To What Extent Does Endometrial Receptivity Influence the Outcome of Assisted Reproductive Technology?

Despite recent advances in reproductive medicine, the role played by endometrial receptivity in contributing to human infertility remains controversial. There are at least two major reasons for this situation. First, implantation is a complex process that is influenced by many interacting variables. Thus it is impossible to design rigorous scientific studies that adequately incorporate all the variables that may influence endometrial receptivity. Second, there are major practical and ethical constraints that prevent the gathering of controlled, objective data about many of the factors that govern embryo implantation in humans.

Understanding of the basic mechanisms controlling implantation in the human is based primarily on animal studies. However, this leads to further uncertainty due to the wide variability that exists from species to species in the manner by which the embryo comes into contact with the endometrium (1). Despite this, numerous animal studies have identified an obligatory role for the endometrium in controlling the success of implantation, leading to the concept of an "implantation window," defined as the period when the uterus is receptive to the implanting blastocyst. Statistical analysis of *in vitro* fertilization (IVF) multiple pregnancy data has provided strong evidence that in the human, as in other species, the uterus has selective mechanisms by which the implanting embryo can be accepted or rejected (2).

The advent of assisted reproductive technologies has led to the clinical requirement for a better understanding of the implantation window in humans and the endometrial features that constitute a receptive endometrium. Based on donor oocyte data (3), it has been estimated that successful implantation can occur when embryo development is anywhere from 39 hr in front to 48 hr behind the uterus, thus giving an implantation window of at least 3.5 days.

Identification of one or more endometrial parameters that definitely indicate receptivity for implantation remains an elusive goal. Unfortunately, despite many well-documented endometrial changes around the time of implantation, it appears unlikely

that obligatory markers for uterine receptivity will be conclusively established in the near-future. The primary reason for this revolves around the ethical dilemma that prevents endometrial sampling from a uterus known to contain periimplantation-stage embryos. As a consequence, it is not possible to plan objective controlled studies in which different endometrial parameters can be correlated with the success or failure of the implantation process.

It is also possible that there may not be any obligatory markers of human endometrial receptivity. Because implantation can occur ectopically in most tissues regardless of endocrine status, it is quite plausible that endometrial receptivity occurs due to the loss of implantation inhibitors [for example, epithelial tight junctions (4)], rather than the appearance of any particular feature. Alternatively, endometrial receptivity may occur only if a number of features are more or less present, rather than any one feature being obligatory. Thus implantation might be successful if any 7 of 10 key events are satisfactory, rather than just 1 event controlling the whole process.

The endometrium undergoes a well-established series of histologic and ultrastructural changes under the influence of estrogen and progesterone during the menstrual cycle. However, there is considerable doubt about the functional importance of these morphological changes with respect to uterine receptivity for implantation. For example, morphometric analysis of a biopsy taken inadvertently from a conception cycle of a patient receiving hormone replacement therapy for premature ovarian failure produced results that were not typical for receptive endometrium (5). Despite this, implantation had occurred. In contrast, detailed morphometric analysis of periimplantation endometrium has failed to demonstrate any difference between fertile controls and infertile subjects (6). Finally, the endometrial glandular volume in IVF patients receiving clomiphene citrate and human menopausal gonadotropin for ovarian stimulation is significantly reduced compared with that in the normal menstrual cycle (7), while patients receiving gonadotro-

pin releasing hormone analogue "flare" stimulation have an elevated glandular area. Despite these differences, which probably reflect differing levels of estrogenic stimulation, successful implantation and pregnancy are common with both types of endometrium. In summary, implantation can occur in an endometrium with morphological features that are significantly different from normal, and there is no conclusive evidence yet available to show that any particular structural defect correlates specifically with reduced uterine receptivity.

Despite the current lack of correlation between structural features and endometrial receptivity, a number of factors have been proposed as markers of uterine receptivity, based either on a known or proposed role in the implantation process or a reduced appearance in cases of infertility where implantation is thought to be compromised. Four such markers of receptivity are briefly discussed below. It has been claimed that integrins may play a role in determining uterine receptivity for embryo implantation, with particular emphasis on the temporal expression of α_1 , α_4 , and β_3 by endometrial glandular epithelial cells (8). However, no objective evidence is available that any integrins are obligatory markers for receptivity. In women who suffer recurrent miscarriage there is evidence for reduced levels of four mucin-related secretory epitopes (9), suggesting that these molecules play a significant role in the establishment and maintenance of early pregnancy. Maternal leukemia inhibitory factor (LIF) is obligatory for successful implantation in mice and LIF RNA elevates significantly in the mid-to-late secretory phase in humans (10). The protein can also be detected by immunocytochemistry in glandular epithelium at this time, and polymerase chain reaction analysis of early human embryos identifies the presence of mRNA for the LIF receptor. Finally, women with unexplained infertility have significantly lower levels of endometrial CD8+ (T suppressor/cytotoxic) and CD56+ (natural killer) cells, and higher levels of CD4+ (T helper/inducer) cells, than fertile controls (11).

Endometrial thickness and ultrasound pattern on the day before oocyte retrieval may be indicators of the likelihood of achieving pregnancy (12). These findings have been supported in part by a report that a multilayered echogenic pattern was predictive of pregnancy but that the endometrial thickness was not (13). Similarly, color Doppler investigations have shown that an increased uterine artery pulsatility index at the time of embryo transfer

may be associated with a reduced implantation rate (14).

Natural fecundity begins to fall from age 30 to age 35, with the decline becoming more noticeable after age 40 (15). Oocyte donation programs have provided an important avenue for investigating the relative contributions of uterine and embryonic factors to this age-related decline in human fertility. Although evidence suggests that the uterus becomes decreasingly receptive to implantation and the maintenance of pregnancy with increasing age, it appears that the primary effect is due to declining oocyte quality (16). Pregnancy rates of 32.7% in women aged 50–62 (17) have been reported using oocytes donated by younger women, thus establishing that the human uterus can support pregnancy well after the end of the normal reproductive life span. On a cautionary note, however, it is important to recognize that significant maternal morbidity is associated with postmenopausal pregnancy. In the aforementioned study (17), gestational diabetes was present in 16.6% of the patients that delivered, compared to 0% of donors and 0.35% of the normal population, and moderate or severe preeclampsia affected 41.6% of the subjects, compared with 0% of donors and 7.3% of the normal population. There is little basic scientific evidence available to indicate what may cause endometrial receptivity reduction with increasing age. It is known that in older women ovulation occurs later in the cycle, the leading follicle diameter is less, follicle stimulating hormone and luteinizing hormone levels are elevated, and, somewhat surprisingly, the endometrial thickness is increased (18).

In conclusion, there is a clear need for more basic research on the mechanisms by which embryo implantation occurs in the human, with particular emphasis on the endometrial factors that influence receptivity. Until this happens, clinical strategies to improve endometrial receptivity will remain very much empirical and scientifically unproven.

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