

The Menstrual Cycle

Basic Biology

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The basic biology of the menstrual cycle is a complex, coordinated sequence of events involving the hypothalamus, anterior pituitary, ovary, and endometrium. The menstrual cycle with all its complexities can be easily perturbed by environmental factors such as stress, extreme exercise, eating disorders, and obesity. Furthermore, genetic influences such as fragile X premutations, X chromosome abnormalities, and galactose-1-phosphate uridylyltransferase (GALT) point mutations (galactosemia) also contribute to perturbations of the menstrual cycle. Although not perfect, mouse models have helped to identify and confirm additional components and pathways in menstrual cycle function and dysfunction in humans.

Key words: biology, menstrual cycle, mouse models, premature ovarian insufficiency (POI), genetics, endometriosis, folliculogenesis

Overview of the Menstrual Cycle in Humans

Figure 1 shows a general overview of the key regulatory factors in the menstrual cycle. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to secrete both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH are heterodimeric members of the glycoprotein hormone family and have an α :FSH β and α :LH β noncovalent structure, respectively. The α subunit is common to all glycoprotein hormone family members. The levels and timing of secretion of each gonadotropin is correlated by GnRH, feedback from sex steroid hormones, and other autocrine and paracrine factors such as inhibin and activin. The gonadotropins stimulate the ovary to produce the steroid hormones, estrogen or progesterone, as well as several key autocrine, paracrine, and endocrine peptides. As with the pituitary, ovarian steroidogenesis is regulated by multiple factors. The ovarian steroid hormones in turn stimulate endometrial proliferation and affect many

end organs. Although estrogen and progesterone have some feedback at the level of the hypothalamus, the more dynamic feedback occurs at the level of the anterior pituitary. Folliculogenesis, ovulation, luteinization, and endometrial growth and decline during the menstrual cycle depend on the above-mentioned autocrine, paracrine, and endocrine factors produced from this axis.¹

Oocyte Development

In humans, germ cells begin to develop at 5–6 weeks of gestation.^{1,2} These cells migrate to the genital ridge and multiply, giving a finite number of germ cells by the time of birth in females. These germ cells will be encapsulated by “pre-granulosa” cells to become oocytes at the primordial follicle stage. At this point, the oocyte will arrest at the diplotene stage of meiosis. Oocytes are surrounded by supporting cells called granulosa cells, while thecal cells surround the follicle after the primary follicle stage. The surrounding cells as well as the oocyte itself secrete factors which regulate folliculogenesis.³ Folliculogenesis is the process of preparing a single oocyte from a primordial follicle for ovulation.^{1,4,5} Figure 2 shows the anatomy of a follicle with representative factors.

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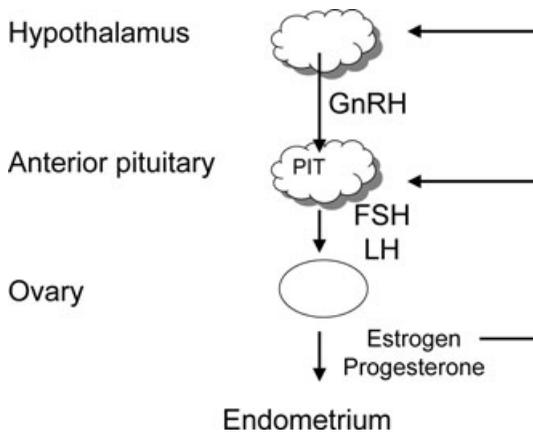


FIGURE 1. General overview of the important factors in the menstrual cycle. Regulation of the menstrual cycle begins with influences at the level of the hypothalamus. The hypothalamus stimulates the anterior pituitary, which stimulates the ovaries. One of the end organs for the ovarian sex hormones is the endometrium. The menstrual cycle is regulated by feedback and crosstalk between these different components.

Overview of Ovarian Folliculogenesis

In the ovary, folliculogenesis can simply be divided into the follicular phase, prior to ovulation, and the luteal phase, after ovulation.¹ Figure 3 depicts the stages of ovarian folliculogenesis in humans. Ovarian folliculogenesis begins with the recruitment from a pool of growing primordial follicles.¹ Despite intense work in both mice and other species, the critical signals that initiate the recruitment of primordial follicles are still unknown.^{1,6–8} After recruitment, these follicles grow and become primary follicles. Once the multilayer (secondary) follicles express FSH receptors, they are then subject to endocrine regulation.

In the presence of FSH, these secondary follicles begin to grow even more and are competent to develop into an antral follicle. Without FSH, the follicles become atretic. The theca, a layer of cells surrounding the follicle, is formed first at the two-layer pre-antral follicle stage, and with exposure to low levels of LH, produces androgens in humans. Androgens are converted to estrogen via a member of the cytochrome P450 superfamily, CYP19 (aromatase) in the granulosa cells. FSH induces granulosa cell proliferation, induction of aromatase, and increased FSH receptors on the granulosa cells, thus leading to a very high estrogen microenvironment. With an increase in estrogen, the antral follicle develops further. At the pre-antral follicle stage, the follicle is a two-cell (granulosa and thecal cells), two-gonadotropin (FSH and LH) system. This crosstalk between the granulosa and thecal cells

results in high estrogen levels within the follicle. This high estrogen level downregulates FSH from the anterior pituitary and begins the process of selecting for a single dominant follicle.¹ Follicles that are not at the appropriate stage and are not able to maintain a high estrogen microenvironment without stimulation from FSH degenerate and become atretic.

The very high estrogen levels feed back to the anterior pituitary to induce the LH surge, which ultimately leads to ovulation. During ovulation, the oocyte is expelled from the follicle with cumulus granulosa cells surrounding it. The remaining follicular cells in the ovary become luteinized as part of the corpus luteum, which secretes progesterone. During the luteal phase, the granulosa cells within the corpus luteum also produce inhibin A, an $\alpha:\beta$ A heterodimeric member of the transforming growth factor β (TGF β) superfamily, which acts as an endocrine hormone to suppresses pituitary FSH, inhibiting growth of other ovarian follicles. With no fertilization or implantation of the embryo, the corpus luteum degenerates, possibly in response to activin homodimers (β A: β A or β B: β B) or heterodimers (β A: β B) that share the β subunits with inhibin A and inhibin B ($\alpha:\beta$ B). When inhibin, estradiol, and progesterone levels fall with regression of the corpus luteum, FSH is suppressed. At the luteal–follicular transition, FSH levels increase, and the next menstrual cycle begins.¹

With fertilization and implantation, the corpus luteum is maintained by stimulation of human chorionic gonadotropin (hCG) by the placenta. HCG (α :CG β) is also a member of the glycoprotein hormone family along with LH, FSH, and thyroid-stimulating hormone (α :TSH β ; TSH), sharing the same common α subunit and binding to identical gonadal LH/CG receptors as LH. HCG will peak at approximately the end of the first trimester. Detection of hCG in the urine (approximately 10 days after fertilization and shortly after implantation, when hCG can enter the woman's bloodstream) is the major test of pregnancy. The rate of rise or fall of serum levels of hCG during the first trimester can be used to detect ectopic pregnancy, miscarriage, multiple pregnancies, and often, placenta-derived cancers such as hydatidiform moles, gestational trophoblastic disease, and choriocarcinoma.¹

Menstrual cycles continue for a woman until her finite population of oocytes is exhausted. Primary hypogonadism occurs in women with gonadal failure, low estrogen, and elevated FSH levels, also known as hypergonadotropic hypogonadism. If these clinical findings are observed in a woman under 40, the condition is known as primary ovarian insufficiency (POI) (OMIM #311360).

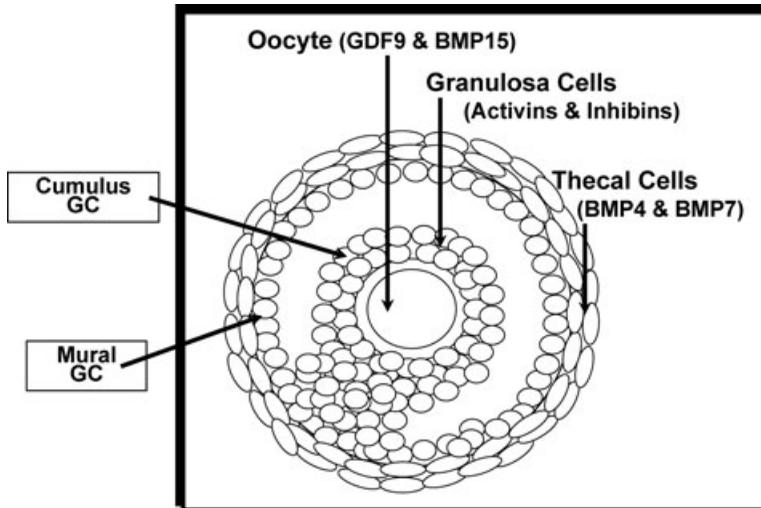


FIGURE 2. Anatomy of an ovarian follicle. This cartoon depicts the various cell types of an antral follicle and some of the factors secreted by each cell type. The oocyte is surrounded by cumulus granulosa cells, whereas the mural granulosa cells surround the antrum. Thecal cells surround the entire follicle. Crosstalk between these cell types by the factors listed and others is important for ovarian folliculogenesis.

Mouse Models with Defects in Folliculogenesis

Folliculogenesis in the mouse is similar to human ovarian folliculogenesis. To date, approximately 100 factors have been demonstrated to affect folliculogenesis or female fertility in mice using knockout or transgenic technology (reviewed in Matzuk and Lamb⁵). Consistent with mouse models, mutations in some of these factors in mice have also been identified in humans, particularly in women with POI. Here, we attempt to review some of the factors shown to cause defects in mouse folliculogenesis that have mutations found in humans with POI.

One of the earliest genes involved in postnatal folliculogenesis is *NOBOX*. *NOBOX* is an oocyte-specific homeobox gene and is thought to be specifically expressed in the germ cells, primordial follicles, and growing oocytes.⁹ *NOBOX* null female mice are infertile and have no follicular development past the primordial follicle stage. Furthermore, as these mice age, they have a decreased number of oocytes, or very early POI.¹⁰

Moving up to the anterior pituitary, the two most important extragonadal factors in ovarian folliculogenesis are FSH and LH. As mentioned earlier, FSH and LH share a common α subunit, but each has a unique β subunit.¹ FSH β null female mice are infertile and have small ovaries. The FSH β null mice have follicular arrest at the secondary follicle.¹¹ Similarly, LH β null

female mice are infertile. The follicles in the LH β null animals arrest at the preovulatory follicle stage and undergo degeneration. Corpora lutea are not observed in these mice.¹² Not surprisingly, the gonadotropins are essential for folliculogenesis in the mouse.

Although orchestrated stimulation of the follicle by gonadotropins is important, the cells within the follicle secrete factors important for their own regulation. This crosstalk between the oocyte and the granulosa and thecal cells additionally regulates folliculogenesis.^{4,13} The factors secreted from these cells include the transforming growth factor β (TGF β) family of proteins. The expression of these factors is not only temporally regulated within the menstrual cycle, but also spatially regulated. The oocyte secretes growth and differentiation factor 9 (GDF9), bone morphogenic protein 15 (BMP15), and BMP6, whereas the granulosa cells secrete activins and inhibins. The thecal cells secrete TGF β 1, TGF β 2, BMP4, and BMP7. All of these factors act as autocrine and paracrine factors and influence folliculogenesis [reviewed in Pangas and Matzuk³].

GDF9, the first oocyte factor discovered, is a member of the TGF β superfamily. GDF9 is expressed in the oocyte from early folliculogenesis through ovulation and controls the function of ovarian follicles. GDF9 null female mice are infertile and have small ovaries. Histologic analysis of GDF9 null mouse ovaries shows a block in folliculogenesis at the primary follicle. Thus, GDF9 is important in early folliculogenesis

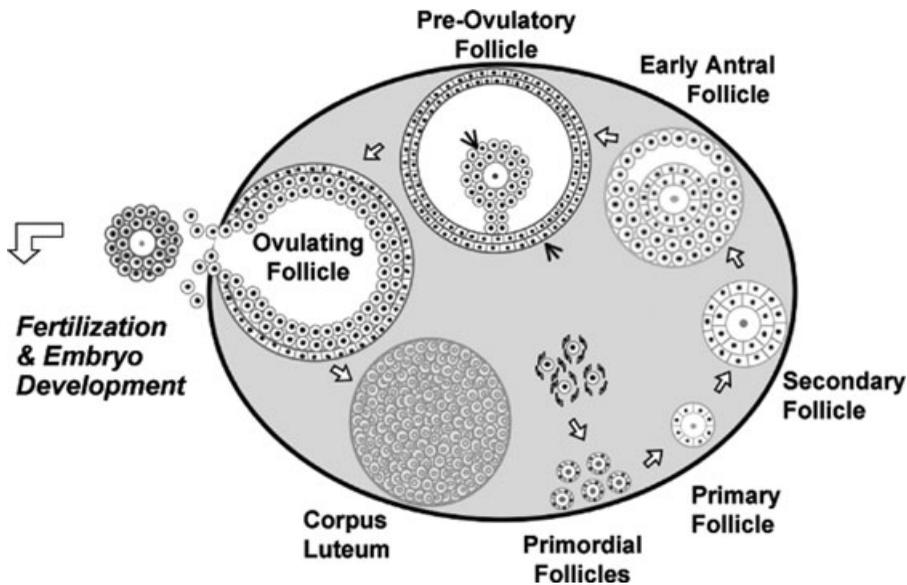


FIGURE 3. Stages of ovarian follicular development. Folliculogenesis requires a coordinated progression of growth of ovarian follicles. The process begins with the germ cells, which are recruited to a pool of primordial follicles. The primordial follicles progress to primary and then secondary follicles. At the secondary follicle stage, theca cells are present. The early antral follicle stage is defined by the presence of the antrum. The periovulatory follicle stage is also known as the dominant follicle and is ready for ovulation. At this stage, cumulus and mural granulosa cells are present. Once the oocyte is released, the remaining granulosa cells become the corpus luteum. This cycle of folliculogenesis occurs for every single oocyte ovulated.

and is essential for the primary and secondary follicle transition.⁷

Additionally, GDF9 is important in later stages of folliculogenesis. Specifically, it is important for cumulus cell expansion. The cumulus is the layer of granulosa cells directly surrounding the oocytes along with its rich hyaluronic acid matrix. The mural granulosa cells line the follicle wall (Fig. 2). During the periovulatory period, the cumulus granulosa cells undergo expansion in preparation for ovulation. The cumulus protects the oocyte from the harsh environment, helps with extrusion of the cumulus oocyte complex, and permits capture of the freshly ovulated oocyte by the fimbria. Importantly, it also enhances the ability of the sperm to fertilize the ovary *in vivo*.^{13–21} *In vitro*, GDF9 exposure results in the expansion of mouse cumulus cells, suggesting its critical role in the function of this complex.^{22–24}

BMP15 is another TGF β family member that is homologous to GDF9 and is also important for folliculogenesis in the mouse. BMP15 null female animals are subfertile but not infertile. Thus, BMP15 is important, but not as essential as GDF9 in the mouse. When the BMP15 null mice were bred with the GDF9 mice, the BMP15 null, GDF9 heterozy-

gote female mice were even more subfertile than those with the BMP15 null mutation alone. These double-mutant mice had late folliculogenetic defects noted on ovarian histologic study, having decreased numbers of late-stage follicles. BMP15 and GDF9 may play synergistic roles in folliculogenesis, as suggested by the more severe fertility defects in the heterozygous GDF9 and BMP15 knockout mice. Furthermore, the ratio of the number of oocytes ovulated to embryos created was extremely low. Of significant note, these double-mutant animals lacked cumulus cell expansion. Thus, BMP15 and GDF9 play important complementary roles in cumulus cell expansion.²⁵

Four major genes downstream of GDF9 in cumulus expansion are cyclooxygenase 2 (COX2), hyaluronase synthase 2, pentraxin 3 (PTX3), and tumor necrosis factor α -induced protein 6 (TNFAIP6). COX2, PTX3, and TNFAIP6 mutant mice have also been produced and show cumulus expansion and female fertility defects.^{26–28} Thus, these studies confirm the importance of these factors downstream of GDF9/BMP pathway in cumulus cell expansion and mouse fertility.

These factors are only the beginning of the list of autocrine, paracrine, and endocrine factors involved in female fertility. Many more mouse models that display

reproductive phenotypes have been created to understand the menstrual cycle, female infertility, and primary ovarian insufficiency [reviewed in Matzuk and Lamb⁵]. The studies reported below in humans will go into the genetic defects and the translational aspect of this work in the clinic.

Human Models of Ovarian Dysfunction

Although the above members of the TGF β superfamily play important roles in folliculogenesis in mice, the correlation with human POI is not so simple. Many of the factors described above as important in mouse folliculogenesis have been directly sequenced in patients with POI. However, mutations in these genes seem to be uncommon factors in the pathophysiology of POI.

Multiple studies over many years have attempted to discover gene mutations involved in POI. Early studies focused on gonadotropin gene and gonadotropin receptor defects (reviewed in Themmen and Huh-taniemi²⁹). Mutations in the α subunit of the glycoprotein hormone family have not been found in women with POI. Until recently, mutations in LH β had not been found in women with POI. Recently, one woman with secondary amenorrhea was found to have a point mutation in exon 2 of the LH β gene. This mutation caused a frame shift of exon 3 and LH deficiency, leading to her secondary amenorrhea. However, she did not have elevated levels of FSH.³⁰ Mutations in the FSH β gene have been found in women with primary amenorrhea and infertility. This mutation is a 2-basepair deletion, resulting in a stop codon, and early ovarian failure (OMIM #229071). Females with mutations in the LH receptor (LHR) have primary amenorrhea with elevated FSH levels, POI. Females with FSH receptor (FSHR) mutations also have POI, demonstrating ovarian dysgenesis and lack of ovarian follicle development (OMIM #233300).²⁹ Overall, these studies reveal that mutations in gonadotropins or their receptors are involved in human folliculogenesis and some isolated cases of POI, but are not a common cause of clinical POI.

Over the years, more sophisticated gene chip and computational experiments have allowed discovery of additional candidate genes for POI. However, mutations in these genes in humans with POI are still uncommon. For example, in humans with POI, NOBOX gene mutations are present in <1% of analyzed population (OMIM #611548).³¹ Additionally, mutations in GDF9 or BMP15 are found in few patients with POI.^{32–38} In one of the largest studies of women with

POI, 6 of 166 women with POI had missense substitutions in BMP15, but 0 of 392 controls had this variation in BMP15. Additional variations were found in BMP15 in both the POI and control population.³⁹ Although statistically significant, the functional significance of many of these mutations (except the BMP15 mutation in two sisters with infertility; OMIM #300510)⁴⁰ have not been demonstrated. Overall, NOBOX, GDF9, and BMP15 mutations do not appear to be common causes of POI, but other factors within the TGF β signaling pathway may be important.

Overview of the Cyclic Endometrium

The endometrium is one of the most sensitive organs to ovarian steroid hormones. The endometrium is composed of two layers. The most luminal layer is the functionalis, which is thickened and sloughed in response to ovarian hormones. The basalis is closest to the myometrium and remains throughout the menstrual cycle.¹

The endometrium can simply be divided into the proliferative phase, corresponding to the follicular phase in the ovary, and the secretory phase, corresponding to the luteal phase in the ovary. Figure 4 shows a representation of the endometrium throughout the menstrual cycle. In menstrual cycle dating, the first day of the menstrual bleed is considered day 1. During the menstrual phase, the endometrium undergoes changes and is sloughed off in women because of low estrogen levels. The proliferative phase is defined as the period of time from the menstrual phase to ovulation. As estrogen levels begin to rise, the endometrial lining thickens, giving a proliferative pattern. Estrogen leads to a proliferation of stroma and glands, and elongation of the spiral arteries. The secretory phase is from ovulation until menstruation. After ovulation, progesterone levels begin to rise in the early secretory phase. This leads to secretion of glycogen and mucus. In the mid-secretory phase, the endometrium becomes decidualized and receptive to a fertilized embryo. In the late secretory phase, in the absence of pregnancy, and with the accompanying decrease in both estrogen and progesterone, the spiral arteries vasoconstrict, leading to involution of the endometrium. The cycle then repeats.¹

Mouse Models with Endometrial Dysfunction

Numerous factors have been demonstrated to play a role in implantation, decidualization, or embryo

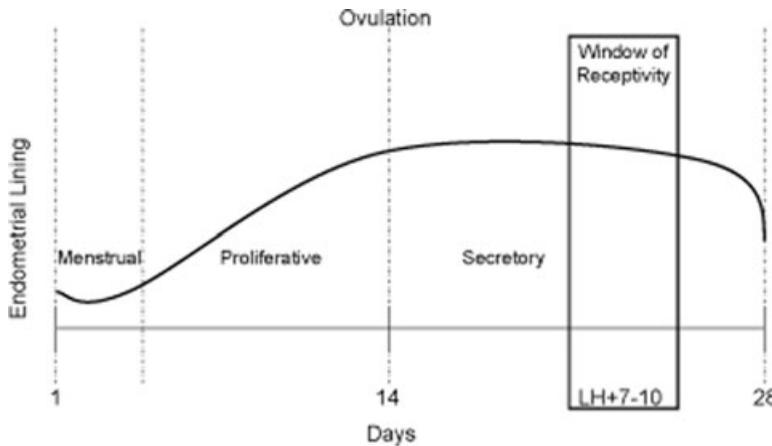


FIGURE 4. Endometrial lining throughout the menstrual cycle. The endometrial lining thickens in response to estrogen in the proliferative phase. After ovulation, the endometrium becomes decidualized in the secretory phase. The window of receptivity is 7–10 days after the LH surge, near the time of ovulation. After the cycle is finished, menstruation occurs and the cycle begins again.

spacing in knockout mouse models. These factors include cytokines, transcription factors, ovarian hormones, and other autocrine/paracrine factors (reviewed in Refs. 41–44). Additionally, a mouse model of endometriosis has been created.⁴⁵

Estrogen (E2) and progesterone (P4) are obviously important in the development of the endometrium. E2 signals through either estrogen receptor alpha (ER α) or beta (ER β) to activate a number of estrogen-responsive genes. P4 signals through progesterone receptor A (PRA) and B (PRB) to activate a number of progesterone-responsive genes in the mouse.⁴²

ER α null mice are infertile, have abnormalities of the female reproductive tract, and cannot support implantation. However, ER β null mice support implantation. Leukemia inhibitory factor is a member of the IL-6 family and is a downstream target for estrogen. LIF null mice do not support implantation, although a similar role of LIF in humans has not been observed. Thus, ER α and cytokines, perhaps acting downstream of ER α , are important to maintain endometrial receptivity.⁴²

Progesterone receptor null mice (lacking both PRA and PRB) also have reproductive tract anomalies and lack of decidualization. However, PRB null mice have normal reproductive features, suggesting that PRA is more important to reproduction and possibly endometrial function in the mouse. Indian hedgehog (IHH) is a progesterone-responsive gene. IHH null mice with conditional deletion in the uterus are infertile because of the lack of a decidual response.⁴² Thus, PRA- and progesterone-responsive genes are im-

portant for the decidual response during endometrial receptivity.

For successful pregnancy to occur, the endometrium must be receptive, the blastocyst must come into contact with the endometrium, and the blastocyst must penetrate the decidua to access a blood supply. The homeobox transcription factors, HOXA10 and HOXA11, are expressed during the window of receptivity in both mice and humans and are important for decidualization. HOXA10 null mice are subfertile. They demonstrate a failure of embryos to implant and the uterus to decidualize, most likely because of a lack of stromal proliferation. HOXA11 null mice have a more severe phenotype with hypoplastic uteri and failure of implantation. FKBP52 null mice have defects in luminal closure of the uterus during implantation and thus defects in apposition of the blastocysts to the endometrium. Prostaglandins are important for increased vascular permeability at the time of implantation. PTGS2 (COX2) null animals are deficient in the enzyme that mediates prostaglandin synthesis and are infertile.⁴¹

Most mouse models of endometriosis (OMIM %131200) use autologous endometrial tissue transplanted into the abdominal cavity to reproduce the phenotypic endometriotic peritoneal implants. However, the single mutant K-ras oncogene mouse developed peritoneal endometriotic implants by 8 months of age. Furthermore, when the K-ras oncogene mouse was crossed with a *Plen* conditional mouse, the mice developed endometrioid ovarian cancers, which are more common in women with endometriosis. Currently, this is the only genetic mouse model for endometriosis.⁴⁵

Human Models with Endometrial Dysfunction

In the human, a coordinated response to estrogen and progesterone leads to the cyclic changes in the endometrium. With inappropriate thickening or decidualization of the endometrium, clinical problems such as breakthrough bleeding, metrorrhagia, or cancer occur. Furthermore, endometrial tissue located outside the uterine cavity, as in the case of endometriosis, is still hormonally sensitive, potentially leading to cyclic pain. Lastly, an endometrium that is not receptive to a blastocyst will not support a normal pregnancy, and thus defects in receptivity of the endometrium lead to infertility or recurrent pregnancy loss.¹

Since the endometrium is a hormonally responsive organ, the gene expression profile changes depending on the phase of the cycle. Gene expression projects over the years have attempted to create a database of gene expression patterns based on timing of the cycle for normal women. Some of these data can be found in the Gene Expression Omnibus <<http://www.ncbi.nlm.nih.gov/geo/>>.

In humans, the receptive phase is 7–10 days into the secretory phase, designated as 7–10 days past the LH surge (LH+7–10) (Fig. 4). Prior to this, the endometrium is not supportive of a blastocyst. After this receptive phase, the endometrium is hostile to the blastocyst.¹ Multiple translational studies during the receptive phase have searched for factors responsible for receptivity defects, but no good candidates have been identified. Additionally, multiple gene expression studies have attempted to identify dysregulated genes at the receptive time point of the endometrium in women with infertility (reviewed in Giudice⁴⁶). Likewise, important factors for these receptivity defects have not yet been identified in humans.

Similar gene expression studies have attempted to determine dysregulated genes involved in endometriosis, but to date no good gene candidates have been discovered.^{47–49} Recently, endometrium from patients with severe endometriosis at different times within the menstrual cycle was compared to endometrium from normal women using robust gene expression arrays. Although the expression of many genes was different, the progesterone-responsive genes showed the most significant dysregulation. This confirms the progesterone resistance found with endometriosis. Furthermore, additional analysis revealed that the gene expression pattern did not fit the timing of the cycle, showing some delay in expression of early secretory genes. Thus, endometriosis and the resulting infertility

may result from a combination of progesterone resistance and a menstrual cycle timing defect.⁵⁰ Additionally, mutation screening studies of women with endometriosis did not reveal any mutations in *K-ras* or *Pten*.^{51,52}

Conclusions

The basic biology of the menstrual cycle is not so basic. However, mouse models have improved our understanding of folliculogenesis, implantation, and endometriosis in mammals. Even though the factors important in mouse folliculogenesis do not play a large role in POI, the concepts open avenues for further study and may lead to an understanding and eventual treatment of human POI. Furthermore, a better understanding of implantation and decidualization defects in mice may lead to treatment for recurrent pregnancy loss, infertility, and possibly endometriosis.

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Conflicts of Interest

The authors declare no conflicts of interest.

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