



## PHYSIOLOGY

Sheet

Slide

Handout

Number

14

Subject

آخر شيت في البيسك

Done By

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Corrected by

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Doctor

Dr. Saleem

Date: 00/00/2016

Price:



- Within 1 year after menarche (*at the age of 13*), **pubarche** occurs.
- Adrenal androgens play a role at the beginning of puberty; as pubarche occurs under the effect of adrenal androgens and this is called **adrenarche**.
- Before puberty (during childhood) the gonads in both females and males are inactive and plasma steroids as well as gonadotropins levels are very low. This is because these hormones are inhibited by:
  1. Most importantly, intrinsic CNS inhibitors. These are genetically determined:
    - a) GABA ( $\gamma$ - AminoButyric Acid)
    - b) Endogenous opioids (peptides in the nervous system)
  2. Although their level is low, steroids and gonadotropins inhibit the release of GnRH during childhood by negative feedback mechanism.
- At the beginning of puberty, the hypothalamic- pituitary axis becomes reactivated. This response involves decrease in hypothalamic sensitivity to steroids and reduction in effectiveness of intrinsic CNS inhibition over the GnRH once generated. *If you want to know more, you can read what's written in the box.*
- The activation of the hypothalamic- pituitary- gonadal axis is also genetically determined.
- There are many factors that determine the time of puberty especially in females. These factors are (*very very important*):
  1. Genetic factors
  2. Nutrition
  3. Climate
  4. Geographical factors
  5. Leptin hormone

Leptin is a hormone produced by adipose tissue and has a permissive effect on the initiation of puberty. It provides signals to the CNS that there are sufficient energy stores to support puberty.

6. Distance from the equator
7. Lower altitudes

Points 6+7 are associated with early puberty.

#### Extra information

The negative feedback effects of gonadal steroids operate in relation to a set point in the gonadostat of the brain (hypothalamus). One hypothesis explaining the prepubertal increase in gonadotropin secretion in both sexes is that the sensitivity of the hypothalamus to steroidal negative feedback decreases as puberty approaches. That is, the set point for negative feedback increases so that higher concentrations of steroid hormones in the blood are required to decrease gonadotropin secretion from the anterior pituitary gland. (Similarly, as you increase the set point of the thermostat in your house, it takes a higher room temperature to shut off the heater.) Thus, even though circulating levels of steroids rise because of the increase in gonadotropin secretion, the levels of these steroids are not high enough to block a further rise in gonadotropin secretion. It has been hypothesized that the hypothalamus of children is 6–15 times more sensitive to steroidal negative feedback than that of an adult. How is this known? One piece of evidence is that it takes a much smaller amount of injected estrogen to lower blood gonadotropin levels in girls than in adult women.

8. Obesity
9. Heavy exercise

Both 8+9 delay puberty.

- “Overweight females (not obese) are very fertile.” Dr. Saleem.
  - Pubertal growth (spurt) requires concentrated action of sex steroids, growth hormone and insulin like growth factor-1 (IGF-1).
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### ❖ Fertilization:

- As you remember, fertilization occurs at fallopian tube. The oviduct transport the germ cells in two opposite directions: sperm ascends toward the ampulla and the zygote descends toward the uterus.
- The diameter of the oviduct is too narrow, so the movement in two directions requires coordination between smooth muscle contraction, ciliary movement and fluid secretion. All of which are under hormonal and neural control.
- The most important factor in the movement of the zygote is peristaltic contractions not gravity. This is similar to what happens in the GIT; ingested food stimulates peristalsis and moves toward the stomach even if you are upside down. In the reproductive system, the size of the zygote is the factor that stimulates peristaltic movement.
- The transport of the sperm through the female reproductive tract is facilitated by female’s response:
  1. Uterine and cervical activity is increased by the spinal reflexes during orgasm.
  2. The cervix dilates during orgasm.
  3. Oxytocin release at the time of orgasm increases uterine contractility.
  4. The mucus of the cervical canal increases the movement of the sperm under estrogen dominance and orgasm.
  5. Peristaltic activity and fluid flow in the oviduct assists transport.
- Sometimes the sperm and the zygote don’t move due to some pathological conditions.

- Millions of sperms move randomly in the vicinity of the ovum. However, not all of the sperms reach the ovum, some of them remain in the uterus and some might exit the uterus to the abdominal cavity!
- The sperm must undergo capacitation to bind and penetrate the zona pellucida. Capacitation is an irreversible process that involves (1) an increase in the sperm's motility, (2) removal of surface proteins, inhibitors and lots of lipids and (3) merging of the acrosomal and plasma membranes of the sperm.
- Capacitation takes place in the female's reproductive system and lasts from an hour to several hours.
- The fact that sperms can be capacitated (washed) in a chemically modified media has enabled in-vitro fertilization.
- Although sperms remain motile for up to 4 days in the female's reproductive system, their fertilizing capacity is limited to 1 or 2 days.

#### کلمات لیست کالکلمات:

→ Before implantation, the embryo is enclosed with the **pellucida zone**. The pellucida zone contains specific glycoprotein receptors that accept specific sperms. It selectively prevents the fusion of inappropriate sperm cells with the ovum. So, the ovum doesn't accept the nonspecific sperms especially when animals of different kinds meet (a dog and a wolf for example). However, if a donkey meets and a horse, the result is a mule which is infertile.

→ Very rarely, fertilization occurs outside or even inside the uterine tube and is called ectopic fertilization. *I think the doctor wanted to talk about ectopic pregnancy which might occur either inside or outside the uterine tube.*

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#### ❖ Implantation:

- *"Implantation occurs after 1 week of fertilization" last year's sheet.*
- Before implantation, retention of zona pellucida is necessary for (1) embryo transport, (2) protection against mechanical damage, (3) adhesion to the oviduct wall and (4) prevention of immunological rejection by the mother.

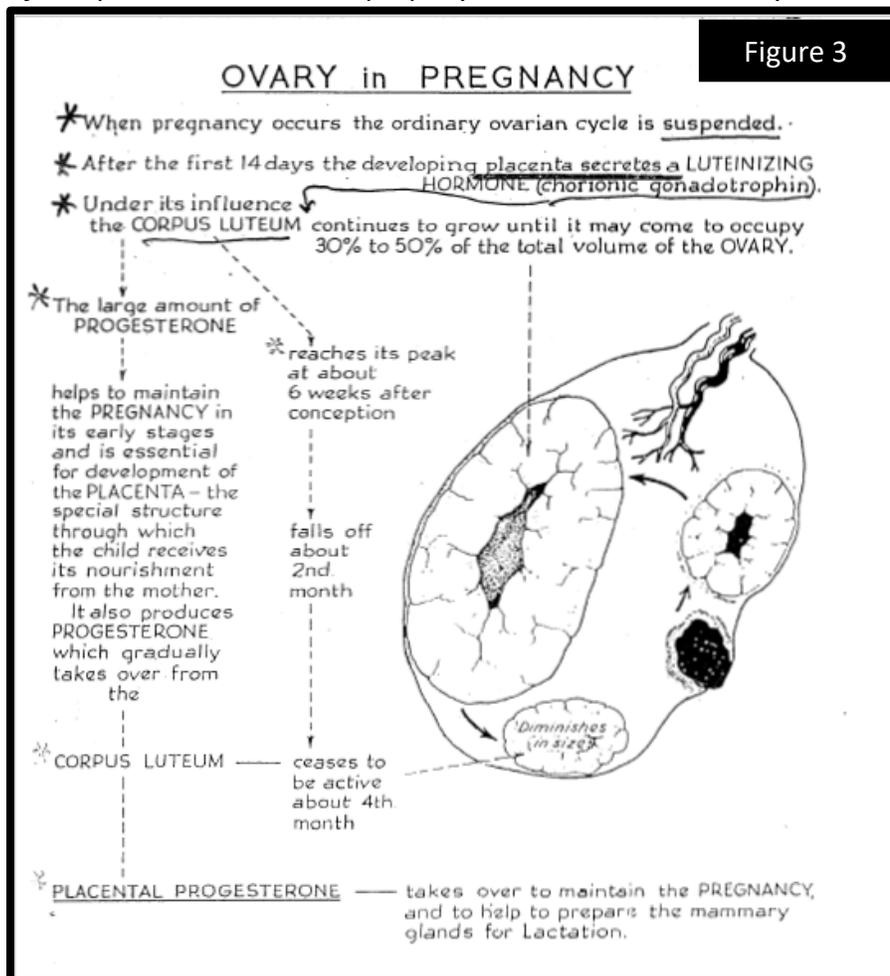
- The developmental stage of the embryo that undergoes implantation is called a blastocyst; this is a mass of cells that produces several agents (*table-1*):
  1. Immunosuppressive agents
  2. Metalloproteases (*facilitate invasion of trophoblast into the endometrium*)
  3. Serine proteases (*facilitate invasion of trophoblast into the endometrium*)
  4. Other factors.

Substances secreted by the blastocyst:	Table1
<p><b>Immunosuppressive agents</b></p> <p>Platelet-activating factor (PAF)</p> <p>Human chorionic gonadotropin (hCG)</p> <p>Early pregnancy factor</p> <p>Immunosuppressive factor</p> <p>Prostaglandin E<sub>2</sub></p> <p>Interleukins 1<math>\alpha</math> and 6</p> <p>Interferon-<math>\alpha</math></p> <p>Leukemia inhibitory factor</p> <p>Colony-stimulating factor</p>	<p><b>Serine proteases</b> (<i>facilitate invasion of trophoblast into the endometrium</i>)</p> <p><b>Other factors or actions</b></p> <p>Ovum factor</p> <p>Early pregnancy factor</p> <p>Embryo-derived histamine-releasing factor</p> <p>hCG: autocrine growth factor</p> <p>Plasminogen activator and its inhibitors</p> <p>Insulin-like growth factor type II (IGF-II): promotes trophoblast invasiveness</p> <p>Estradiol</p> <p><math>\beta_1</math> Integrin</p> <p>Fibroblast growth factor (FGF)</p> <p>Transforming growth factor-<math>\alpha</math> (TGF-<math>\alpha</math>)</p> <p>Inhibins</p>
<p><b>Metalloproteases</b> (<i>facilitate invasion of trophoblast into the endometrium</i>)</p> <p>Collagenases: digest collagen types I, II, III, VII, and X</p> <p>Gelatinases: 2 forms, digest collagen type IV and gelatin</p> <p>Stromelysins: digest fibronectin, laminin, and collagens IV, V, and VII</p>	

- Note: “No need to memorize the table, just know the important things” Dr. Saleem
- Human chorionic gonadotropin is one of the most important factors secreted by the blastocyst, both preimplantation and postimplantation. Besides rescuing the corpus luteum, hCG acts as an **immunosuppressive agent**, has growth-promoting activity, and acts as an autocrine growth factor that promotes trophoblast growth and placental development. Thus, hCG may have a role in the adhesion of the trophoblast to the epithelia of the endometrium. hCG has protease activity, and hCG levels are high in the area where the trophoblast faces the endometrium.
- Also, remember that this hormone is important for fetal adrenal gland and testis as it works instead of LH. (*you can refer to sheet 11*)

❖ **Placenta formation:**

- The placenta is formed after 2 weeks of fertilization. It produces hormones, such as; human chorionic gonadotropin (hCG):
  - This hormone maintains growth of corpus luteum
  - It is an indicator of pregnancy; it can be tested after 2 weeks in the plasma and after 3 weeks in the urine.
- **The corpus luteum** grows secreting more and more hormones (progesterone & estrogen) reaching its peak about 6 months after fertilization. It may come to occupy 30-50% of the ovary. (figure 3)
- During the second month corpus luteum falls off, it ceases to be active during the 4<sup>th</sup> month and the placenta takes over.
- *"If this period doesn't occur properly, abortion occurs"- last year's sheet.*



- The placenta also secretes many other chemicals, actually all of the female hormones are secreted by the placenta. We can divide these chemicals into (table 2):
  1. Peptide hormones and neuropeptides.
  2. Steroid hormones.

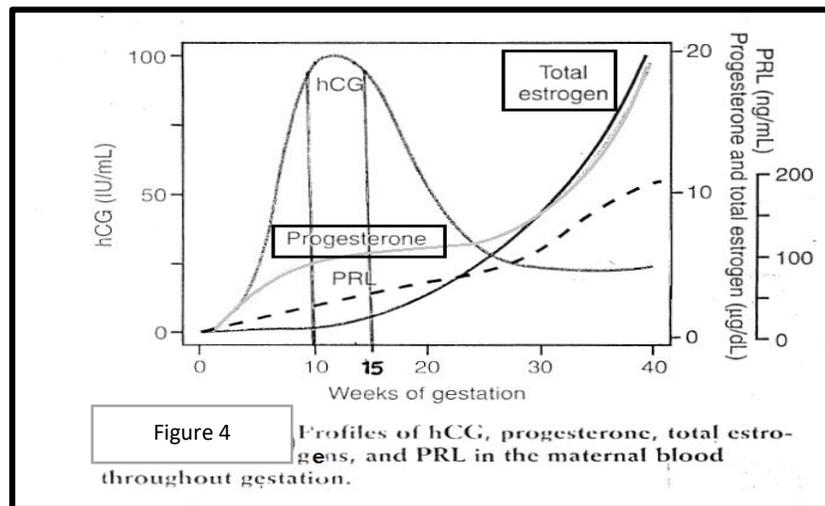
HORMONES MADE BY THE PLACENTA		Table2
<b>Peptide Hormones and Neuropeptides</b>	<b>Steroid Hormones</b>	
Human chorionic gonadotropin (hCG)	Progesterone	
Thyrotropin (thyroid-stimulating hormone [TSH])	Estrone	
Placental-variant growth hormone	Estradiol	
Human chorionic somatomammotropins 1 and 2 (hCS1 and hCS2), also known as human placental lactogen (hPL: hPL1 and hPL2)	Estriol	
Placental proteins PP12 and PP14		
Thyrotropin-releasing hormone (TRH)		
Corticotropin-releasing hormone (CRH)		
Growth hormone-releasing hormone (GHRH)		
Gonadotropin-releasing hormone (GnRH)		
Substance P		
Neurotensin		
Somatostatin		
Neuropeptide Y		
(ACTH)-related peptide		
The inhibins		

- *“The most important placental peptide hormones is hCG. In the developing blastocyst, and later in the mature placenta, it is the syncytiotrophoblast cells that synthesize hCG, perhaps under the direction of progesterone and estrogens. The placenta also produces two human chorionic somatomammotropins, hCS 1 and hCS 2, also called human placental lactogen (hPL). hCS1 and 2 are polypeptide hormones that are structurally related to growth hormone and placental-variant growth hormone, as well as to prolactin (table 2). They play a role in the conversion of glucose to fatty acids and ketones, thus coordinating the fuel economy of the fetoplacental unit. The fetus and placenta use fatty acids and ketones as energy sources and store them as fuels in preparation for the early neonatal period, when a considerable reservoir of energy is necessary for the transition from intrauterine life to life outside the uterus. hCS 1 and 2 also promote development of maternal mammary glands during pregnancy.”*

After reading the paragraph, the doctor said the following:

- There are 4 hormones that play a role in the conversion of *glucose to fatty acids and ketones (the energy sources for the fetus and the placenta)*. These hormones are:

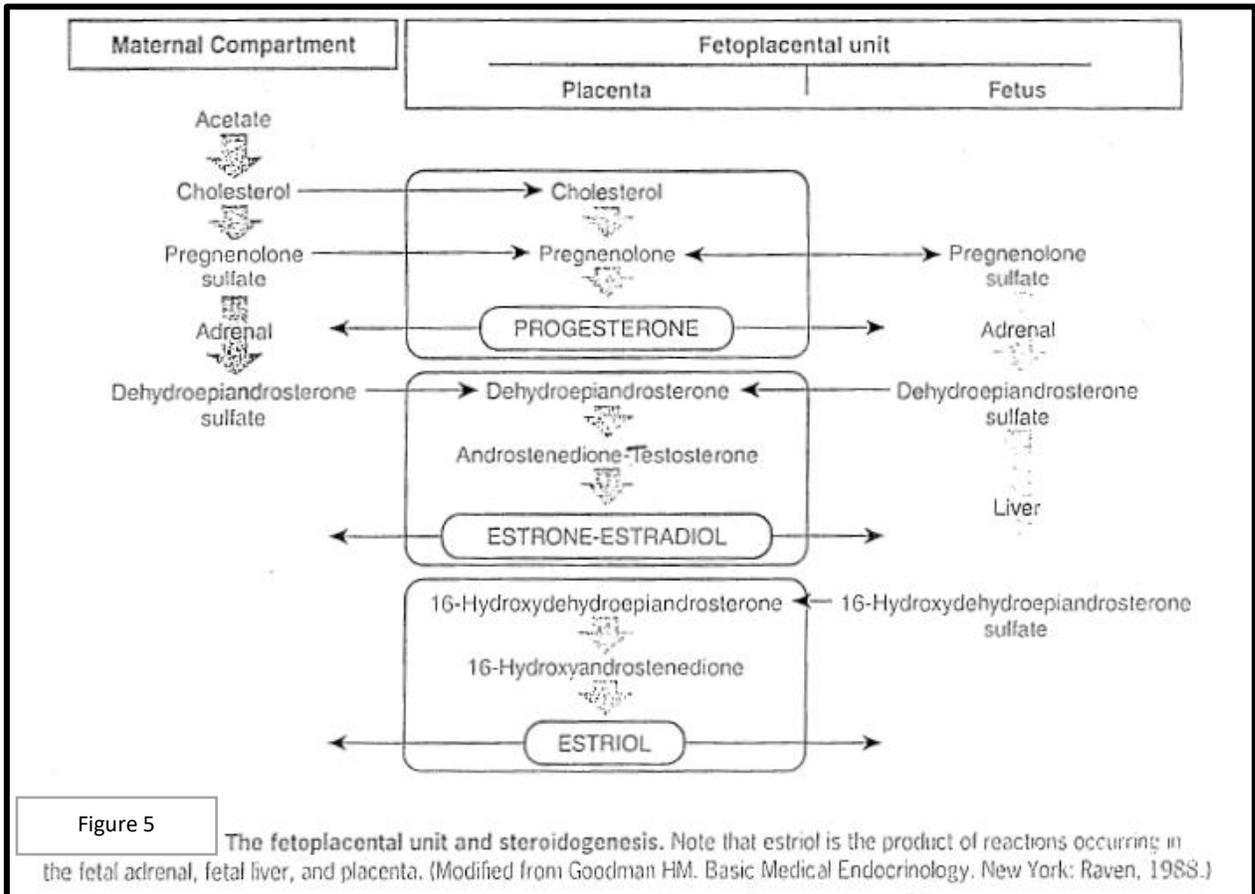
1. Human chorionic gonadotropin (hCG)
  2. Human placental lactogen (hPL: hPL1 and hPL2), also known as Human chorionic somatomammotropins 1 and 2 (hCS1 and hCS2).
  3. Placental- variant growth hormone
  4. Prolactin
- hCG and hPL are produced by the same placental cells but are secreted in different patterns to allow their control by different regulatory mechanisms.
  - The cause of morning sickness in pregnant women is the increased concentration of hCG and thyroxin in the first trimester of pregnancy. Actually just these two hormones are high during early pregnancy.
  - The high level of hCG between weeks 10-15 indicate the importance of this hormone to the fetus. (figure 4)



#### ❖ Fetoplacental unit and steroidogenesis:

- In pregnancy, both maternal and fetoplacental compartments function as one unit to produce progesterone, estrogens and estradiol by the process of steroidogenesis. (figure 5)
- The substrate for this pathway is cholesterol. Cholesterol that reaches the placenta comes from the maternal compartment only. However, Progesterone sulfate comes from both the fetus and the mother.

- When these hormones (progesterone, estrogens (estradiol and estrone) and estriol) are produced in the placenta, they pass to the fetus and to the maternal compartment.
- The levels of estriol in plasma, amniotic fluid, or urine are used as an index of fetal well-being. Low level of estradiol would indicate potential fetal distress, although rare inherited sulfatase deficiencies can also lead to low estriol. (*Important*)



The nervous system and the immune system of the fetus develop slowly but the fetal endocrine system plays a very important role in fetal growth, development and homeostasis. Fetal hormones perform the same functions of the adult and serve unique functions such as sexual differentiation and initiation of labor.

Adrenal gland is very important in the fetus and also is unique in both structure and function. At 4<sup>th</sup> month of gestation they are larger than the kidneys

- Cortex produces: *androgens, estrogens and cortisol*.  
Cortisol has multiple functions including promotion of the pancreas, lung maturation, the induction of liver enzymes, the promotion of intestinal tract cytodifferentiation.
  - Premature babies born with difficulty breathing are given low dose of cortisol and immediately they start to breathe normally. (I think the doctor is talking about neonatal distress syndrome in which surfactant deficiency causes alveolar collapse)
- The development of the adrenal medulla happens by week 10. It is capable of producing epinephrine and norepinephrine.

In the last 3 months of pregnancy the fetus grows significantly. The maternal and fetal growth hormones play very minor role. But studies have proved that insulin plays a very important role in fetal growth.

Glucose is the main metabolic fuel of the fetus. Fetal insulin produced by the pancreas by week 12 of gestation, regulates tissue glucose use, controls liver glycogen storage, and facilitates fat deposition. It doesn't control the supply of glucose; however, this is determined by the maternal gluconeogenesis and placental glucose transport. The release of insulin in the fetus is relatively constant.

\*\*So fetal insulin is responsible for fetal growth

### **Parturition/Delivery:**

- Throughout pregnancy the uterus is inactive (no contractions) under the effect of progesterone and relaxin.
- During the last month of pregnancy, weak and irregular uterine contractions occur, these contractions end in regular rhythmic forceful contractions that end in delivery. These contractions might last for several hours or even longer and eventually the result is expulsion of the fetal placenta and membrane. *Not all the pathways leading to delivery are known*, but endocrine, paracrine and mechanical stretching of the uterus all play a role.

### The mechanism of initiation of labor- ACTH initiates delivery

- *Fetal pituitary ACTH* is the initiator of labor. When it increases, it affects fetal adrenal glands. (especially the cortex).
  - The **fetal adrenal gland** synthesizes the androgen dehydroepiandrosterone-sulfate (DHEA-S).
  - this affects the placenta → increase in local estrogen to progesterone ratio → increases local prostaglandins. It also affects the maternal pituitary which produces oxytocin.  
(1)The high local estrogen progesterone ratio,(2) local prostaglandins (both of these from the fetus)(3) catecholamines (both maternal and fetal), and (4)oxytocin *maintain the uterine contractions of until labor occurs.*
- Once labor is initiated it is sustained by a series of positive feedback mechanisms.

### Lactation

After delivery, the baby needs milk. And prolactin is the major hormone responsible for milk production in the breast

**Estrogen** (estradiol)modulates prolactin secretion by two ways:

(1) estrogen increases the sensitivity of lactotrophs for stimulation by **PRH** (prolactin releasing hormone).

(2) Estrogen decreases the sensitivity of the lactotrophs for inhibition by **dopamine**.

- If the mother doesn't nurse the baby, prolactin levels generally return to non-pregnant levels within **2 weeks**.
- If the mother nurses the baby, increased prolactin secretion is maintained as long as *suckling* continues. (i.e. lactation is maintained by suckling)

**The ovarian cycle is suppressed** by suckling/ lactation because prolactin inhibits the synthesis and release of GnRH from the hypothalamus. (sheet#3)

However if the mother continues to nurse her infant for a long period, the ovulatory cycle eventually resumes. (so if the mother nurses her baby for two years, after one year the cycle will resume)

A study that was conducted about “Breast feeding in **Bangladesh** women” shows that the anovulatory period averages for 18-24 months. If the mother doesn't nurse her young after delivery the cycle will resume after 8-10 weeks, up to 18 weeks oxytocin and suckling stimulate milk ejection.

## **Female Fertility**

Infertility affects 1 out of 5 women in the US.

Understanding female biology, anatomy and physiology is essential to gain insight and be able to solve this major health problem. Several factors may cause infertility:

1. Environmental factors.
2. Disorders of the central nervous system.
3. Hypothalamic diseases.
4. Pituitary diseases
5. Ovarian abnormalities.

These can interfere with follicular development and/or ovulation.

However, *the most common cause of female sterility is failure to ovulate.*

- Contraceptive use and efficacy rates in the US

**TABLE 39.A** Contraceptive Use and Efficacy Rates in the United States

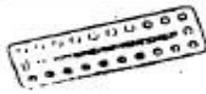
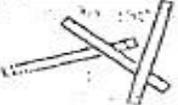
Method	Estimated Use (%)	Accidental Pregnancy in Year 1 (%)
Pill	32	3
Female sterilization	19	0.4
Condom	17	12
Male sterilization	14	0.15
Diaphragm	4-6	2-23
Spermicides	5	20
Rhythm	4	20
Intrauterine device	3	6

From *Developing New Contraceptives: Obstacles and Opportunities*. Washington, DC: National Academy Press, 1990.

### Notes:

- Female sterilization: a reversible technique where we ligate or cut the Fallopian tubes (I have no idea how the doctor will reverse cutting the Fallopian tube! But generally speaking, ligation is reversible)
- Pills cause side effects but are widely used.
- IUD has almost no side effects

- Types of contraceptive pills :

Types of hormonal contraceptive					
	Combined oral contraceptive pill (COCP)	Progestogen-only pill (POP)	Emergency pill	Depot (contraceptive injection)	Implants
					
Composition	synthetic oestrogens and progestogens	synthetic progestogens	high dose of synthetic oestrogens and progestogens	synthetic progestogens (medroxy-progesterone)	synthetic progestogens
Administration	oral, daily for 21 days with a 7-day gap before the next course of pills (during the 7 day gap a withdrawal bleed occurs)	oral, daily without a break between packs, and must be taken at the same time every day	oral, must be taken within 72 h of coitus if no other contraception was used	intramuscular injection, lasts 8–12 weeks	small soft tubes inserted under the skin, lasts up to 5 years
Mode of action	principal action = suppression of <u>ovulation</u>	does not reliably suppress <u>ovulation</u>	inhibits <u>implantation</u>	does not reliably suppress <u>ovulation</u>	prevents <u>ovulation</u>
Effectiveness if taken/applied according to instructions	>99%	99% less effective in young women and if >70 kg)	>95%	>99%	>99%
Advantages	often decreases menstrual bleeding, pain, premenstrual tension, and acne, and may protect against ovarian cancer	useful for women who cannot use the COCP (because POP contains no oestrogen)	postcoital contraceptive	do not have to remember to take pills, may protect against endometrial cancer	same as for depot
Disadvantages	increased risk of thromboembolic disease (e.g. deep vein thrombosis, pulmonary embolism, cerebral thrombosis), dyslipidaemia, hypertension	side effects include: irregular uterine bleeding ('breakthrough bleeding' or amenorrhoeal), breast discomfort, premenstrual tension, skin reactions, increased risk of ectopic pregnancy	same as for COCP, although risk is increased owing to high dose of oestrogen, often cause nausea and vomiting	side effects are same as for POP, plus: weight gain, loss of bone density	some as for depot, plus: often difficult to remove owing to fibrosis
Comments	not reliable if taken >12 h late, or after vomiting/diarrhoea	not reliable if taken >3 h late, or after vomiting/diarrhoea	should not be used as a regular form of contraception	not immediately reversible	

Notes:

- contraceptive pills are either:
  1. Combined (estrogen and progesterone)
  2. Progesterone only
  3. Emergency
  4. Depot
  5. Implants (from months to years)
- Take a look into the mode of action
- They are a very effective method of contraception

- There is no evidence that these pills cause breast cancer, but if they do, it is because they are in high concentrations

### Rhythm method of contraception

Gyuton 12<sup>th</sup>ed p.1001:” *The ovum remains viable and capable of being fertilized after it is expelled from the ovary probably no longer than 24 hours. Therefore, sperm must be available soon after ovulation if fertilization is to take place. A few sperm can remain fertile in the female reproductive tract for up to 5 days. Therefore, for fertilization to take place, intercourse must occur sometime between 4 and 5 days before ovulation up to a few hours after ovulation. Thus, the period of female fertility during each month is short, about 4 to 5 days.*

*One of the commonly practiced methods of contraception is to avoid intercourse near the time of ovulation. The difficulty with this method of contraception is predicting the exact time of ovulation. Yet the interval from ovulation until the next succeeding onset of menstruation is almost always between 13 and 15 days. Therefore, if the menstrual cycle is regular, with an exact periodicity of 28 days, ovulation usually occurs within 1 day of the 14th day of the cycle. If, in contrast, the periodicity of the cycle is 40 days, ovulation usually occurs within 1 day of the 26th day of the cycle. Finally, if the periodicity of the cycle is 21 days, ovulation usually occurs within 1 day of the seventh day of the cycle. Therefore, it is usually stated that avoidance of intercourse for 4 days before the calculated day of ovulation and 3 days afterward prevents conception. ”*

The average duration of normal menstrual cycle is 28 days

The first 5 days are the menstrual phase. Ovulation happens in day 14. Life span of the ovum and sperm (in the female reproductive tract) is 2 days. So, if a couple doesn't want to have children they should avoid intercourse for 3 days before and 3 days after the day of ovulation (i.e. between days 11 and 17 in a typical 28 days cycle)

In almost 85% of women, the duration of the cycle is 28 days, but in the remaining 15% it's around this figure (+-7days). The second half of the cycle (after ovulation) is constant; always two weeks, what changes is the period before ovulation.

The safe period: From day 17 to the end of the typical cycle (day 28) and from the end of menses to the 11th day. This is the period during which conception is least likely to occur.

This method can be used in both ways; if you want to have a child, or not. Nowadays, it's actually mostly used *to have* children.

Eg: if the cycle is 35 days

35-14=21 → ovulation will happen in day 21

3 days before and after ovulation: day 18 to day 24; this is the unsafe period

Possible safe period: the rest of the cycle

You can apply these calculations to any cycle of any duration.

Cycles that are 42 days long were recorded.

Normally, the length of the cycle doesn't change during reproductive life of a single female.

Hormonal therapy (Hormone-replacement therapy):

Most women take estrogen, which is good if taken under the supervision of a physician

Women are advised to take estrogen 2-3 years before menopause when during this period some signs of menopause could be seen

Signs of menopause: Irregular cycles, etc

. Estrogen:

- 1- prevents osteoporosis
- 2- maintains the beauty of a woman and prevents wrinkling
- 3- treats extreme facial and body hair
- 4- increases sexual desire
- 5- maintains size of breasts
- 6- prevents urine incontinence (recall anatomy of female genital organs)
- 7- contributes to treatment of Alzheimer's and amnesia

## NOT INCLUDED: TEST YOUR KNOWLEDGE

### Question 1

After menopause, hormone replacement therapy with estrogen-like compounds is effective in preventing the progression of osteoporosis. What is the mechanism of their protective effect?

They stimulate the activity of osteoblasts

They increase absorption of calcium from the gastrointestinal tract

They stimulate calcium reabsorption by the renal tubules

They stimulate parathyroid hormone secretion by the parathyroid gland

Need help with this one? [Show answer.](#)

CHECK ANSWER

### Question 1

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They stimulate the activity of osteoblasts ✓

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They stimulate calcium reabsorption by the renal tubules

They stimulate parathyroid hormone secretion by the parathyroid gland

### That's correct!

Estrogen compounds are believed to have an osteoblast-stimulating effect. When the amount of estrogen in the blood falls to very low levels after menopause, the balance between the bone-building activity of the osteoblasts and the bone-degrading activity of the osteoclasts is tipped toward bone degradation. When estrogen compounds are added as part of hormone replacement therapy, the bonebuilding activity of the osteoblasts is increased to balance the osteoclastic activity. Text reference: [pages 927, 1017](#)

ولآخر لحظة، اصنع معروفًا واغرس فكرة..

نهاية آخر شيت في البيسك

اللهم انفعنا بما علمتنا و علمنا ما ينفعنا و زدنا علمًا واجعله حجة لنا لا علينا

