Sheets Physiology

Number	15
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Development of the embryo

a- Initial Stages:

- The development of the embryo is tied to the female sexual organs (the uterus specifically and to a lesser extent, the fallopian tube).
- As a recap, after ovulation, high levels of progesterone are released→ secretions by the mucosal lining of the fallopian tube increases + increased secretions in the uterine endometrium.
  Endometrial secretions increase the thickness of the membrane through an increase in blood supply, as metabolism increases blood flow.
- In the first 40 hrs, the cytoplasm of the oocyte provides enough nutrient supply for itself. Afterwards, other sources will provide the appropriate nutrient supply [secretions from the fallopian tube + secretions from the uterine endometrium]. In other words, the newly formed embryo gets nutrients from the surrounding.

b- Implantation of the Embryo:

- The embryo will start to implant within the uterine endometrium.
- At that stage, simple molecular diffusion is not sufficient to supply the embryo, so an appropriate vascular system is formed to allow mass movement or flow of nutrients to the embryo and the newly formed thickened endometrium.

Recap: Three important aspects of the development of the embryo should be taken into consideration:

1- The timed development of the embryo→ After fertilization of the embryo, the embryo undergoes changes through several stages (ie. 2-cell stage, 4-cell stage, morula-stage, then blastocyst stage) within the first few days. For the blastocyst stage to develop, a period between 4 to 6 days after fertilization is needed.
2- Nutrient supply
3- The structural changes in the uterine endometrium→ As ovulation occurs due to a surge in LH, progesterone levels increase, leading to development of the endometrium. At that point, the endometrium is in a well-developed state (ie.thick, Rich in nutrients, good blood supply). In other words, the endometrium reaches the secretory stage.

So,

The embryo is in the blastocyst stage + the endometrium is in the secretory stage (growing and proliferating further). Consequently, a specific form of communication results between the growing endometrium and the embryo.

The endometrium and embryo secrete many materials and regulators which allow attachment of the newly formed embryo.

Requirements for implantation or attachment:

1- A functionally, normal, well-developed *blastocyst.*
2- The endometrium has to be in the *secretory phase*.
3- The *zona pellucida* which surrounds the fertilized oocyte **must** be *dissolved* for implantation to happen.
4- An adequate *cross-communication* at the same time between endometrium and embryo: certain factors which determine attachment and implantation (markers of implantation) *:
Endometrium: Integrin molecules, L-selectin ligands, mucin-1 Heparin-binding EGF. (Not for memorization)
Embryo: cytokines and growth factor interleukins; prostaglandins, VEGF receptor for endometrial signals LIF receptor, insulin-like GF and heparin-binding epidermal growth factor receptor. (Not for memorization)

*(The doctor focused on the general idea of communication here and did not focus on each and every marker of implantation.)

Implantation Window

At the 6th day after which the blastocyst formed, full implantation of the embryo occurs.

The time frame for implantation is important. If we have a fully developed embryo with all the requirements above fulfilled, yet we did not achieve such requirements during the required time frame (implantation window), no implantation will occur.

LH surge is the determinant for the time frame of the implantation window.

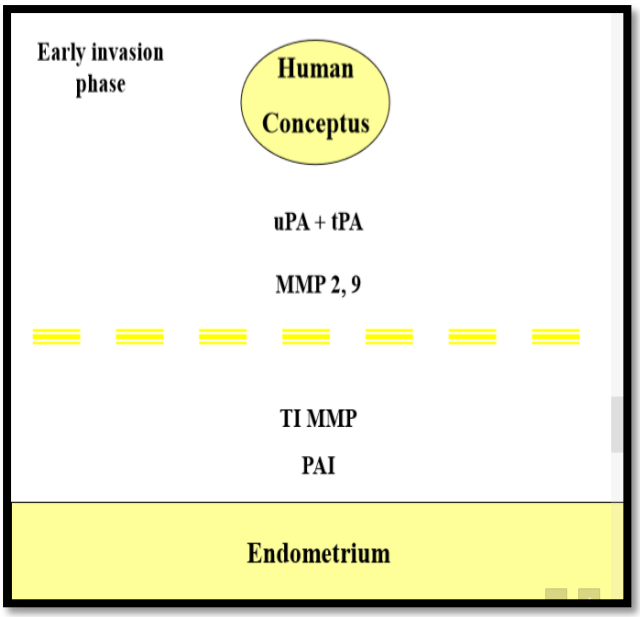
- ✓ ***Usually, implantation occurs 6+ to 10+ days after LH surge***.

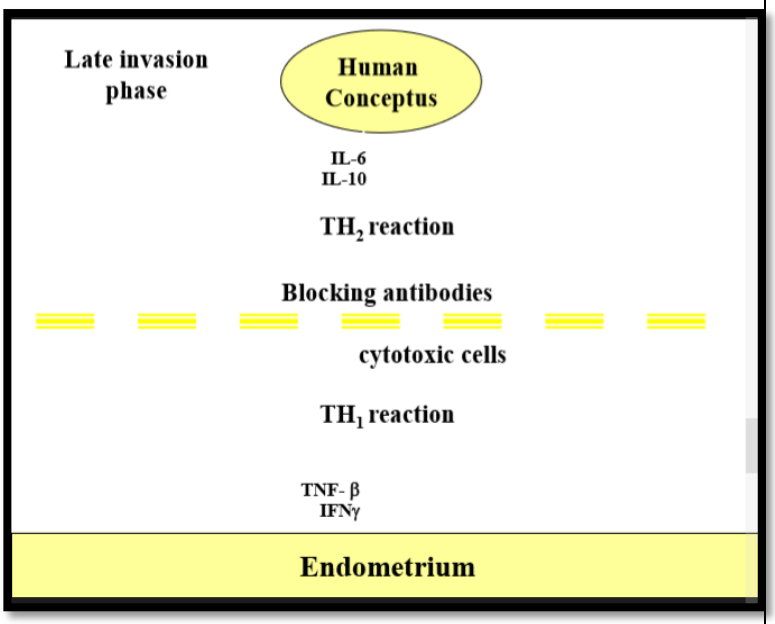
- ✓ ***Implantation occurs 4 to 8 days after ovulation*** because ovulation occurs 1 to 2 days after LH surge.
- ✓ ***From fertilization, 4 to 5 or 6 days (blastocyst stage).***
- ✓ ***From last menstrual cycle, 18 to 22 day "if we assume that ovulation occurs at day 14 of last menstrual cycle; follicular phase is two weeks***", but this is not accurate because there is a great variation in follicular phase.

Phases of implantation (in sequential order---each step won't happen unless the one preceding it occurs):

1- Signalling
2- Apposition
3- Attachment (chemical binding)
4- Invasion

Again, the names of the multiple factors used in signalling are not the focus of this course. Just know that there are multiple factors and regulators which work to allow attachment to happen.





In the late invasion phase, certain chemical substances are sometimes released to prevent attachment of the embryo→ happens during certain diseases (unusual pathological condition).

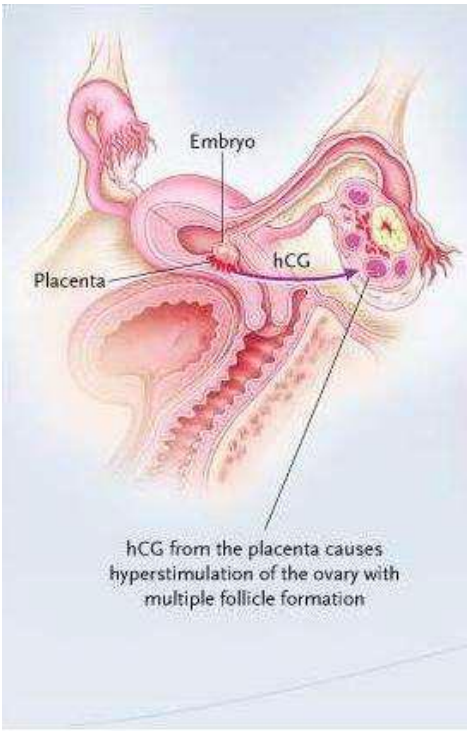
Now, beyond the implantation window (if implantation does not happen during the required time frame---the four mentioned criteria gets bypassed), the

endometrium will start to degenerate, losing the presence of the chemical signals and substances and causing failure of the implantation of the embryo.

After day 8 or 9 after ovulation, the endometrium will start to degenerate→ not appropriate for further development of the embryo, even if attachment did occur, as the endometrium weakens further and further.

To prevent degeneration of the endometrium following implantation and attachment of the embryo, the outer cell mass of the embryo will start to secrete human chorionic gonadotropin (hCG) at about day 7 or 8 after ovulation. At the time of secretion of hCG the embryo is still not attached well to the endometrial wall.

Human chorionic gonadotropin:



It is released from the embryo proper (*syncytial trophoblast cells*), picked up (absorbed) by the endometrial wall, and it will enter (in small amounts) to the maternal circulation. This hormone -hCG- stimulates corpus luteum, which initially secretes progesterone and estrogen and will itself degenerate at day 8 (or 9 or 10) after ovulation if not maintained. So, hCG prevents the apoptosis and degeneration of the corpus luteum and stimulates it further. In other words, the secretion of progesterone by the corpus luteum is still maintained→ no decline in progesterone levels→ endometrium will not degenerate→ the newly structural form of the endometrium as well as the implanted embryo will be maintained→ further development of the embryo will continue.

Therefore, all the events mentioned above indicate that no degeneration of the endometrium results in the (temporary) cessation of the menstrual cycle.

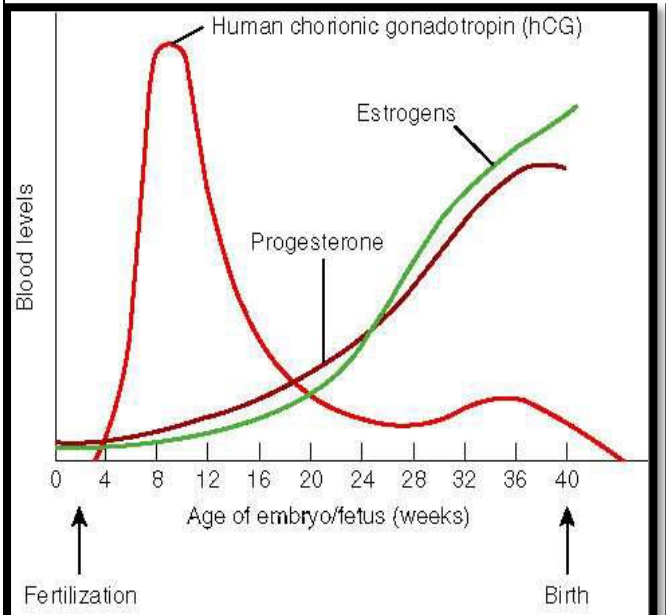
Implantation Failure:

<u>*In normal fertile women*</u>, 78 to 83 % of embryos fail to implant (Wilcox et al, 1988; Ellish et al, 1996)→ failure to implant even though successful oogenesis and fertilization did occur. In other words, even if one of the factors and criteria for implantation is not achieved, it will result in mismatch and

miscommunication between the embryo and the endometrium resulting in failure of implantation.

In infertile women, 85 % of embryos fail to implant (Edwards et al, 1995)→ embryos formed through IVF (in vitro fertilization) fail to implant.

Many failed pregnancies are due to failure in implantation, indicating the difficulty of implantation. Such situation is like a protective mechanism to prevent the population from drastically increasing in number.



(b) Blood levels of hormones during pregnancy

29.16b

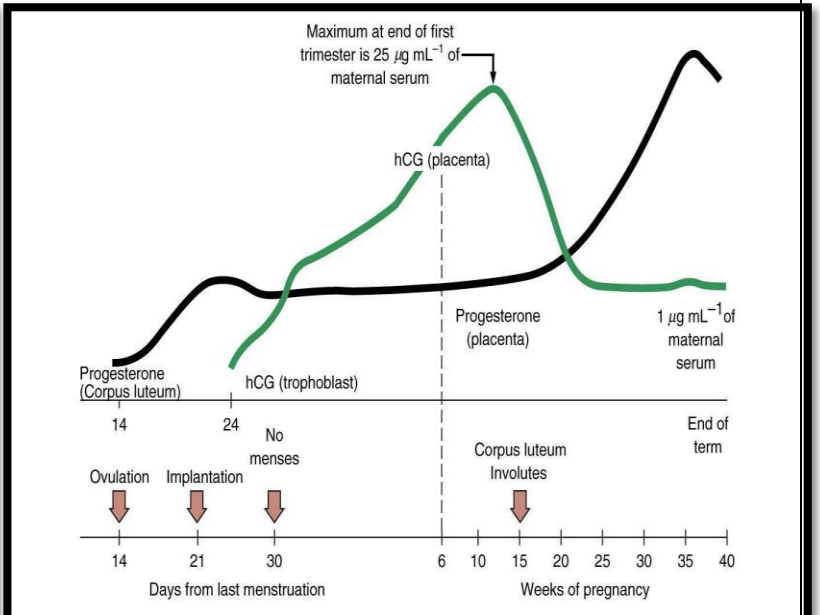


Figure 23.20. Effect of fertilization on ovarian cycle in terms of secretion of progesterone and human chorionic gonadotropin (hCG).

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Hormonal changes during pregnancy:

- ***Human chorionic gonadotropin***:

Again, it Prevents programmed cell death of the corpus luteum→ progesterone at the early stages of pregnancy will not decrease (it will in fact increase).

Referring to both figures above, by the end of the 1st trimester, hCG starts to decline. That is because functionally, hCG won't be needed anymore, because when the placenta is fully formed and functional, the corpus luteum is not needed anymore (it will degenerate 10 to 12 weeks of pregnancy; after first

trimester) and in that regard, hCG (which its main function is to maintain corpus luteum) is not needed.

Now, consider a case in which the ovaries are removed for whatever pathological reason before the first trimester ends—when the corpus luteum is still needed and the placenta is still not fully mature→ the result would be the removal of the corpus luteum which is essential at that time for progesterone secretion. Consequently, decreased levels of progesterone will result in loss of maintenance of the uterine wall and function which will result in cessation of formation of the placenta (placenta will not develop fully) and eventually pregnancy will not continue.

In another case where the ovaries are removed after the first trimester and after the placenta is fully developed, the ovaries are no longer needed to maintain pregnancy as the corpus luteum at that time has already degenerated and the placenta takes over instead and will in turn produce progesterone.

Note: The level of hCG does not disappear completely after complete formation of the placenta because the remnants of the trophoblastic structure surrounding the embryo still secrete it, but it will be completely removed from the maternal circulation once pregnancy ends and the placenta and all other layers are removed from the maternal body. However, we do expect low levels of hCG to be found in the maternal circulation, and they will be removed from the body within two weeks after pregnancy.

- ***Progesterone:***

It's produced from corpus luteum and the newly formed placenta in the 1st trimester. After that, the placenta becomes fully functional and mature structure, so it takes over the secretion of progesterone and other hormones. So, referring to the first figure, progesterone is produced from two mixed sources, from the corpus luteum (major) and the developing placenta (minor) in the 1st trimester, after that the corpus luteum degenerate; the mature placenta is the only source.

The function of progesterone is:

- ✓ To maintain the uterine endometrium, providing a solid base for the formation of the placenta.
- ✓ To decrease contractility of uterine muscle thus preventing spontaneous abortion.

- ***Relaxin:***

It's secreted by the placenta during pregnancy.

The function of relaxin is:

- ✓ To increase elasticity and flexibility of joints to allow delivery.
- ✓ To help in dilate uterine cervix during labour.

- ***Human chorionic somatomammotropin (hCS)*** [*human placental lactogen*]: somatotropin (growth hormone), mammotropin (related to breast). It is secreted by the placenta.

Before talking about this hormone, we have outside the placenta estrogen secreted goes to maternal circulation and as we said earlier, estrogen function is proliferative (mitotic) on most reproductive and associated organs in mother and on follicular cells. It has also mitotic activity on pituitary gland; it will stimulate lactotroph cells to secrete more prolactin. So, we have *prolactin from maternal anterior pituitary*, we may have *prolactin from the placenta* and we have *human chorionic somato**mammotropin*** from the placenta. They are all ***essential for the breast development.***

The function of human chorionic somatomammotropin is:

- ✓ To allow more breast development in mother.
- ✓ To increase growth of tissues (fetal & maternal) by increasing protein synthesis.
- ✓ To reduce glucose utilization by maternal circulation to allow for fetal utilization. At the end we have more glucose in the maternal plasma. It can be controlled by the pancreas but when the pancreas can't cope, the mother will develop gestational diabetes.

The placenta forms all kinds of growth factors, hormones and regulators needed to maintain pregnancy and needed for the embryo's development. The important hormones secreted by the placenta are: estrogen, progesterone, and human placental lactogen.

The placenta has life span like corpus luteum, it has programmed cell death. Around 40 weeks of gestation, it will start to degenerate structurally and functionally, we will start to have reduction in all hormones secreted by the

placenta (remove the uterus from suppression effect of progesterone); this reduction in hormones will start to initiate local factors in the uterus and pituitary factors in hypothalamus to stimulate release of oxytocin from posterior pituitary thus stimulate delivery.

The placental hormones have inhibitory effect of gonadotropin releasing hormone. So, we will have suppression of LH an FSH release in pregnant woman; almost zero concentrations.

Fertility period

Fertility period of the male:

Any time as long as we have normal sperms, if we don't have sperms we don't have fertility ability.

Fertility period of the female: it's the ability to have a newly formed individual.

We have the fertility ability in the female only if we have oocytes, we release oocyte after ovulation and it can live up to one day only. Can we exactly define that one day? No, except when using ultrasound and hormonal balance we can detect it almost exactly. The easier solution is that we have fertility period. In normal female as long as she is menstruating (she has ovulation), we have land mark which is the first day of menstruation but there is a great variation between first day of menstruation and the time of LH surge "peak"(but there are certain markers for it, like increase estrogenic activity and increase cervical & vaginal secretions).

- *Remember that LH surge happened one day to two days before the ovulation. We will consider it one day before the ovulation to calculate fertility period (discussed below).*

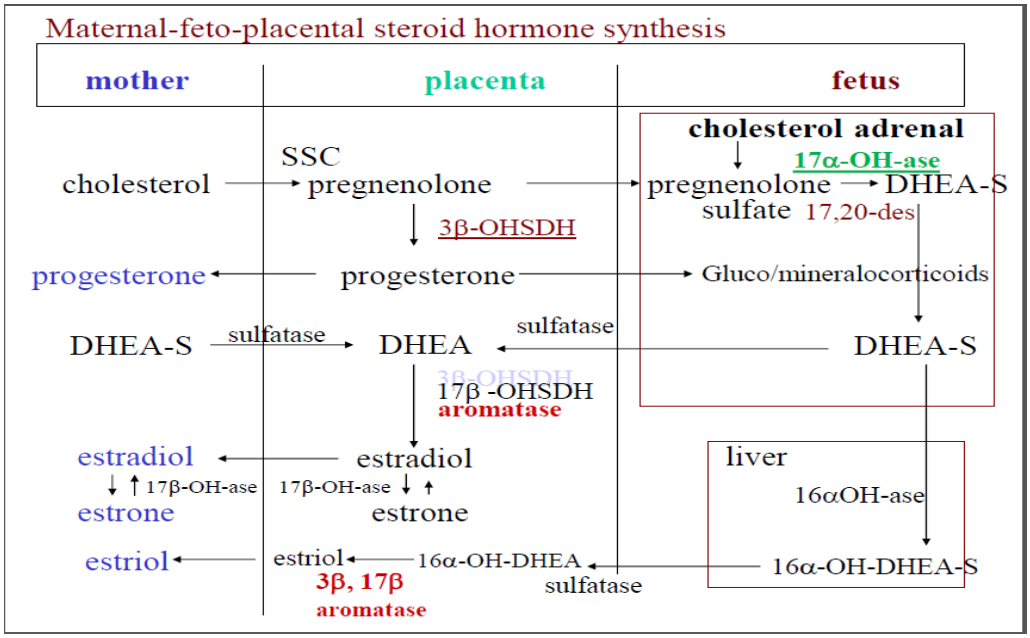
The fertility period or window is ***up to 3 days before the ovulation and up to 1 day after it*** **OR** ***2 days before LH surge and 2 days after it***. WHY? We have already known that the lifespan of oocyte after ovulation is up to one day, and the lifespan of sperms in female reproductive tract is up to 96 hours or 3 days for simplicity. So, if we have deposition of sperms two days before the ovulation we may have fertilization, the probability is less when the deposition is three days before the ovulation and it is more when the deposition is one day before the ovulation. When we go beyond fertility period (3 days before & one day after ovulation) no way the female is able to be fertile.

We can say that fertility period is up to 15 days after the menses "assuming that ovulation take place on day 14 after menses" but this is not accurate because follicular phase could be 3 weeks. *But the better is to depend on ovulation and LH surge.*

The importance of fertility period is on family planning.

Maternal-feto-placental steroid hormone synthesis:

At the time of delivery, the adrenal gland of the fetus will be large not because of zona glomerulosa or fasiculata but because of reticularis and deep layer beneath it, this layer is called "fetal adrenal" (important structure to form steroid hormones during pregnancy). We have materno-feto-placental system; it will cooperate to produce different hormones like progesterone and different dehydroepiandrosterones (DHEAs) which ends in estrogens.



For progesterone secretion:

Both mother (from corpus luteum; up to 3 months) and placenta can produce progesterone from cholesterol →pregnenolone→ progesterone pathway. Then it will go to maternal circulation.

Don't confuse because the above figure doesn’t show the mother formation of progesterone; it's produced by mother too.

For estrogen secretion:

Estrogen can be produced from corpus luteum in the mother; up to 3 months but in low amounts and ***cannot*** be produced ***only*** from the placenta. ***17α-hydroxylase*** enzyme which is an essential enzyme to convert pregnenolone or progesterone to DHEAs which end in estrogens; is functionally *inactive in the placenta* but it's *active in fetal adrenal*. So, we need the integration of mother-feto-maternal system to produce estrogens. If we have adrenal fetal problem we will end up in low levels of estrogens and there is no continuation of pregnancy (important).

GOOD LUCK ^_^