Both slowly developing embryos and a variable pace of luteal endometrial progression may conspire to prevent normal birth in spite of a capable embryo

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Embryonic implantation requires synchrony between the endometrium and the embryo. When analyzed in isolation, competent embryos may be unsuccessful when placed on a nonreceptive endometrium or vice versa, contributing to the "black box" of implantation failure. It is when the two are assessed together that dyssynchrony becomes evident, due to premature progesterone stimulus on the endometrium, physiologic displacement of the window of implantation or late blastulation of the embryo, or all combined. From the embryonic component, detailed assessment of the timing of blastulation is essential. The molecular diagnosis of endometrial receptivity based on its transcriptomic signature could be superior to other techniques used in the past for defining the endometrial window of implantation. (Fertil Steril® 2016;105:861–6. ©2016 by American Society for Reproductive Medicine.)
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EMBRYO AND ENDOMETRIAL SYNCHRONY: IT TAKES TWO

Normal implantation requires synchrony between the endometrium and the embryo. That is, to attain optimal clinical outcomes, the endometrium must be optimally receptive at the same time that the embryo is ready to implant. A loss of synchrony—termed *dyssynchrony*—occurs when the endometrium is not optimally receptive when the embryo is ready to implant. Dyssynchrony is particularly concerning as it may lead to implantation failure even when the endometrium is capable of being receptive and the embryo is capable of implanting and progressing through pregnancy to delivery.

Traditionally, dyssynchrony has been presumed to represent a true pathophysiology. When a poor outcome occurs—failed implantation—it seems intuitive to attribute that failure to either an abnormality in the embryo or an impaired endometrium. Over the past 35 years, investigators have sought to identify and isolate the specific pathophysiologic changes that result in failed implantation. In medicine, most clinical disorders are attributable to a single underlying pathologic abnormality. Thus, even though no one believes that all failures can be attributed to a specific pathologic abnormality, it has been presumed that failures may be attributed to a particular pathology in a given patient.

The investigators who have been studying failed implantation are largely

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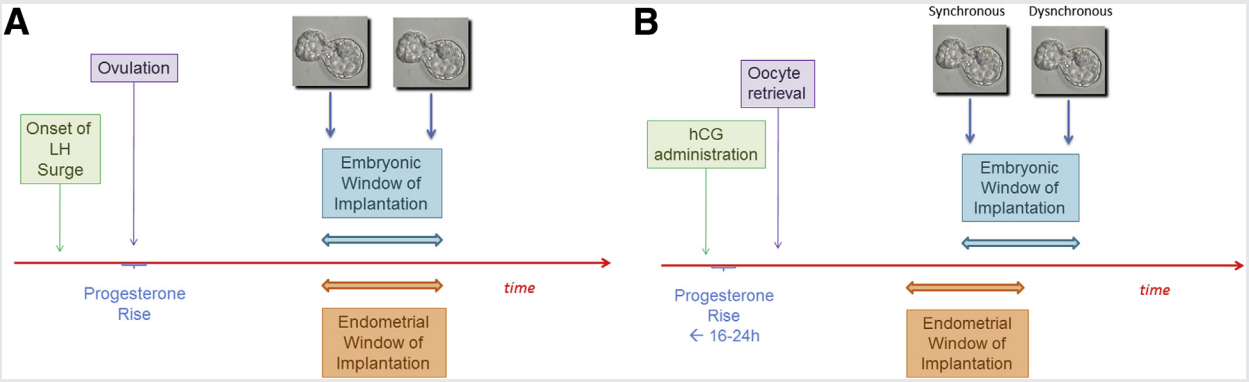
FIGURE 1



Embryo and endometrial synchrony involves both the endometrium, whose window is determined by the progesterone stimulus, and the embryo, whose widow is relative to blastulation. (**A**) During natural conception, a rise in progesterone follows the luteinizing hormone surge and leads to the opening of the endometrial window of receptivity, which overlaps with the window of embryonic blastulation and implantation. (**B**) In in vitro fertilization, natural coordination can be lost. The rise in progesterone after the ovulation trigger is faster and more robust, and the progesterone stimulus shifts the endometrial window of receptivity by 16 to 24 hours. Additionally, blastulation may be delayed, particularly in older, low responders. These two factors, either alone or together, result in a physiologic dyssynchrony that cannot be predicted before the cycle start and may not necessarily be reproduced from cycle to cycle.

Franasiak. Endometrial and embryo dyssynchrony. Fertil Steril 2016.

divided into two groups: embryologists and endometrial physiologists. Embryologists have focused on the morphologic and temporal aspects of embryo development. A retrospective review of clinical experience reveals that these investigations have determined the criteria for optimal embryo morphology as well as temporal milestones for both early cleavage events and for the timing of blastulation, which commonly ranges from days 5 to 6 and rarely even day 7 of development (1, 2). Meanwhile, the endometrial physiologists have focused on abnormal endometrial development and have evaluated endometrial sonography, histology, including specific cytokines and markers of inflammation, and the endometrial transcriptome (3, 4).

There is no doubt that some patients have specific pathologic abnormalities that can impair implantation, but a much larger question remains. It is possible for a completely normal embryo and a completely normal endometrium to be dyssynchronous, leading to failed implantation. Given that synchrony requires temporal coordination between both the embryo and the endometrium, is it possible that these two events, which are regulated independently, may not occur at the same time during a given in vitro fertilization (IVF) cycle? The simple answer is yes.

During natural conception, embryonic development and the window of endometrial receptivity are controlled by the follicle. A meaningful rise in progesterone occurs shortly after ovulation (Fig. 1A). The oocyte is exposed to spermatozoa at approximately the same time that secretory transformation begins in the endometrium. If both are normal, then development will be synchronous and implantation is possible. In the case of an IVF cycle, this natural coordination is lost. The hormone signals that control the onset of secretory transformation may occur much earlier, which may shift the window of implantation (WOI) and result in embryonic–endometrial dyssynchrony (see Fig. 1B).

Because the timing of the stimulus for secretory transformation may vary from cycle to cycle, this window's contribution to dyssynchrony is not always reproducible from cycle to cycle, so it may not be screened for in advance. This concept of physiologic changes leading to dyssynchrony stands in contrast to true pathologic changes in the endometrium. The hypothesized alterations in the rate of secretory transformation that alter the timing of the window of receptivity, such as those studied with the endometrial receptivity array (ERA) test (5) among others, characterize true pathology, but this pathology would impact only a relatively small percentage of the population and should be reproducible from cycle to cycle. In contrast, it could be hypothesized that all patients undergoing superovulation during IVF are at risk for embryonic–endometrial dyssynchrony, based on the timing when a critical level of progesterone is attained.

The Endometrium

Central to the endometrium's role in synchrony is the timing of the onset of the progesterone stimulus. Once progesterone levels reach a critical threshold, a well-timed and orderly secretory transformation begins. Reaching the threshold is much like activating a natural timer, with the window of receptivity opening several days later and then subsequently closing. Although adequate hormone support is required, the window of receptivity depends more on the timing of the onset of the stimulus than the midluteal progesterone levels.

Traditionally, the window of endometrial receptivity was thought to be quite wide, with implantations occurring in a 3- to 5-day window (6). This would occur with the transfer of day-2 embryos from ovum donation cycles between days 16 and 24 of the cycle. Initially pregnancies were reported on days 17 through 19, with subsequent pregnancies reported from days 16 to 20. Later studies refined this window from