the subsequent course of pregnancy versus embryo control in rodent implantation. This preponderance of the rodent embryo directing implantation is exemplified by the interesting process known as delayed implantation, or embryonic diapause (14). In mice and rats, ovariectomy or hypophysectomy prevents preimplantation estrogen secretion and results in delayed implantation with blastocysts becoming dormant within the quiescent uterus (15). A single injection of 3 ng estrogen will initiate blastocyst activation and implantation in progeterone-primed mice undergoing delayed implantation (16).

The control of implantation by the endometrium versus the embryo clarifies the low IVF efficiency in humans and the frequent failure of implantation even after embryo transfer of a perfectly normal human embryo. The maternal endometrium is an important limiting factor; we should pay more attention to it!

URBAN LEGENDS

"The plural of anecdote is not data." (Marc Bekoff)

Modern evidence-based medicine is based on the scientific method, conceived by Francis Bacon, whose end goal is greater understanding of various phenomena that can be verified in an unbiased way. Simplified, this approach requires that any tentative description, a hypothesis, must be supported or refuted by evidence. When evidence is consistent, the hypothesis becomes a theory that provides a coherent set of principles to explain a class of phenomena; these principles can then be applied clinically. Biased data, beliefs, conjectures, presumptions, premises, and putative mechanisms without scientific plausibility do not advance our quest toward excellence in the advancement of human health.

It Is Not About Scratching

Because decidualization is induced in rodents and other nonmenstruating species by injuring the endometrial cavity, let's assume that humans are like rodents and injure the endometrial cavity of our patients. The patient, informed by the media, asks for endometrial scratching: Should I do it?

Endometrial scratching (ES) refers to intentional damage to the endometrial lining in the hope of "improving" endometrial receptivity and pregnancy rates. Data do not support the efficacy of this approach, and the biologic responses induced by ES remain uncertain. No consensus exists in published literature about what ES is, how to perform it, how often, when, or in whom. Many such endometrial interventions have been described, including endometrial manipulation during hysteroscopy alone or in addition to endometrial biopsy or curettage, as well as endometrial biopsy alone (17–32). During endometrial biopsy, different types of catheters have been used—Pipelle de Cornier, Novak curette, Tao Brush, Karman cannula, forceps—with no indication of where in the uterine cavity the procedure was performed (19–30, 32). Furthermore, endometrial tissue obtained from the curettage has never been analyzed to determine how deep the "intervention" reached. The number of "scratchings" performed varied (one or two), as did the timing of the procedure within the menstrual cycle: during the follicular phase, during the luteal phase, or during both phases of the same cycle (18–32). In addition, variation exists in the length of time from ES to embryo transfer; it has been performed in the previous cycle or in the same cycle (18–32). The study populations included heterogeneous infertile women undergoing different treatments, including programmed intercourse, intrauterine insemination, and IVF with at least one IVF failure, or patients with recurrent implantation failure (RIF) (20–26, 28–32).

Despite this great number of variables, ES has been considered as a singular method and has been the subject of 15 randomized controlled trials (RCTs) and five meta-analyses (20–39). A close examination of published data indicates no beneficial effect in reproductive outcome (38, 39). The best study to date was a properly powered RCT involving 300 unselected infertile women undergoing IVF randomized to ES or not in the midluteal phase of the menstrual cycle. No significant differences were found in implantation rate (32.8% vs. 29.7%; $P=.120$), cumulative pregnancy rate (34% vs. 38%; $P=.548$), or ongoing pregnancy rate (26.7% vs. 32.0%; $P=.375$) (23). ES is an