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Chapter

Implantation: Cross Talk of the Developing Embryo and Endometrium

Lauren Grimm, Amber Cooper, Angie Beltsos and Roohi Jeelani

Abstract

The window of implantation has long posed as a challenge in understanding the exact synchronized cross talk that must take place in order for a developing embryo to be appropriately received by the endometrium. This is due mostly to the fact that it is difficult to study human models of implantation without sacrificing the potential for pregnancy. For many who present with a diagnosis of infertility with an otherwise unexplained etiology, recurrent implantation failure or a displaced window of receptivity may be an underlying, silent cause. As assisted reproductive technology (ART) continues to advance and offer new scientific breakthroughs allowing greater insight and understanding to reproductive failure and infertility, endometrial receptivity testing may offer answers to struggling patients.

Keywords: window of implantation, uterine receptivity, endometrium, blastocyst, embryo

1. Background

In order for pregnancy to occur, two events must take place:

1. Fertilization: the moment the sperm fertilizes the oocyte

2. Implantation: the moment the developing embryo meets the uterus, creating a nest from which to grow and develop

Following fertilization, the developing embryo must embed itself within the endometrium. In order for this to take place, both the embryo and uterus require the secretion and suppression of specific proteins that allow for implantation, including the expression of adhesion molecules on the cell surface, secretion of growth factors, and morphologic cell differentiation. Similarly, the embryo must also have developed to the blastocyst stage and be able to secrete appropriate protein factors for invasion and immunosuppression. These events between the embryo and endometrium must occur concomitantly in order for proper implantation to occur. If either the embryo or endometrium is asynchronous to the other, implantation will not take place, inducing the next cycle of menses. While great scientific advances have been made in the field of assisted reproduction since its inception in 1978, it is only within the last

10 years that we have really begun to understand this intricate network of synchronized events that allows the embryo and uterus to meet and become one.

2. The window of implantation

The uterus is constantly preparing itself for the possibility of implantation. As will be described in depth throughout this section, the uterus undergoes two phases throughout the normal menstrual cycle. To quickly summarize, following regular menses, estrogen released from the growing follicles in the ovaries causes the uterine lining to grow and thicken in what is known as the uterine proliferative phase. Following ovulation and the release of the oocyte into the canal of the fallopian tubes, the resulting corpus luteum acts to secrete progesterone, which plays a vital role in the ability of the endometrium to become receptive and available for implantation. This phase of the uterine cycle that correlates to the luteal phase of the menstrual cycle is known as the secretory phase, characterized by increased vascularization of the endometrium, uterine secretions, and reduced contractility of the surrounding smooth muscle [1]. While the uterine secretory phase lasts for about 2 weeks, coming to an end with the onset of menses, the window of implantation is thought to only occur over the course of a few hours, roughly 7–9 days following the LH surge or 6–8 days after ovulation (roughly days 20–24 of the menstrual cycle). During this time, the cells of the endometrial lining form small, finger-like protrusions, known as pinopods, which act to absorb fluid and macromolecules within the uterus. As the embryo begins to invade the endometrial tissue, a variety of cytokines, glycoproteins, and plasminogens are secreted by the embryo and uterus alike, allowing for changes in the cytoskeleton of decidual cells in the uterus and adhesion of the embryoblast to the succeeding layers of the endometrium [2]. Once implantation is complete, the embryo can continue to grow and develop into a maturing fetus, receiving blood and nutrients from the mother (**Figure 1**).

2.1 The proliferative phase

The proliferative phase of the endometrium corresponds with the follicular phase of the menstrual cycle. As estrogen is produced and released by the granulosa cells of
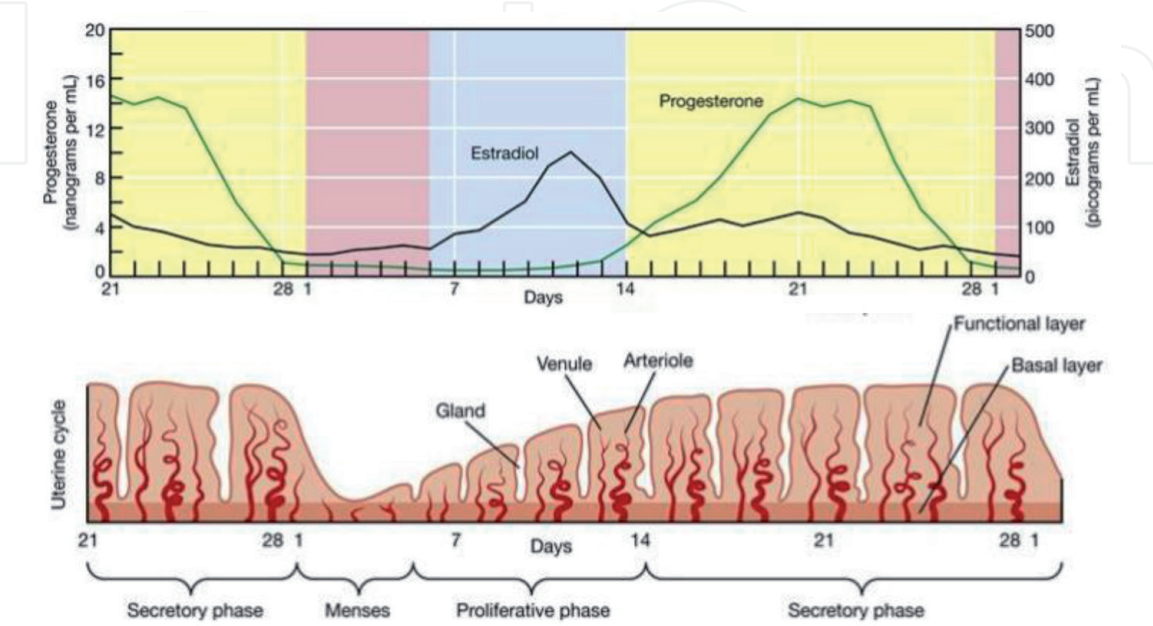

Figure 1.
The menstrual cycle: ovarian hormone production and uterine phase diagram.

the developing follicle, it is secreted into the bloodstream where it can bind a number of tissues, including the brain, breasts, uterus, and ovaries. As it pertains to the uterus, estrogen binds to estrogen receptors (ER; alpha and beta) in the cytoplasm or nucleus of endometrial glandular and epithelial stromal cells. The resulting E2-ER complex can then directly interact with the promoter regions of specific sequences of DNA related to the G1 phase of the cell cycle and induce mitotic proliferation by regulating cyclins, cyclin-dependent kinases (cdk), and cyclin-dependent kinase inhibitors [3]. One of these cyclins includes cyclin E, which increases in concentration during the endometrial proliferative phase and in response to estrogen signaling. Along with cdk2, cyclin E is believed to be the rate-limiting activator of G1 to S phase [4]. Other cyclins that are directly regulated by binding of the E2-ER complex include cyclin B1 and cyclin D1 [3]. Throughout the ovarian follicular phase, as serum estrogen levels continue to rise in response to folliculogenesis, the transcription of cell cycle-related genes in the endometrial tissue increases.

Estrogen not only has a transcriptional effect on endometrial tissue but on a variety of other important proteins is necessary for uterine preparation. This includes the induction of a variety of cytokines and growth factor proteins that help to stimulate uterine lining proliferation and endothelial growth. Many of these growth factors include transforming growth factors (TGF family), epithelial growth factor (EGF), and platelet-derived growth factor (PDGF), which all help to contribute to an overall thickened endometrium [5]. However, one of the most important growth factors that aids in the building and thickening of the endometrium is vascular endothelial growth factor (VEGF), which is believed to mediate angiogenic activity within the endometrium. The expansion of heavy vasculature throughout the endometrial lining contributes to not only an abundant supply of nutrients to the growing tissue but also a rich supply of vasculature for the growing fetus to attach to following implantation.

As the uterus continues to prepare for the moment of implantation, estrogenic binding also results in the presentation of progesterone receptors on the cell surface [3]. This effect on endometrial cells is important as the uterus begins to prepare to enter into the next uterine cycle phase.

2.2 The secretory phase

Once ovulation has occurred, estrogen levels abruptly decrease, resulting in a shift of the endometrium from the proliferative phase to the secretory phase. Once the oocyte is released from the surrounding granulosa cells, the resulting follicle turns into a corpus luteum that begins to secrete progesterone. Progesterone (p4) is one of the key steroid hormones that contributes to the ability of implantation to be successful. While estrogen ensures the endometrial lining is thick and heavily vascularized, progesterone makes the uterine lining sticky, providing the perfect environment to accept a growing embryo.

With the onset of ovulation and the dramatic decrease in estrogen levels, much of the proliferation that had previously taken place along the endometrial surface of the uterus begins to slow down. There is a slowing down of proliferation rather than a complete halt due to the small amount of estrogen the corpus luteum continues to secrete following release of the oocyte [6]. However, with the induction and secretion of progesterone now underway, the endometrial lining shifts focus in its preparation for implantation. One of the ways progesterone aids in this shift is via the activation of cyclin-dependent kinase inhibitor p27. As a reminder, following the formation of the E2-ER complex, initiation of transcription and translation of cycle E, and its partner cdk2, provides initiation of the mitotic cell cycle within the endometrial tissue. However, p27 acts as an inhibitor of this complex and thus prevents cell cycle progression [4]. Therefore, via the

secretion of p4 and the induction of an active p27, endometrial proliferation is down-regulated during the uterine secretory phase (**Figure 2**).

Apart from slowing down proliferation, much of the secretory phase of the uterine cycle consists of the transcription and translation of molecules necessary for embryo implantation. Implantation can be classified into three stages: apposition, adhesion, and invasion [2]. During blastocyst apposition, the embryo makes its way across the endometrial lining and is guided towards the optimal spot for adhesion. Once the embryo subsequently anchors to the endometrial lining, the embryo-endometrial binding can no longer be dislodged from uterine flushing [2]. It is at this point the embryo can begin to invade the endometrial lining tissue. As you will see, much of this process uses many of the same biomarkers and molecules well known to the immune system and necessary for cellular migration, adhesion, and invasion during infection.

2.2.1 Apposition

Blastocyst apposition is primarily thought to take place as a result of mucins that line the basal lamina of the endometrium. Mucins are a heavy molecular weight glycoprotein that contain an intracellular cytoplasmic tail and a variable extracellular domain. Of all the mucins known to exist within the human genome, only Mucin-1 (MUC1) and Mucin-6 (MUC6) have been found in the human endometrium [7]. When highly expressed along the endometrial cell surface, MUC1 and MUC6 interfere with cellular adhesion between the embryo and uterine lining due to steric hindrance.

Normally, the apical surface of epithelial cells found throughout the body are protected by a shield of thick glycocalyx that is highly composed of mucins meant to guard the tissue surface from any surrounding pathogens. In the case of the endometrium, MUC 1 extends beyond this thick glycocalyx barrier, repelling the blastocyst from premature adhesion until it finds the optimal space and time for implantation. It has been found that the distribution and regulation of MUC1 and MUC6 varies throughout the menstrual cycle, in which both are downregulated right before implantation in the mouse model [8]. Thus, it is believed that the high progesterone levels exhibited during the window of implantation must inhibit MUC1 and MUC6 expression, thus facilitating embryo to endometrium interactions.

2.2.2 Adhesion

The primary type of molecules that contribute to cell-to-cell adhesion of the developing embryo and endometrium are cellular adhesion molecules (CAMs).
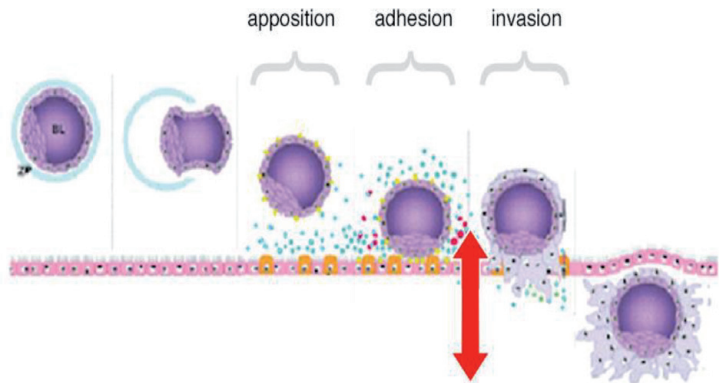

Figure 2.
Blastocyst hatching, followed by implantation via apposition, adhesion, and invasion of the endometrial tissue.

The CAM family of proteins is composed of four known members: integrins, cadherins, selectins, and immunoglobulins. How these adhesion molecules aid in embryo to endometrial linkage and embryonic invasion can be seen in **Figure 3**.

To start, a large variety of integrins have been associated with the luminal and glandular endometrial cells of the endometrium [9]. Most integrins are consistently expressed throughout the basal lamina of the uterine lining. However, some are expressed and regulated at specific times throughout the menstrual cycle. These include cycle-specific integrins a1b1, a4b1, and aVb3, which have been shown to be co-expressed during the window of implantation [10]. Similarly, integrins have been found to be expressed by the human trophoblast at the time of optimal implantation of the embryo. It is thus thought that integrins play a significant role in endometrial and embryonic adhesion, in which the integrins present on both the epithelial surface of the endometrium and the trophoblast of the developing embryo bind to specific extracellular matrix components [10, 11]. The ECM components are typically thought to include oncofetal FN secreted by the trophoblast and osteopontin, which has been positively identified by immunohistochemistry of the receptive endometrium [11].

It is true that just like the rest of the uterine cycle, ovarian steroid hormones also play a large role in the expression and inhibition of adhesion molecules like integrins. Accordingly, integrin aVb3 expression has been shown to be induced by EGF, among other growth factors, and negatively regulated by estrogenic factors [12]. Therefore, during the proliferative phase, high E2 levels effectively suppress integrin expression on the endometrial cell surface, while luteal phase progesterone acts to downregulate estrogen receptor activity, thus indirectly mediating the activation of integrin activity. Progesterone also has a direct effect on the presentation of integrin ligands, like osteopontin, by stimulating its gene expression [13].

Selectins, specifically L-selectin, of the CAM family of proteins also play a major role in blastocyst adhesion and implantation. L-selectin consists of a large, heavily glycosylated extracellular domain, and a small cytoplasmic tail, similar to that of integrins. Selectins are best known to play important roles in leukocyte
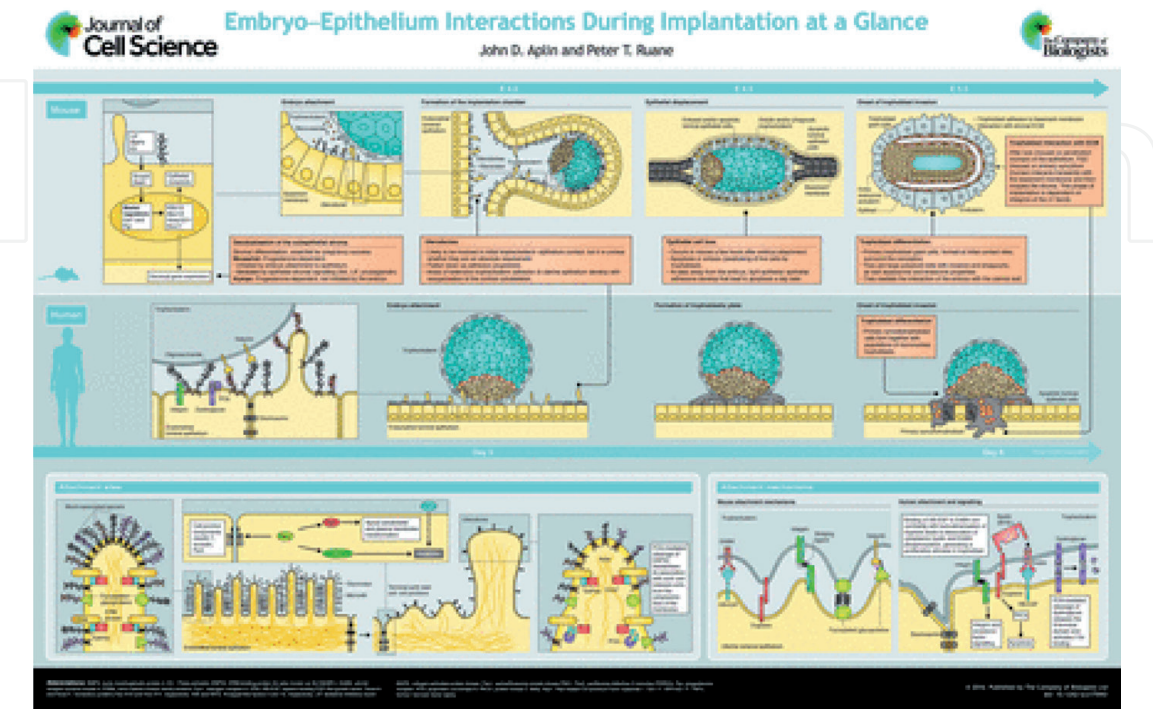

Figure 3.
Embryo epithelial interactions during implantation at a glance.

transendothelial cellular trafficking. Just like with leukocytes, selectins have been found to be heavily expressed along the trophectoderm of the blastocyst [14]. The endometrium, on the other hand, thus expresses oligosaccharide-based ligands such as HECA-452 and MECA-79 that bind selectively to L-selectin on the embryonic cell surface [14]. While MECA-79 has been shown to be immunolocalized along the luminal and glandular epithelium of the endometrium, its expression is known to intensify during the mid-secretory phase, in which implantation typically occurs [15]. Previous experimental findings suggest that the interaction between L-selectin on the trophoblast cells and its oligosaccharide ligand on the endometrium may make up the initial step in the implantation process of embryonic binding [16].

2.2.3 Invasion

Once adhesion has taken place, invasion of the embryo into the endometrial lining is necessary for continued blastocyst development. Cellular adhesion molecules play a role not only in the adhesion of the blastocyst but also in its invasion of uterine tissue. The most well-understood example of this is the downregulation of cadherins among the endometrial cells.

Biomarkers present during embryo implantation as seen in the mouse model and human endometrium.

Cadherins consist of a group of glycoproteins that are responsible for calcium (Ca^+)-dependent cell-to-cell adhesion mechanism. Among the three subclasses, E-, P-, and N-cadherins, E-cadherin represents the most studied subclass in relation to implantation. The regulation of E-cadherin at the epithelial cell surface enables cellular control [17]. Intracellular Ca^+ is essential in the E-cadherin regulation and assembly, in which a rise in intracellular Ca^+ induces a signaling cascade that results in cytoskeletal reorganization and the disassembly of E-cadherins between cellular junctions. Consequently, calcitonin expression is induced by increased progesterone secretion, which results in an increase in intracellular Ca^+ concentrations [18]. This specifically seems to take place during the mid-secretory phase, at which time the window of implantation is implicated to occur. It is thus believed that progesterone indirectly regulates E-cadherin expression via the calcitonin pathway, providing the developing blastocyst an opportunity for invasion, following initial apposition and adhesion.

2.2.4 Histologic dating

Back in 1950, Noyes et al. described histologic dating of the endometrium [19]. For decades, histologic dating was a commonly used tool to diagnose a displaced window of implantation based on the endometrial samples' physical appearance. In some women, the menstrual cycle date can lag behind the actual cycle date [2]. When the menstrual cycle lags more than 2 days from the actual cycle date, the endometrium is considered "out of phase." For those that were diagnosed with an out of phase endometrium, exogenous hormonal supplementation could be used to treat and manipulate the window of implantation.

While histologic endometrial dating is now somewhat outdated due to the advancements in new and updated methodologies of evaluating the window of implantation, one important cell structure characteristic of uterine receptivity is worth noting. Pinopodes are bulb-like projections found on the apical surface of endometrial cells that are several micrometers wide and project into the lumen of the uterus above the microvilli. Pinopod physiologic expression is specific and limited in its expression to the 2 days of the menstrual cycle corresponding to implantation [20]. Morphologic expression of pinopods has been found to be progesterone dependent. Moreover, HOXA-10, a homeobox gene whose expression is required for implantation, has been

found to have an essential role in pinopod formation [21]. While the exact function of pinopods remains unknown, studies have shown developing embryos preferentially attach to and invade specific areas of the endometrium where pinopod formation was allowed to occur in vitro [22]. Further studies have also demonstrated that endometrial pinopod morphogenesis is associated with increased mid-luteal phase expression of LIF as well as progesterone and integrin aVb3 [13, 23, 24].

2.2.5 Other important biomarkers related to implantation

There are a number of other important endometrial biomarkers specifically expressed during the uterine secretory phase that have major roles in coordinating successful implantation.

One of the most important biomarkers not yet mentioned is that of cytokines. Cytokines make up a type of protein that affects a variety of cellular functions, including cellular proliferation and differentiation. Cytokines that have been found to be present during the window of implantation include LIF, IL-6, and IL-1 [2]. Studies have demonstrated the importance of all three cytokines via knockout experiments in mice, in which lack of LIF, IL-6, or IL-1 resulted in decreased implantation [2, 25]. Importantly, all three cytokines have also been shown to have temporal expression throughout the menstrual cycle, where their expression and activity peaked during the mid-secretory phase [26, 27]. Receptors for LIF and IL-6 have been found to be expressed on both the endometrium and blastocyst, suggesting a paracrine- and autocrine-like function during implantation [28]. While steroid hormone regulation of these cytokines has not been confirmed, their regulation being similar in appearance to peak progesterone secretion implies that there is most likely a linkage between them.

Another important biomarker present during the secretory phase of the uterine cycle that has been shown to affect blastocyst implantation is prostaglandins. As mentioned previously, similar to an immune reaction, implantation can be thought of as a pro-inflammatory reaction with the premise that blastocyst attachment, invasion, and further development requires connection to the maternal vasculature. Thus, prostaglandins play a vital role in endometrial vascular permeability and cellular differentiation, as well as embryo transport and invasion. While prostaglandins (PG) are constitutively expressed throughout the menstrual cycle, specific PG receptors have shown to be preferentially transcribed and translated at different times throughout the two uterine phases [2]. This means that prostaglandins can then exert specific rolls along the endometrium at different times throughout the menstrual cycle. The importance of prostaglandins during the window of receptivity has been demonstrated in the mouse model, in which knockout mice were shown to exhibit various implantation defects, including failure to implant or late implantation.

Finally, while not a specific biomarker, it is important to mention the Maximal Implantation Potential (MIP) of the endometrium. When we think about the shape of the uterus, most find it helpful to visualize as an inverted triangle, with the cervix at the apex and the fallopian tubes at either ends of the base. The MIP is a region along the endometrium at the intersecting points of the two straight lines coming out of the openings of the fallopian tubes. It is at this region of the uterus and endometrial lining that the blood supply is richest, and the biomarkers of implantation present themselves in greater concentrations. During natural implantation, the MIP is the point of the uterus that the developing embryo most often optimally and preferentially implants.

As you can see, implantation and the process of uterine preparation are extensive and delicate processes. While many of the important players in implantation have been readily identified and mentioned here, still very little is known about the exact mechanisms, effects, and processes required to achieve implantation.

2.3 Menses

If implantation does not occur, either due to asynchrony of the previously described events or the lack of fertilization of the oocyte, the onset of menses is initiated, and a new uterine cycle begins. In order for progesterone secretion during the uterine secretory phase to be maintained, the corpus luteum must receive a positive feedback, and it must be received from an implanted and developing embryo via human chorionic gonadotropin hormone (hCG). Without the presence of hCG, the corpus luteum begins to degenerate after about 10 days, resulting in a decrease in progesterone production and a breakdown of the uterine lining.

3. Recurrent implantation failure

As one of the most intricate and sensitive processes that takes place in the human body, the relative inefficiency of implantation is ironic given that continuous reproduction is critical to species survival. For those seeking fertility treatment, recurrent implantation failure remains a frustrating and difficult possible underlying cause to an otherwise unexplained diagnosis of infertility or in conjunction with another inhibitory diagnoses. While there is no universal definition for recurrent implantation failure (RIF) despite multiple publications on the topic, broadly speaking, Das et al. defined it as "the repeated transfer of morphologically good embryos to a normal uterus without achieving successful implantation or clinical pregnancy" [29].

Ordinarily, the probability that an embryo will successfully implant is about 30% [30]. This means there is a 70% chance of implantation failure. In these cases, implantation failure may be due to one of two factors: inadequate uterine receptivity and/or problems with the embryo itself. When it comes to selecting good quality embryos, few objective methods of embryo assessment exist. Most rely on embryo morphologic grading, a subjective assessment of embryonic development based on the expansion and quality of the inner cell mass and trophectoderm (see **Figure 4**). Embryo grading has long stood as the gold standard of embryonic assessment for quality and to this day continues to be a reliable indicator of embryonic competence.

Over the last decade, preimplantation genetic testing has made its way onto the market as a means of objective chromosomal evaluation of the embryo. Preimplantation genetic testing for aneuploidy (PGT-A) requires a small biopsy of a few cells from the developing embryo. Currently, this is most often done during the blastocyst stage, in which a small biopsy is taken from the cells of the trophectoderm. Yet, biopsies can also be performed at the blastomere stage, and new research suggests improved efficacy when the biopsy is taken from the inner cell mass of the blastocyst or the spent media culture where the developing embryo has grown in vitro [31, 32]. From there, chromosomal evaluation is done to attest for the number of chromosomes present, with the assumption that euploid embryos (blastocysts with a normal 46 chromosome count) are healthy and deemed optimal for embryo transfer. However, PGT-A is expensive, costing patients thousands of dollars, and imperfect, where many embryos often result as mosaic (some cells have normal chromosomal count, and some do not) or "undetermined."

Yet, for those who opt to undergo PGT-A and continue to suffer the loss of RIF, asynchrony in uterine receptivity is most often the cause. A displaced window of implantation may be caused by a variety of factors, including abnormal cytokine and hormonal signaling, among other things, in which the endometrium is not prepared to accept a blastocyst at the otherwise appropriate time. Thus, evaluation
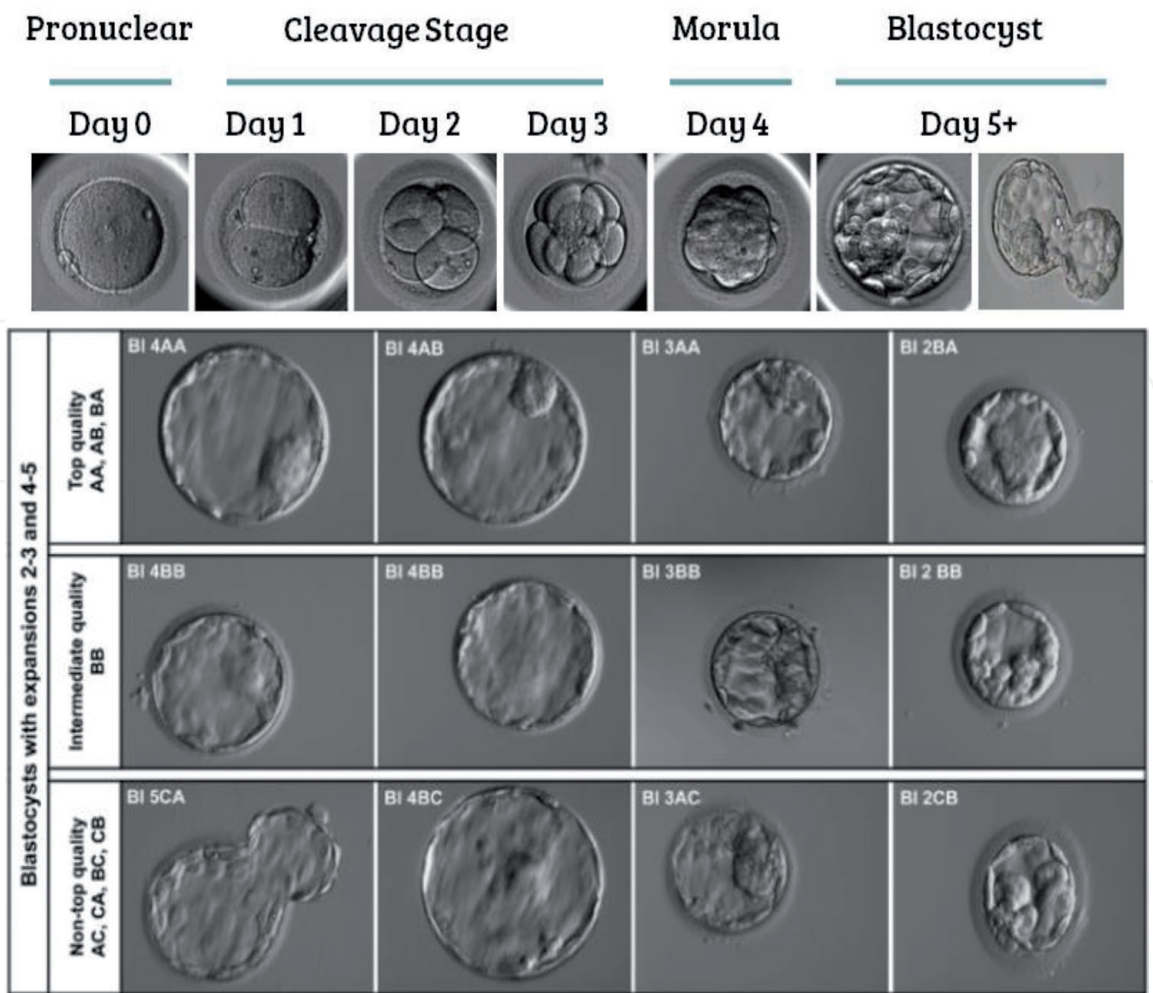
Figure 4.
Visual of embryonic development and morphologic grading according to blastocyst expansion and cellular differentiation receptivity at embryo transfer.

of implantation markers via an endometrial biopsy taken at the time of supposed implantation may be the key to predicting pregnancy outcome and adequate progesterone administration for optimal uterine.

4. Endometrial receptivity testing

Over the last decade, advancements in technology have made it possible for us to evaluate the window of implantation and diagnose displacements in one's uterine cycle activity. Of the numerous tests that exist, including the window of implantation test, which uses reverse transcriptase PCR analysis of endometrial tissue, and the endometrial function test, a histologic analysis of endometrial sampling, the most well-known example remains the endometrial receptivity array (ERA) by Igenomix. ERA utilizes next-generation sequencing (NGS) to analyze the RNA composition of the endometrial tissue to detect for expression and suppression of known endometrial biomarkers characteristic of the window of implantation. These biomarkers include LIF, MUC16, as well as various integrins and cytokines mentioned earlier in this chapter [33]. Diagnosis of a displaced window of receptivity is based on the RNA expression and transcriptomic signature found within the endometrial cell sampling. Based on this genetic analysis, technology is then able to diagnose whether or not the endometrium is receptive, pre-receptive, post-receptive, or non-receptive. **Figure 5** is a display of the transcriptomic signature of
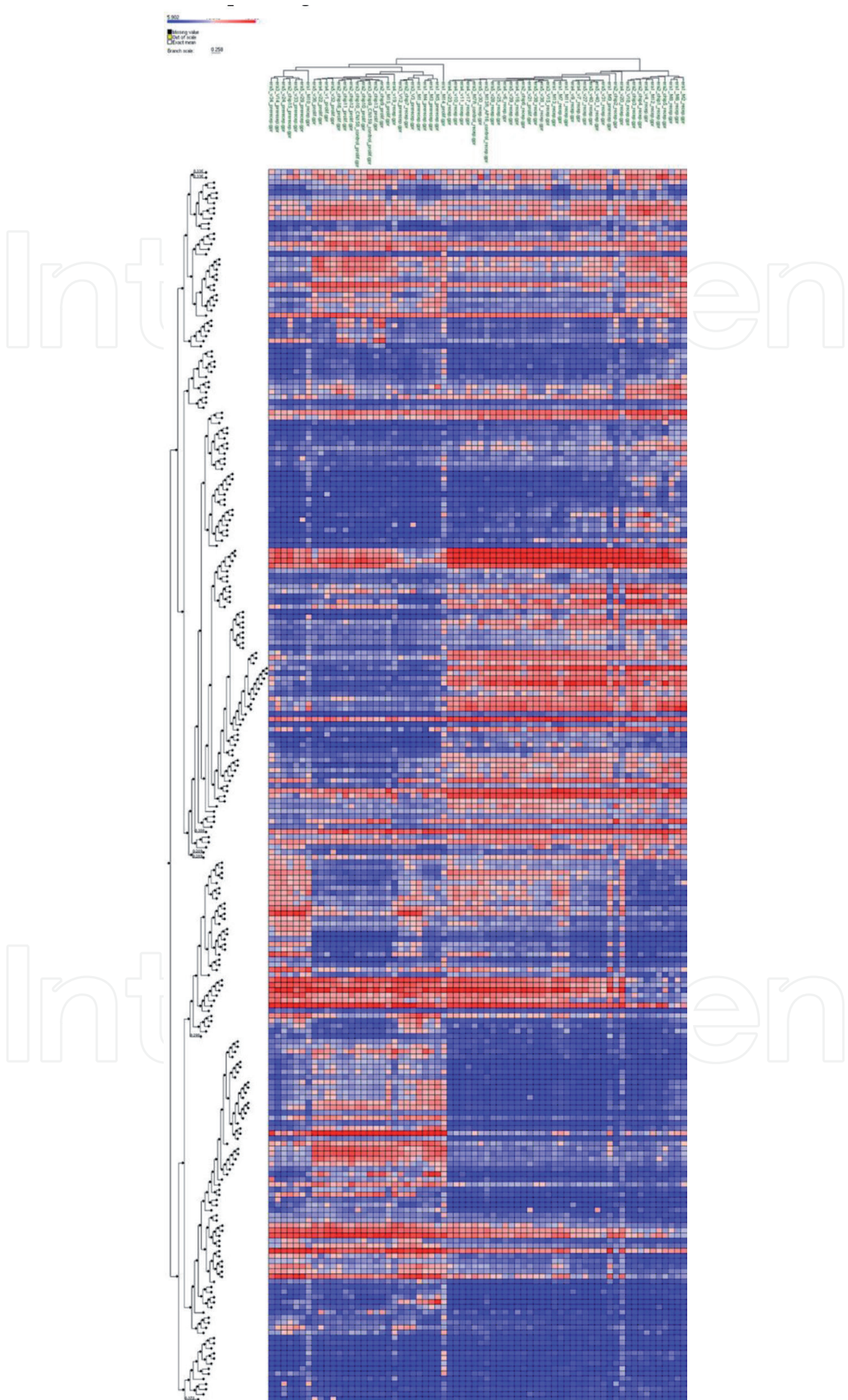
Figure 5.
Transcriptomic signature of the human endometrium based on next-generation sequencing.

the endometrium at its various phases throughout the menstrual cycle, including the proliferative phase, pre-receptive secretory phase, and receptive secretory phase.

A receptive endometrium indicates that the endometrial lining consists of all the correct biomarkers for proper implantation to take place, indicating the embryo should be transferred the same time as the biopsy took place. A non-receptive endometrial lining, on the other hand, refers to one of two cases: an endometrium that is either pre-receptive or post-receptive [34]. A pre-receptive endometrium refers to a window of implantation that takes place 12–48 h after the time of biopsy, whereas a post-receptive endometrium occurs when the window of implantation takes place at an earlier time (12–48 h) than the time of biopsy. In these cases, a corrective course of exogenous progesterone administration is typically advised wherein the embryo transfer takes place earlier or later to when the biopsy took place/the original time implantation was otherwise thought to occur, resulting in more or less overall progesterone exposure. Recently, letrozole, an aromatase inhibitor, and GnRh agonist drug therapies have also been found to correct a displaced window of receptivity, especially in women diagnosed with endometriosis, in which both letrozole and GnRh agonists have been shown to alter integrin expression in the endometrium and induce uterine receptivity [35].

Since it was first brought onto the market, endometrial receptivity testing has offered a novel approach to what had otherwise been a black hole in assisted reproductive technology treatment. For those that experience significant RIF, the ERA has been shown to increase clinical pregnancy rate to upwards of 75%, a figure previously unheard of for those facing infertility [34].

Yet, while endometrial receptivity testing has come a long way since its original inception, increasing in accuracy and offering hope to patients who otherwise had no other answers, skepticism still exists as to the clinical utility of this relatively new and evolving technology. Some have posited that the act of biopsying the endometrium has a similar effect to uterine scratching, which is a technique that involves superficial wounding of the endometrial lining and is thought to improve uterine receptivity in subsequent menstrual cycles. Others, however, point to the lack of research and evidence-based medicine to prove these tests accurately diagnose uterine receptivity and truly improve pregnancy rates, arguing more research into our understanding of the window of implantation is still needed.

5. Summary

Uterine receptivity and the window of implantation are incredibly intricate and complex processes that are meant to result in pregnancy. Following initial apposition of the embryo to the endometrium by MUC1 and MUC6, cytokines, such as LIF, recruit the blastocyst to the optimal spot for implantation along the endometrial lining. Through cellular adhesion molecules, like integrins and L-selectin, the embryo is able to bind the basal lamina of the endometrium, adhering to the uterine wall before invading the epithelial tissue and completing the process of implantation.

While this complex biological system often works accurately for the majority, giving way to a healthy pregnancy, many still experience asynchronies between the endometrium and developing embryo, resulting in infertility. As such, in an effort to optimize assisted reproductive technologies, scientists have sought out new and innovative techniques in order to understand and diagnose irregularities in the most important processes of human reproduction. The invention of endometrial receptivity testing now allows clinicians the ability to predict an individual's personalized window of implantation, offering new understanding to the field and hope for those who previously faced recurrent implantation failure (**Figure 6**).
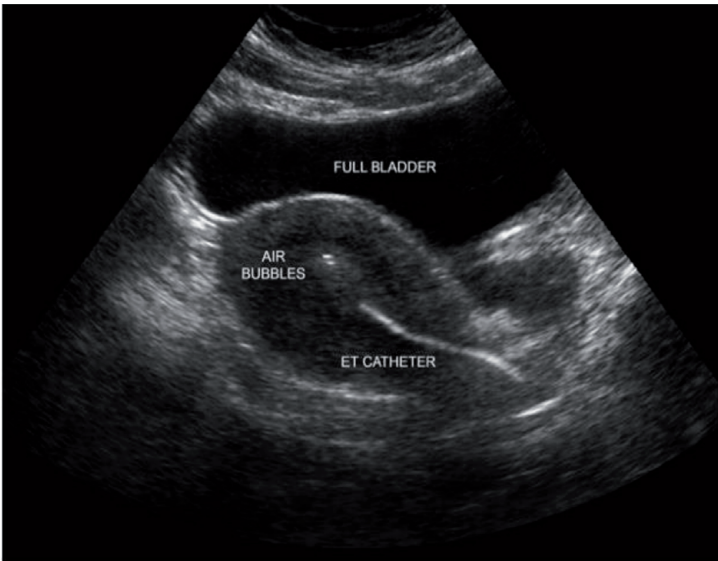
Figure 6.
Ultrasound imaging of an embryo transfer (ET).

Overall endometrial receptivity testing allows us greater insight into the understanding of reproductive infertility and the timing of the window of implantation. While research remains ongoing as to the clinical utility of these tests, including validation studies and the rate of pregnancy and live birth outcomes, endometrial receptivity testing offers another piece to the puzzle in our attempt to completely understand the underlying etiologies of infertility.

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Notes

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