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Chapter 1

Oogenesis and Spermatogenesis

Mandeep Kaur, Ajitabh Shukla

Chapter Outline

- Indifferent Stage of the Gonad
- Differentiation of the Gonad (6–9 Weeks)
- Stage of Oogonial Multiplication and Oocyte Formation
- Follicle Formation
- Neonatal, Childhood, and Adult Ovary
- Role of Anti-Müllerian Hormone
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INTRODUCTION

The human ovary has two main physiologic responsibilities—monthly release of egg and steroid hormone production. The ovary is made up of cortex, medulla, and the hilum. Oocytes are covered with layers of cells called the follicles, and they are enclosed in the inner part of cortex. During fetal life, the human ovary passes through four stages:

1. Indifferent stage of the gonad
2. Differentiation of the gonad
3. Stage of oogonial multiplication and oocyte formation
4. Follicle formation

INDIFFERENT STAGE OF THE GONAD

- Ovaries are formed at 5 weeks of gestation from the gonadal ridges **(Fig. 1)**.
- Gonadal ridges are coelomic prominences overlying the mesonephros.
- Primordial germ cells first appear as a group of about 100 cells in dorsal yolk sac endoderm between 3 and 4 weeks of gestation.[1]
- Indifferent stage lasts for about 7–10 days.
- By 6 weeks of gestation, the germ cells increase in number by mitosis to about 10,000.
- The germ cells migrate along the dorsal mesentery to the gonadal ridge between 4 and 6 weeks of gestation.[2] Gonadal ridge provides a place where these germ cells can survive.
- Fibronectin and laminin are the factors that seem to be involved in the migration.

DIFFERENTIATION OF THE GONAD (6–9 WEEKS)

- Differentiation to testis or ovary will occur according to the genetic constitution and receptivity of the tissues.
- If the indifferent gonad has to become testis, differentiation will occur; in absence of testicular differentiation, formation of ovary occurs.
- Both testis and ovarian development require dominantly acting genes. *SRY* (sex-determining region on Y chromosome) via upregulation of *SOX*-9 (SRY box 9 region) causes testis development and *WNT*-4 (member of wingless family of genes) and

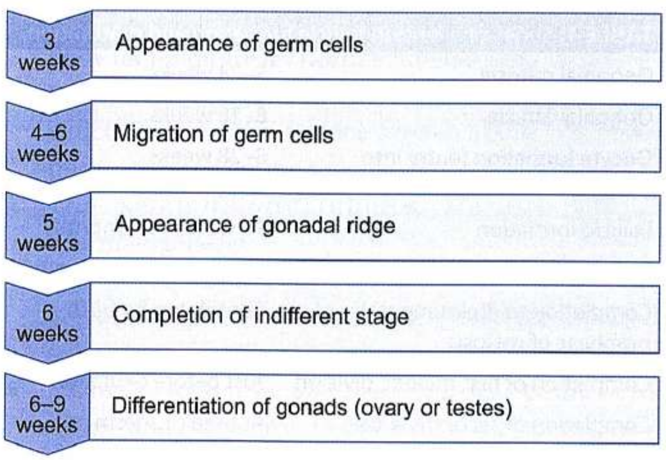

Fig. 1: Series of events in development of gonads.

RSPO1 (R-spondin-1) by suppression of *SOX*-9 cause development of the ovary **(Flowchart 1)**.[3]

STAGE OF OOGONIAL MULTIPLICATION AND OOCYTE FORMATION

- *WNT-4* and *RSPO1* are the genes responsible for ovarian development and activate beta-catenin signaling pathway, which results in loss of adhesion between cells and that is required for entry into meiosis.[4]
- Germ cells multiply by mitosis and reach 6–7 million in number at 16–20 weeks, and this is the maximum number. After this point, the number keeps decreasing.
- Germ cells give rise to oogonia by week 7.
- Oogonia forms oocyte at first meiotic division (week 8), which gets arrested in the prophase.
- Retinoic acid is considered to be a meiotic inducing factor.[5]
- Meiosis progresses to diplotene stage during the pregnancy and gets completed by birth.
- Ovum is formed by two meiotic divisions of the oocyte, one just before ovulation and one at the time of sperm penetration **(Table 1)**.

FOLLICLE FORMATION

- Follicle formation starts at 18–20 weeks, and as vascularity increases, perivascular cells become pregranulosa cells.[7]

Flowchart 1: Development of the gonad.

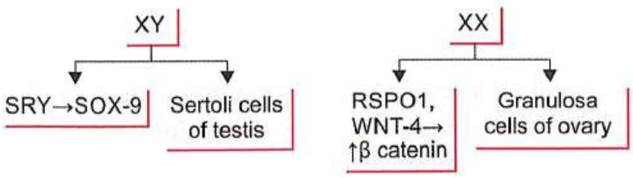

TABLE 1: Series of events in follicle formation and maturation.

Oogonial mitosis	5–28 weeks
Oogonial atresia	8–28 weeks
Oocyte formation (entry into meiosis)	8–28 weeks
Follicle formation	16 weeks to 6 months[6]
Follicle atresia	24 weeks to menopause
Completion to diplotene stage of prophase of meiosis	Completed by birth
Completion of first meiotic division	Just before ovulation
Completion of second meiotic division	At time of sperm penetration

- Primordial follicle consists of oocyte, which is arrested in prophase of meiotic division, which is covered by a layer of spindle-shaped granulosa cells.
- Primordial to preovulatory follicle may take up to 1 year.
- Primary follicle is formed by change of pregranulosa cells from spindle-shaped to cuboidal-shaped cells and formation of multiple layers of granulosa cells is called secondary follicle.
- Primary to preovulatory follicle may take up to 85 days.
- Preantral follicle is formed by more complete granulosa cell proliferation by sixth month of gestation.
- Formation of antrum and theca cell formation from the surrounding mesenchyme occurs and forms the antral follicle and is seen by the end of pregnancy.
- Anti-Müllerian hormone (AMH) is a dimeric glycoprotein produced by the granulosa cells of growing preantral and small antral follicles.[8]
- Primordial follicles grow and pass through various stages of development and reach the antral follicle stage and this process is known as initial recruitment (gonadotropin independent) as factors other than gonadotropins are responsible for this process.
- A set of antral follicles are recruited for further growth, dominance and ovulation by cyclic stimulation of gonadotropins, and this is known as cyclic recruitment (gonadotropin dependent).
- The primordial follicles start growing into primary follicles during fetal life and this continues after birth until the ovarian reserve is depleted, and only 1,000 primordial follicles are left in the ovary at the time of menopause **(Flowchart 2 and Table 2)**.[9]

Flowchart 2: Diagrammatic representation of the series of events.

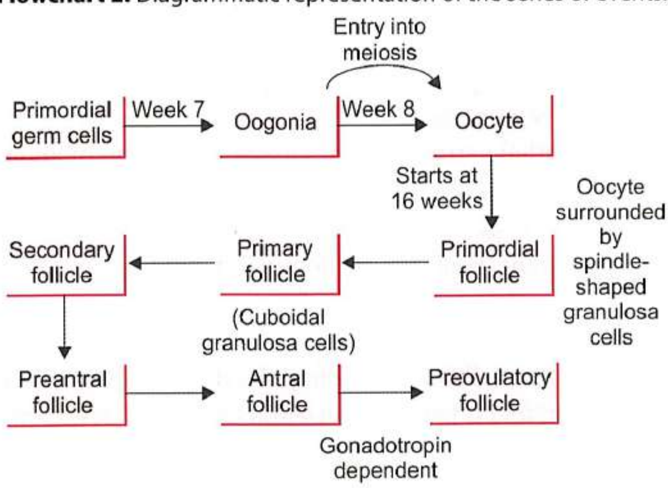

TABLE 2: Germ cell number in relation to age.

Age	*Number of follicles*
3 weeks	100
6 weeks	10,000
8 weeks	600,000
20 weeks	6–8 million
Birth	1–2 million
Puberty	300,000
35 years	25,000
Menopause	1,000

NEONATAL, CHILDHOOD, AND ADULT OVARY

- Germ cell content in the neonatal ovary is 500,000–2 million at birth, and 80% of the germ cells are lost before the female newborn enters life.
- Right ovary is larger, heavier, and more in protein as well as DNA content than the ovary on the left side.[10]
- Each ovary contains similar total number of follicles.
- Levels of gonadotropins are higher in female fetus compared to male as there is no negative feedback by sex steroids.
- Most common abdominal masses in female fetuses and newborn are ovarian cyst as a result of gonadotropin stimulation.
- Ovary increases in size during childhood by almost 10-fold due to active synthesis of proteins.[11]
- Each follicle that ovulates, about 1,000, undergoes atresia in that process.
- And as women age, cycles become shorter due to early recruitment in the initial years and later on the cycles become longer due to more anovulatory cycles.
- Rising follicle-stimulating hormone (FSH) reflects reduced quality and quantity of follicles in ageing ovary.

ROLE OF ANTI-MÜLLERIAN HORMONE

- Anti-Müllerian hormone is first detected at 36 weeks of fetal life in the granulosa cells of developing preantral follicles. The levels peak at puberty and reduce to undetectable levels at menopause.[12]
- AMH is an important marker of ovarian reserve.
- AMH has the least inter- and intracycle variability and as a result a good test for evaluation in random blood samples.
- AMH levels correlate well with the number of antral follicles in the ovary and also the number of oocytes retrieved.[13]

SPERMATOGENESIS

Sperm is a unique cell having a specialized ability to migrate through the female genital tract and fertilize the egg, carry genetic material for zygote formation, and carry centrosome to enable cell division.

Development

- The testis begins its differentiation at 6–7 weeks by appearance of Sertoli cells and spermatogonia from the primordial germ cells.
- Development of male phenotype depends on production of AMH and testosterone.
- Sertoli cell differentiation begins at 7 weeks and is a site for production of androgen-binding protein (ABP) to maintain high local androgen environment and inhibin.
- Leydig cells appear at 8 weeks from the interstitial component.
- Leydig cells produce testosterone and the secretion increases with increase in number and peaks at 15–18 weeks.
- Male primordial germ cells unlike in the female do not start with the meiotic division before the onset of puberty.
- The testosterone production in the local tissues causes the differentiation of the Wolffian system.
- Testis is an oval-shaped organ that is located in the scrotum and has a volume of about 15 mL (measured with Prader Orchidometer), length of about 5 cm, and rubbery in consistency.
- Testis needs a temperature of 2–3°C lower than the body temperature for normal functioning.
- Each testis contains 200–300 seminiferous tubules, which increase the surface area to about 1–2 m, and this is required for the process of spermatogenesis.
- The seminiferous tubules are the site for spermatogenesis.
- The seminiferous tubules are lined by stratified germinal epithelium and contain germ cells and supporting cells/Sertoli cells.
- 5% of the total testicular tissue consists of the Leydig cells, and they are responsible for testosterone production.