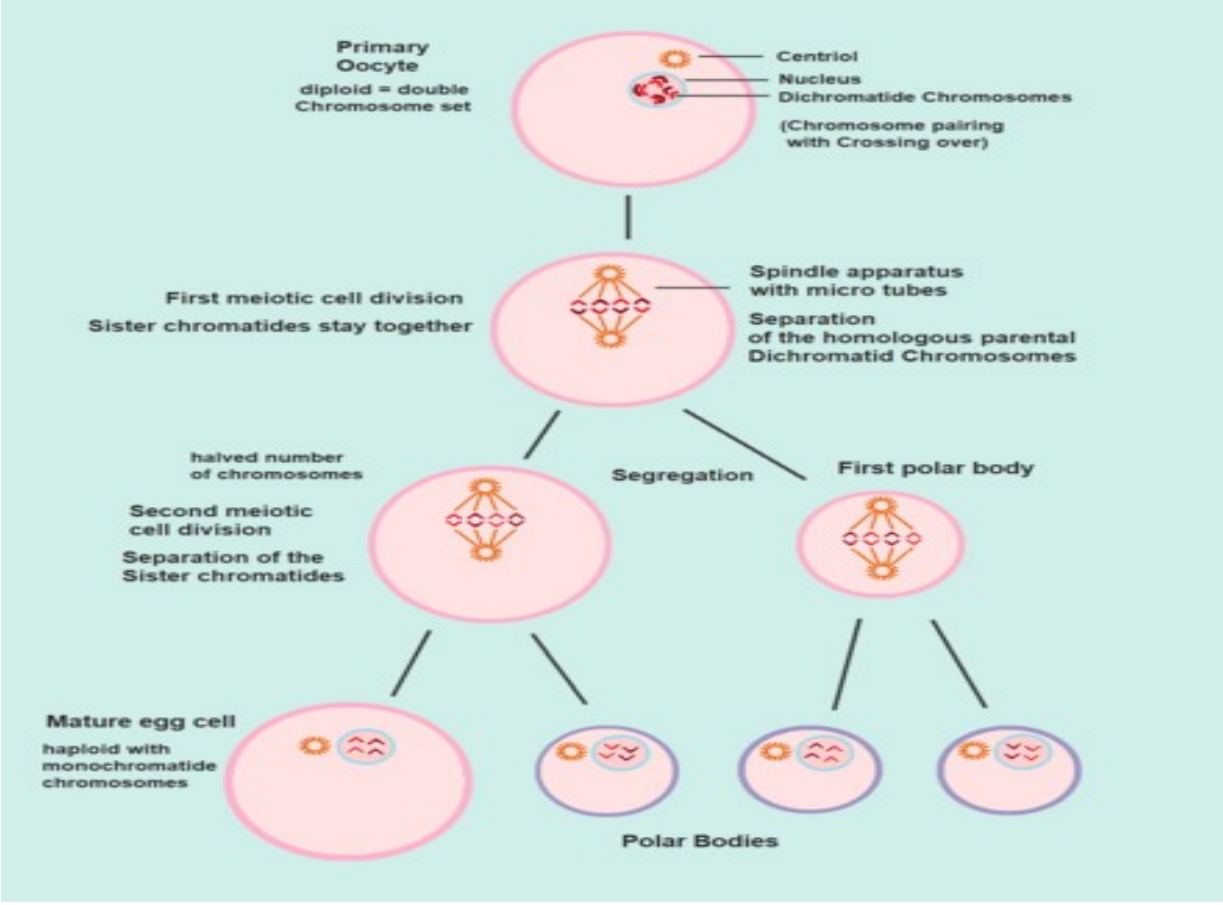
OOGENESIS IN MAMMALS

In contrast to most other vertebrates , mammals do not replenish the stores of oocytes present in the ovary at birth. At birth the human ovaries contain about 1 million oocytes (many of which are already degenerating) that have been arrested in the diplotene stage of the first meiotic division . These oocytes are already surrounded by a layer of follicular cells or granulosa cells , and the complex of ovum and its surrounding cellular investments is known as a follicle . Of all the germ cells present in the ovary ,only about 400 (one per menstrual cycle) will reach maturity and become ovulated. The remainder develop to varying degrees and then undergo atresia (degeneration).

Oocytes first become associated with follicular cells in the late fetal period , when they are going through early prophase of the first meiotic division . The primary oocyte (so called because it is undergoing the first meiotic division) plus its incomplete covering of flattened follicular cells is called a primordial follicle . According to Gougeon (1993) a follicle passes through three major phases on its way to ovulation.



The first phase is characterized by a large pool of nongrowing follicles , approximately 500,000 per ovary at birth. In this pool are primordial follicles, which develop into primary follicles by surrounding themselves with a complete single layer of cuboidal follicular cells . By this time , the oocytes have entered the first period of meiotic arrest , the diplotene stage . In human , essentially all oocytes , unless

they degenerate ,remain arrested in the diplotene stage until puberty ; some will not progress past the diplotene stage until the woman's last reproductive cycle (age 45 to 55 years). Both the oocytes and follicular cells (or granulosa cells , as they are later called)develop numerous microvilli . These are connected by gap junctions, which allow low molecular –weight substances to pass from one cell type to other . After the oocyte is covered by a complete layer of follicular cells , it begins to produce the *zona pellucida*, a translucent noncellular membrane located between the oocyte and the follicular cells.

The second phase of follicular development is characterized by growth of both the oocyte and its covering of granulosa cells , probably under the influence of gonadotrophic hormones from the pituitary . The granulosa cells actively proliferate , and the overall growth of the follicular covering is mediated by FSH receptors on the granulosa cell surfaces.Outside the granulosa cells another cellular layer , called theca folliculi , begins to form from the ovarian connective tissue . A basement membrane ,called the membrane granulosa, takes shape between the granulosa cells and the overlying theca , and the inner part of the theca becomes increasingly vascular . During the second phase , a fluid –filled space begins to form within the multilayered granulosa cell covering . When this space , called antrum is identifiable , the follicle is said to have progressed to a secondary follicle . Late in the second phase of folliculogenesis the thecal cells develop LH receptors on their surfaces , and the thecal cells begin to produce testosterone , which is transported across the membrana granulosa into the granulosa cells. The granulosa cells by this time have synthesized an enzyme , aromatase , which converts the testosterone to estrogens within the granulosa cells .

The third phase of follicular development is characterized by dramatic growth in the dimensions of a population of follicles and final selection of only one follicle that will become dominant and ultimately undergo ovulation . this phase , which begins late in the secretory phase of the menstrual cycle preceding ovulation , sees several follicles responding strongly to the circulating gonadotropins . Early in the follicular period following menstruation , the largest of the growing follicles (and the one which appears to have acquired the highest receptivity to FSH) increases greatly in size , both by an increase in the amount of fluid in the antrum and by an increase in the number of granulosa cells .The granulosa cells ,as well as theca cells , acquire the ability to bind LH. From the late follicular phase until ovulation the diameter of this follicle increases from approximately 7 to 19 mm , and the number of granulosa cells increases from somewhat less than 5 million to nearly 100 million . After the midcycle LH surge, proliferation of the granulosa cells stops , although the volume of antral fluid continues to increase . Angiogenic factors (factors that stimulate the formation of new blood vessels) produced by the follicle cause a significant increase in the density of blood vessels in the inner thecal layer of the follicle . Through their synthetic activities , the granulosa cells of the maturing follicle produce significant amounts of estradiol , which spills out into the blood . there is some evidence that the dominant follicle secretes a factor that blocks the effects of gonadotropins on other expanding follicles and thus maintains its dominance .

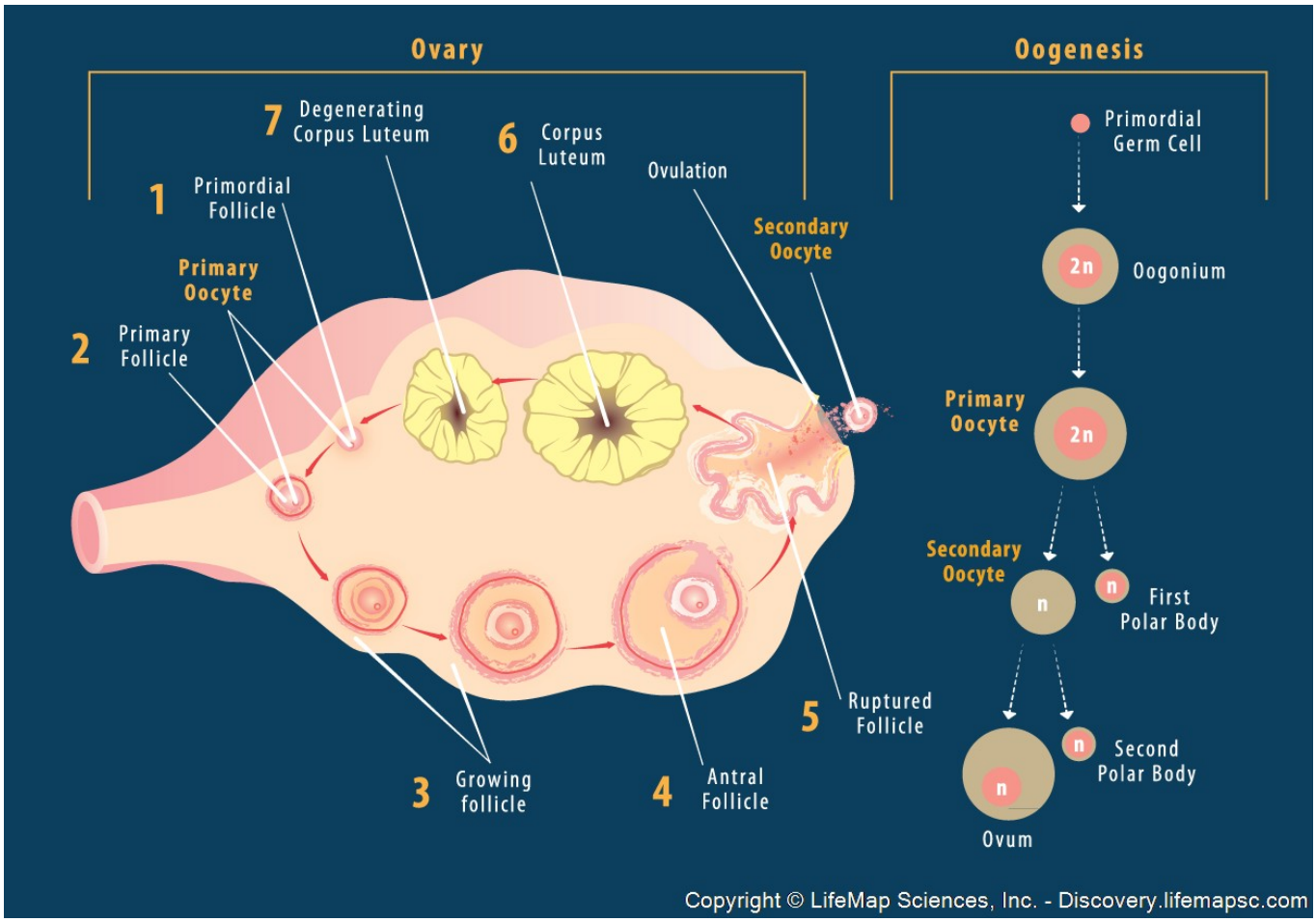
The mature follicle which is nearly ready to rupture is called a tertiary (Graafian) follicle .

Within the follicle , the egg , surrounded by several layers of granulosa cells , protrudes into the antrum as the *cumulus oophorus* .Just before ovulation the ovum is released from its first meiotic block in the diplotene phase and goes on to finish its first meiotic division , releasing the first polar body in the process. The follicle is now ready to respond to the preovulatory LH and FSH surge and complete the first stage of its cycle by releasing the ovum , which by this time is in its second meiotic block , this time at the metaphase II stage.

Atresia of Follicles : only a minute percentage of ova and follicles in the ovary reach maturity . The others undergo various degrees of maturational changes and then begin to degenerate. This process is known as *follicular atresia* , and a follicle that is involved in degeneration is said to be *atretic* . The regulatory factors underlying atresia of follicles have not been completely defined , but there is increasing evidence that atretic follicles are deficient in receptors for gonadotropins or estradiol .

Ovulation : The LH peak in the blood in conjunction with FSH , and perhaps with estrogen , sets in motion the final stages of follicular maturation that lead to ovulation . The follicle continues to swell as a result of both increased amounts of follicular fluid and growth of the follicle itself . The apex of the follicular protrusion is called the *stigma* ,and within a day after the LH surge some characteristic changes take place in this area. The final preovulatory events begin with hemostasis of blood in the area around the stigma . Within an hour , the follicular wall in the stigma breaks down and the antral fluid , along with the ovum , which is surrounded by the cells of the cumulus oophorus, is expelled from the follicle.

The precise mechanism that precipitates the rupture of the ovarian follicle is not completely understood. In all probability several factors are involved . An early hypothesis held that increased antral fluid pressure within the follicle causes bursting of the follicular wall, but measurements have shown no significant increase in fluid pressure . More recent hypotheses involve weakening of the follicular wall because of ischemia or possibly the action of local lytic enzyme activity, the latter being stimulated by a pituitary hormone (LH).



Corpus Luteum : The history of an ovarian follicle by no means ends when the follicle has liberated its contained ovum . Cells of both the stratum granulosum and the theca interna become involved in the formation of the *corpus luteum*. The corpus luteum ,so called because of its yellow color in fresh material , grows rapidly and becomes an endocrine organ , secreting both estrogen and progesterone .

When the ovarian follicle ruptures, escape of most of the contained fluid and contraction of the stroma of the ovary reduce the size of its lumen. Bleeding of the small vessels injured in the rupture of the follicle may partially fill the antrum with clotted blood . Several concomitant changes occur during the transformation of the ruptured follicle to the corpus luteum . The granulosa cells swell and develop the cytological characteristics of cells that secrete large quantities of steroid hormones .

Formation and maintenance of corpus luteum in the human require the continuous presence of LH from the pituitary. Hormonal relations vary among the mammals for instance, in rats and sheep both LH and prolactin are required . The corpus luteum produces large amounts of progesterone and some estrogens. One of the major functions of progesterone is to prepare the lining of the uterus for receiving and implantation of the fertilized ovum . If pregnancy does not occur, the corpus luteum gradually loses its sensitivity to pituitary gonadotropins, probably by losing LH and FSH receptors on its

cells, and then it regresses. If however, pregnancy occurs , the corpus luteum undergoes a greatly prolonged period of growth and may attain a diameter of 2 to 3 cm in humans.The *corpus luteum of pregnancy* is maintained by chorionic gonadotropin secreted by the cells of the embryo and its surrounding membranes .

When either type of corpus luteum begins to degenerate , the cellular part of the organ disintegrates and fibrous connective tissue takes its place. As this connective tissue grows older and more compact , it gradually takes on the characteristic whitish appearance of scar tissue and is called a *corpus albicans*.

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Ref. Book* : *Foundations of Embryology by Bruce M Carlson.