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REVIEW ARTICLE

Prostaglandins and Ovarian Follicles

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ABSTRACT
Prostaglandins are primary mediators of pain and are involved in pathological conditions such as hypertension, cancer, and inflammation but are also needed for the normal function of the female reproductive system. The involvement of prostaglandins (PGs) in the regulation of ovarian follicular function was first postulated based on the demonstration that inhibitors of prostaglandin synthesis, such as aspirin and indomethacin, were capable of blocking ovulation in rats. These initial findings were also confirmed in several other species, including mice, rabbits, rhesus and marmoset monkeys, pigs, and goldfish. A comprehensive investigation into the role of prostaglandins in the regulation of normal body function is required. The female reproductive system appears to be an ideal study model in this regard. One major disadvantage of current therapeutic strategies for PG control is that they target the early stages of biosynthesis, thus blocking all PGs, good and bad. PGs, on the other hand, frequently work in opposing dyads, such as PGI2-TXA2 in the vascular system and $PGF_{2\alpha}$-PGE_2 in the female reproductive system. The use of pharmacological doses of the medications rather than physiological doses may be the cause of many of these varied responses of PGs. As a result, the paradigm appears to be affecting the selective synthesis, transport, and action of individual PG isoforms. Statistics from animal and human-animal genome projects were used to identify the corresponding members of the PG system's biosynthetic and signal transduction components in various animal species. Based on studies in the female reproductive system, we propose here an integrated perspective of PG activity concerning ovarian follicles.
Keywords: *Prostaglandins, Granulosa cells, ovarian follicles, oocyte, Theca, Primordial follicles*

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INTRODUCTION

Prostaglandins are well-known mediators of pain, fever, inflammation, and hypertension, and their synthesis has long been a target for pharmacological treatment using nonsteroidal anti-inflammatory medications (NSAIDs). All nucleated cells in the body generate PGs, which operate locally in a paracrine or autocrine manner.

The release of arachidonic acid from membrane phospholipids by phospholipases is the first limiting step in the synthesis of eicosanoids, and the most important for the formation of PGs from arachidonic acid is cPLA2 [1]. Arachidonate may subsequently be converted into leukotrienes, which are not addressed in this study. Prostaglandin synthase produces PGH2, from arachidonic acid (AA), the common precursor of all PGs.

Cyclooxygenase 1 (COX-1), the constitutive isoform, is extensively expressed in a range of tissues and cells, while COX-2, the inducible isoform, is controlled by stimuli such as cytokines or tumor promoters [2]. COX-3 was named after a splice variation of COX-1, although its role in physiological or pathological circumstances is unknown. COX-1 is found in most tissues and is responsible for housekeeping activities as well as a rapid reaction to AA levels greater than 10 mM. COX-2 is controlled by cytokines and tumour promoters, and it allows for the

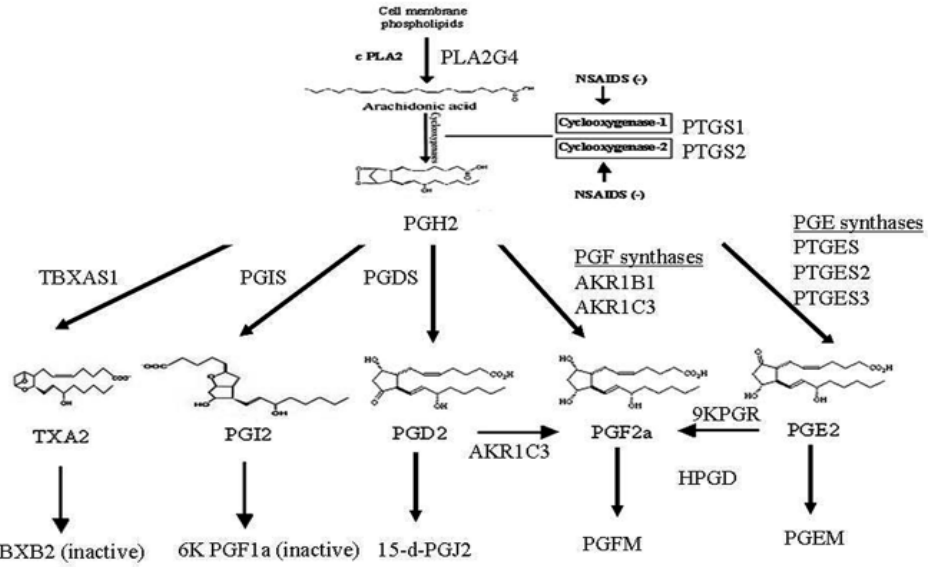

Figure1. Biosynthesis of prostaglandins: The COX enzymes (PTGS1, PTGS2) convert arachidonic acid (AA) from membrane phospholipids to PGG2 and PGH2, the common precursor for all PGs, in the cytosolic PLA2 (PLA2G4). Specific terminal synthases such as PGE synthases (PTGES, PTGES2, and PTGES3), PGF synthases (AHR1B1, AHR1C3), PGD synthase (PGDS), PGI synthase (PGIS), and Thromboxane synthase convert PGH2 into one of the active PGs (TXA1S). HPGD inactivates PGE_2 and $PGF_{2\alpha}$, converting them to PGEM and PGFM, respectively. PGD2 changes spontaneously to active PGJ2, while unstable PGI2 and TXA2 convert to inactive 6H-PGF1 and TXB2 [3].

Synthesis of PGs to be maintained even at low levels of AA (below 2.5 M) (Parent et al., 2003). PGH2 generated by COXs is a common precursor for cell-specific isomerases and synthases such as PGES, PGFS, PGDS, PGIS, and TXAS to create main PGs such as PGE_2, PGF2, PGD2, PGI2, and TxA2.

In homozygous null mice, targeted disruption of COX-1 [4] or COX-2 genes [5] results in severe nephropathy or decreases reproductive efficiency, confirming the physiological significance of prostaglandins. Female COX-2 null mice, in particular, possess a number of reproductive problems [6]. In COX-1 defective animals, COX-2 is able tocompensate the COX-1 deficiency partly [7]. COX-1 and COX-2 double knockouts caused the pups to die soon after birth, indicating that PGs are more essential for survival than previously thought [8, 9].

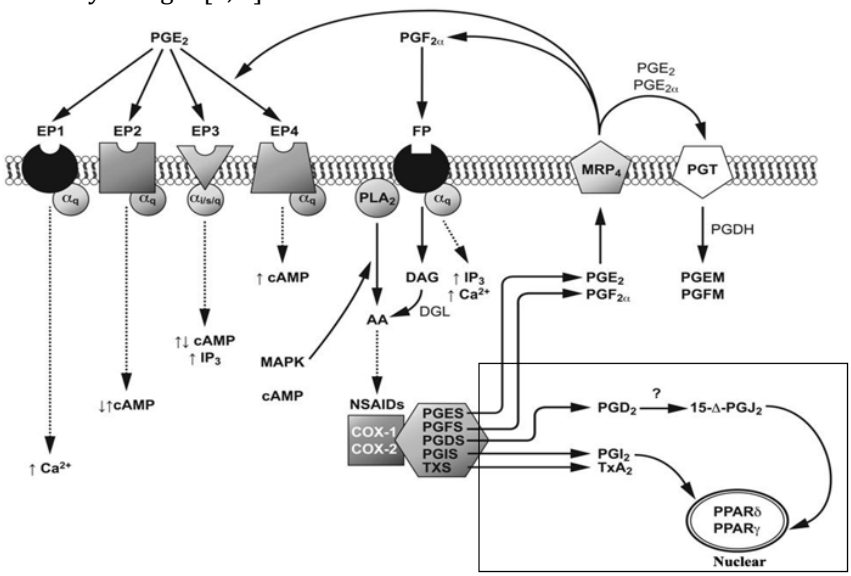

Figure2:*Signaling mechanisms involving prostaglandins: PGs leave the site of biosynthesis either passively orthrough constitutively expressed facilitated transport (MRP4) and bind to particular membrane receptors in an autocrine or paracrine manner. PGE2 and PGF2 may pass via PGT and reach target cells to act on nuclear receptors, or they can be inactivated by 15-PGDH. As shown, the membrane DP, EP1-4, FP, IP, and TP receptors are linked to a variety of G proteins and second messengers. The physiological ligand for the nuclear receptor PPAR is PGJ2, the spontaneous active metabolite of PGD2, while PGI2 binds to PPAR [3].*

Pharmacological regulation of PG biosynthesis has been around for over a century. Aspirin (ASA) was the first non-steroidal anti-inflammatory medication (NSAID) to enter the market. ASA, like newer medicines like ibuprophen (ADVIL), has the potential to inhibit COX-1 and COX-2 activities non-selectively [10]. New inhibitors like NS-398 and SC-560 have recently been demonstrated to block COX-2 (Klein et al., 1994) or COX-1 [11] selectively, paving the way for the development of more targeted NSAIDs like CELEBREX and VIOXX. However, significant COX-2 inhibition adverse effects such as heart failure (Hudson et al., 2005) and infertility [12] led to VIOXX's widespread removal from the market. The total blockage of all PGs by NSAIDs relieves symptoms quickly but does not offer a physiological cure [13]. Targeted action at the level of terminal synthases such as PGES and PGFS, which are responsible for the selective synthesis of PGE_2 and $PGF_{2\alpha}$, seems to be promising and essential to investigate in this regard [14].

Over the last 30 years, significant attempts have been undertaken to create selective agonists and antagonists of PG receptors, although most therapies aimed at regulating PG activity are still dependent on systemic COX inhibition [15]. Nuclear receptors for PGD2 and PGI2 have been suggested as peroxisome proliferators-activated receptors (PPAR) [16]. EP2 and EP4 have recently been discovered in the nuclear envelope, indicating the existence of functional PGE2 nuclear receptors [17]. The potential activities of nuclear receptors, on the other hand, are little understood.

THE OVARY AND OVARIAN FOLLICLES

The ovary is a paired amygdaloidal-shaped organ on each side of the pelvic cavity that is responsible for germ cell generation and steroid synthesis for important female reproductive physiological processes such as folliculogenesis and pregnancy [18]. The ovary develops as a thickening along the ventral cranial mesonephros known as the genital ridge, and the developing embryo's epiblasts differentiate into primordial germ cells (PGCs) that enter the undifferentiated gonad at around 18-31 days in cattle [19, 20], 7-11 days in mice [21], and 17-21 days in sheep [22]. Later, owing to the differential gene expression of gonadal ridge epithelial-like (GREL) cells present in the gonadal ridge, the ovaries and ovarian epithelium grow and differentiate, and the migrating PGCs become oocytes that begin meiosis [23, 24]. PGCs are surrounded by a few pre-granulosa cells, which are believed to be derived from GREL cells [25], after meiotic arrest, the primordial follicles are subsequently recruited for growth and maturation during folliculogenesis [26, 27].

Each ovary contains two specialized regions: outer cortex and inner medulla, according to morphological investigations of the mid sagittal section of the ovary. The cortex has two layers: an exterior layer termed tunica albuginea and an interior layer covered by surface epithelium. The resting follicles are located in this avascular layer of the cortex; however, the developing and atretic follicles, as well as the involuting corpus luteum, are found at the highly vascularized cortical medullary boundary [28]. The medulla, or inner part of the ovary, includes thick connective tissue, blood vessels, and embryological remains. An ovarian reserve contains three types of follicles after birth: primordial follicles with flattened granulosa cells, transitory follicles with both flattened and cuboidal GCs, and tiny primary follicles with a single layer of cuboidal cells alone [28].

Prostaglandins are known to have vast roles in the ovary such as involved in LH-induced progesterone production [29] and to play a function in luteolysis (luteolysis is the breakdown of ovaries) [30]. Recent research in animals indicates that they may be intimately connected to the process of ovulation itself [31, 32].However, there is some evidence that prostaglandins act as central neurotransmitters [33, 34] and have an impact on the hypothalamic pituitary axis [35, 36].

Developing follicles

Primary follicles are those that have entered the growth phase, which is characterized by proliferating GCs and oocytes that are growing in size. The GCs are immature, with a greater amount of rough endoplasmic reticulum for protein synthesis, which is necessary for proliferation. Inter-cellular metabolic communication occurs as a result of the connexins gap connection between cells; the oocyte produces zona pellucida, which is made up of ZP1, ZP2, and ZP3 glycoproteins, and the basal lamina envelops granulosa cells, isolating them from thecal and stromal cells [37].

The follicles with follicular diameter 80-100 μm with two or more complete layers of GCs surrounding oocytes are secondary follicles. One or two arterioles terminate just outside basal lamina to form anastromal network. Due to this, the follicle gets exposed to various circulating factors that cause stromal cells to align near basal lamina; these stromal cells later form thecal cells that further proliferate and develop, differentiating into theca externa and theca interna (consisting of steroid secreting cells). At this point, follicles contain 6-7 GCs layer forming 103-163 μm size follicle called Pre-antral follicles. Antral

follicles or tertiary follicles: Within class I pre-antral follicles, a fluid filled cavity emerges between granulosa cells; these follicles with follicular antrum are termed as Class II antral follicles. The granulosa cells differentiate into cumulus GCs surrounding oocyte and the one encircling antral cavity are mural GC cells [38]. The cumulous cells develop processes that pass through oolemma, penetrating zona pellucida, forming a region of striated appearance called cumulus oophorous. With progression and growth of antral follicles, the size of antral cavity increases and enhanced GCs proliferation; such follicles are classified from Class III to Class VIII [39].

Folliculogenesis is the process of ovarian follicles growing and progressing from the primordial stage to the antral follicular stage, as well as the maturation and ovulation of the egg from the ovulatory follicles [40]. The whole series of events is governed by the endocrine system, with different variables and substances playing critical roles (Figure 2.4). PGCs produce approximately 7 million oogonia that begin meiosis by the twentieth week of pregnancy; by the twenty-fourth week, the first meiotic arrest occurs at the diplotene stage, and their number continues to decline dramatically until delivery. Only one-two million oogonia remain at birth, which are surrounded by pre-granulosa cells and produce primordial follicles (PMFs), which act as ovarian reserve [41]. These PMFs are in the dormant or resting state; during puberty, only a few follicles leave the reservoir and join the pool of developing follicles to reach the ovulatory stage; otherwise, they disintegrate. The cycle is repeated and is regulated by a number of intra- and extra-oocyte factors [42].

The interaction of the oocyte, pre-granulosa, and pre-thecal cells in the recruitment of primordial follicle for folliculogenesis is complicated [43]. In response to basic fibroblast growth factor (FGF-7) and leukemia inhibitory factor (LIF) synthesized by pre-thecal cells and oocyte (only FGF-7), pre-granulosa cells up-regulate the expression of kit ligand, called stem cell factor (SCF), which promotes the transition of primordial follicle to primary follicle [44-48]. In goats, mice, hamsters, and rats, but not in rabbits, SCF is expressed at all phases of folliculogenesis, while in pigs; SCF is expressed at all stages of folliculogenesis [49, 50].

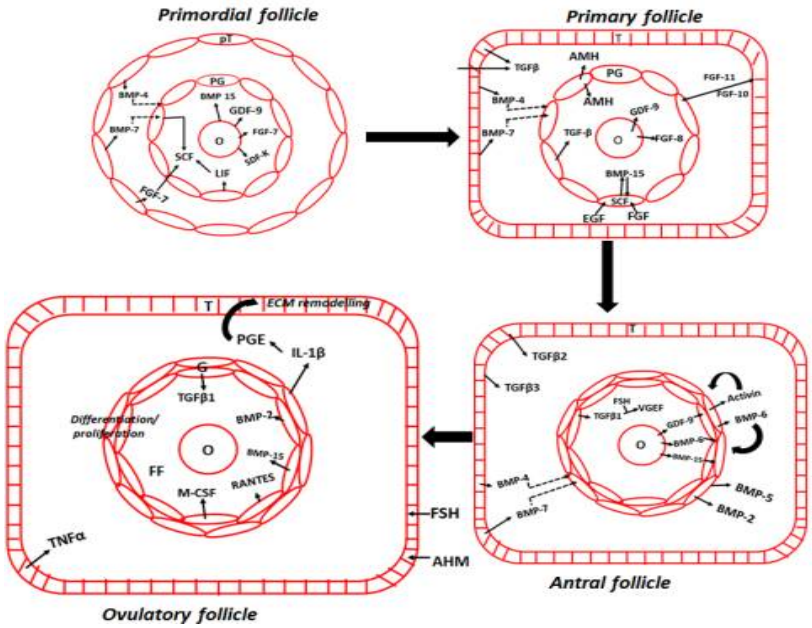

Figure 3: *Schematic representation of various factors involved in folliculogenesis and interactions between different follicular cells (Field et al., 2014). O-oocyte; PG-pre-granulosa cells; G-granulosa cells; PT-pre-theca cells; T-theca cells*

Bone morphogenic proteins (BMP4 and BMP7) are also secreted by pre-thecal cells, which enhance the mitotic index and DNA content of pre-granulosa cells, aiding the follicular transition from primordial to primary stage [51, 52]. There's also evidence that oocyte-derived Growth differentiation factor-9 has a function in avoiding atresia in primordial follicles [53]. The oocyte-produced stromal cell-derived factor-1a (SDF-1a) has also been linked to the generation of cytokines, proteases, and other vasoactive compounds [54]. Anti-mullerian hormone (AMH) prevents the development and transition of primordial follicles (Grondahl et al., 2011). The function of Follicle stimulating hormone (FSH) in the beginning of

folliculogenesis is still debated; nevertheless, FSH receptors have been identified in both transitory and primary follicles in certain instances [55].

Interactions between the oocyte, granulosa, and thecal cells are required for the growth of a primary follicle into a pre-antral follicle. TGF, GDF-9, and BMP-15 from oocytes, BMP-4 and BMP-7 from thecal cells, and kitL expression in granulosa cells all control follicle development up to pre-antral follicles [56, 57]. GDF-9 and BMP-15 are produced by the oocyte, which promotes secondary follicle development, GC proliferation, and GC transition to cGCs (cumulus granulosa cells) (Spicer et al., 2008). GDF-9 is inhibited by oocyte development through the oocyte-granulosa signaling link as a result of GCs secreting Kit L (oocyte specific growth factor), which down regulates GDF-9 and BMP-15 production and inhibits oocyte growth [58, 59]. Epidermal growth factor and KitL function as thecal cell organizers generated from granulosa cells, causing stromal cells to differentiate into thecal cells. Other follicular factors that induce neo-angiogenesis include FGF-2, leptin, circulating VEGF, keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) [60, 61]. Mural and cumulus granulosa cells surround a single oocyte in a mature follicle. An antrum develops during follicle development and is filled with fluid that contains PGs, steroids, peptide growth factors, and metabolites. In patients undergoing in vitro fertilisation (IVF), the ovarian follicular fluid is collected together with cumulus-oocyte complexes from mature follicles, offering a window into the physiological signalling mechanisms that occur in fertile and infertile women.

Primary follicular growth is independent of FSH (Follicle Stimulating Hormone) in the early stages, although evidence of a synergic involvement of FSH with other variables has been discovered in the later stages [62]. After reaching the 3 and 4 mm diameter stage in sheep, cattle, and humans, follicles become sensitive to gonadotropin [63]. Gonadotropins become active in the latter stages of folliculogenesis.

Later stages of folliculogenesis become responsive to gonadotropins. Antral follicles that are selected are 2-5mm in size and 3-11 per ovary in number; among these only one ovulate. The selected follicles are more receptive to gonadotropins with presence of certain factors in follicular fluid that inhibits steroidogenesis, thus response is in terms of GCs proliferation rather estrogen production. The follicles with low FSH threshold exhibit increased activity of IGF that besides GCs proliferation and differentiation produces estradiol, increases expression of LH receptors on GCs at low FSH level making them ovulatory follicles. Growth of antral follicle also involves the action of several factor exhibiting autocrine and paracrine action. Activin and BMP-6 derived from granulosa and GDF-9, BMP-6 and BMP-15 from oocyte exerts autocrine and paracrine action respectively on GCs that stimulates GCs proliferation and differentiation via SMAD 3 pathway and FSH dependent follicular development. BMP-15 plays a significant role in follicular selection to ovulatory stage by inhibiting the FSH receptor expression thereby decreasing the recruitment of follicles in rats. Theca derived BMP-4 and BMP-7 regulates GCs along with BMP-2, BMP-5, and BMP-6 produced from granulosa cells itself, interacting with activin/inhibin and estrogen produced that assists in follicular selection and prevention of atresia. TGF-β1, TGF-β2 and TGF-β3 from theca and granulosa cells stimulate FSH receptor expression synergizing VEGF mediated angiogenesis.

There is strong evidence that gonadotrophic hormones act on their target cells by stimulating specific receptor-linked adenylate cyclase, resulting in the production of cyclic adenylate monophosphate (cAMP), which acts as an intracellular "second messenger" [64], cAMP production in granulosa cells exposed to FSH and hCG was measured. FSH, but not hCG, increased cAMP synthesis by human granulosa cells. These cells at younger stage when these are devoid of LH (hCG) receptors, do not react to hCG by producing more cAMP or estradiol. LH receptors are acquired late in follicular development and are indicative of granulosa cell maturity, according to research involving granulosa cells from a variety of species [65, 66]. Prostaglandin E_2 was extremely efficient in increasing cAMP generation by these granulosa cells at doses that seemed to be within the physiological range for other species. As a result, PGE response seems to be developed earlier in life than LH responsiveness. The ability of PGE-stimulated cAMP synthesis by granulosa cells to promote production of both estradiol (in the presence of testosterone alone) and progesterone (in the absence and presence of testosterone) suggests that it is likely of physiological importance.

Prostaglandins (PGs) are essential chemicals in reproductive function [67], especially in ovulation and implantation. Although it has been suggested that it has a function in sex determination [68], no roles in the early stages of oogenesis or folliculogenesis have been found. COX enzymes and particular terminal prostanoid synthase enzymes generate PGs from arachidonic acid. COX1 and COX2 are the most common COX enzyme isoforms [69]. Many cell types express COX1 by default, while COX2 is activated by cytokines and tumour promoters [70]. COX enzymes convert arachidonic acid to PGH2, an intermediate PG that PGE synthase then converts to PGE2 (PTGES). PGs function in an autocrine or paracrine way after being produced by binding to a class of prostanoid-specific G protein-coupled receptors [71]. There are four

separate receptors for PGE2 (EP1–EP4), each with a different tissue distribution and activating various intracellular signalling pathways and gene expression [72]. Gs activate EP2 and EP4 receptors, causing intracellular cAMP buildup [73].

Oocyte

A female gametocyte or germ cell involved in reproduction is known as an oocyte. It's an immature ovum, or egg cell, in other words. During female gametogenesis, the ovary produces an egg. Oogonia are formed when female germ cells create a primordial germ cell (PGC), which subsequently undergoes mitosis. The oogonia become main oocytes during oogenesis.

The paranuclear complex of organelles forming Balbiani's vitelline body moves away from the nuclear envelope with the initiation of growth in the primordial oocyte, and its components are distributed in the outer ooplasm [74-78]. The proliferation of Golgi complexes, mitochondria, free ribosomes, endoplasmic reticulum profIles, and heterogeneous phospholipid bodies of varying sizes are seen as the oocyte grows [79, 80]. The majority of these organelles, including heterogeneous phospholipid bodies, are dispersed throughout the cortical and perinuclear ooplasm, leaving the core regions of the oocyte sparsely populated or virtually devoid of them. The ultrastructure and cytochemistry of oocytes from various species vary significantly. All of the Golgi aggregates ultimately congregate immediately underneath the oocyte's plasma membrane, indicating a definite local preference. Weakley et al. (1981) studied the Golgi apparatus in the developing oocyte of the golden hamster using thiamine pyrophosphatase and acid phosphatase enzyme methods, as well as the zinc iodide-osmium tetroxide impregnation technique. As the size of the oocyte grows the responsiveness of all of these methods decreases with phosphatase methods, certain Golgi bodies are negative while others are positive inside a single oocyte, indicating that the developing oocyte has two or more functioning forms of this organelle. Multivesicular bodies develop in the ooplasm of the expanding oocyte, which are thought to correlate with the heterogeneous lipid structures of histochemical preparations [81].

Early studies revealed that PGE_2 stimulates oocyte meiotic maturation in rodents both in vivo [80] and in vitro [82-86], and that indomethacin, a nonspecific COX inhibitor, reduces gonadotropin-induced cumulus expansion and GVBD in mouse and sheep oocytes [72, 25]. It has been shown that intrafollicular injection of PGE_2 may counteract the inhibitory effects of indomethacin on oocyte meiotic maturation in sheep ovaries [87. 88]. On the other hand, despite the fact that indomethacin inhibits ovulation triggered by gonadotropin-releasing hormone and angiotensin II by decreasing PGs synthesis, it fails to block GVBD in rabbit ovaries that have been perfused in vitro. According to the literature, PGs play important roles in meiotic maturation of the oocyte.

Granulosa Cells

Granulosa cells are a major component of ovarian follicles, appearing as clustered and linked cells. These cells are primarily involved in steroidogenesis (the synthesis of estradiol and progesterone at various phases of folliculogenesis) and are incompatible with oocyte development and maintenance, as well as the creation of the antrum and antral fluid [89]. Granulosa cells go through a number of alterations to achieve their functional purpose, including a conformational shift from flattened to cuboidal, differential rearrangement, and other sub-cellular modifications [90, 91]. The cellular and cytoplasmic components of granulosa cells in humans, African giant rats, and certain bovines and porcines have been disclosed via histomorphological research [2, 8, 9, 10, 18]. Granulosa cells are described as loosely packed clusters of cells with homogeneously dispersed chromatin, one or two nucleoli, extensive network of endoplasmic reticulum, Golgi vesicles, secretory-like granules, mitochondria, free ribosomes and polysomes, lysosome-like bodies, microfilaments, and lipid droplets [90-95]. The structural integrity of the nucleus, which is required for granulosa cells to be metabolically active, is represented by a double membrane nuclear lamina with uniformly distributed chromatin [96, 97].

Due to the existence of heterochromatin, a few clumps may be seen in the nucleoplasm [79]. The importance of cytoplasm and its organelle in preserving the functional integrity of granulosa cells is shown by a lower nucleus to cytoplasm ratio. The presence of lipid reserves indicates that granulosa cells are involved in steroidogenesis and estrogen synthesis. To enable the production of hormones needed during folliculogenesis, lipid droplets and acyl lipase-mediated lipid release are essential to maintain cholesterol homeostasis inside the cells [98]. The tight relationship discovered in the peri-nuclear area between mitochondria, endoplasmic reticulum, and nucleus bolstered the hypothesis. Another significant characteristic that aids in inter-cellular signal transmission is the presence of linear and annular gap junctions between granulosa cells [77]. Granulosa cells are classified according to their location and function within a follicle: those in direct contact with and surrounding the zona pellucida are known as cumulus granulosa cells (cGCs), those enveloping the follicular antrum are known as mural granulosa cells (mGCs), and those within the basement membrane are known as basal granulosa cells (bGCs) [85].

By co-culturing granulosa cells with oocytes, Nottola and colleagues [77] showed the functional involvement of granulosa cells in oocyte development. Gap junctions are formed when many filiform appendages from stratified granulosa cells layer intercalate the oocyte's zona pellucida [91, 92]. It has previously been shown that granulosa cells transmit 85 percent of an oocyte's metabolic requirements through gap junctions; furthermore, granulosa cells regulate oocyte transcriptional and post transcriptional activity, both of which are required for oocyte maturation [93]. Furthermore, granulosa cells play an essential part in the development of the follicular antrum; a limited number of granulosa cells undergo remodelling and produce glycosamino–glycans into tiny cavities that grow to create the antral cavity. The granulosa cells in touch with the follicular cavity regulate and coordinate its expansion and regression [94].

Theca

The thecal layer is formed as the follicle begins to develop and cells that are similar to fibroblasts are oriented concentrically around the follicle [99]. As a result, the secondary or preantral follicles are encircled by a concentric sheath of undifferentiated stromal components or fibroblasts that exhibit some blood vascularity development [100]. Theca cells contain a few organelles that are specific to common undifferentiated ovarian stromal cells, such as a small Golgi complex, rod-shaped mitochondria with transversal cristae, profiles of granular ER, and some free ribosomes [101-104].

In the developing antral follicles, the layer is divided into two sections (theca externa and theca interna). The theca interna, the inner portion, is made up of polyhedral or elongated cells that have all of the morphological features of steroid-secreting cells. Their nucleus is vesicular, with a slightly undulating nuclear membrane on occasion, and one distinct reticular nucleus. In addition to plate-like mitochondria, the cytoplasm includes ovoid mitochondria with tubular cristae, many smooth ER profiles, the ubiquitous Golgi complex, and lipid droplets. There are also polysomes and lysosomes present. Granular ER isn't as common as granular ER. The cell membrane is smooth, with just a minor uneven contour on the cell surface. Numerous capillaries enter the theca interna cells, completing the endocrine gland's appearance [106].

The theca externa, or outside portion of the theca, is made up of cells that resemble fibroblasts in appearance. The theca externa forms a continuous layer surrounding each follicle in the hamster, [105]. It comprises of one to three layers of spindle-shaped cells with morphological characteristics of either smooth muscle cells or fibroblasts. ER, Golgi bodies, free ribosomes, and coated vesicles are abundant in fibroblasts.

Prostaglandins and follicular cells (Granulosa and theca cells)

Bridges and fortune [94] revealed that oxytocin increases both PGE_2 and $PGF_{2\alpha}$ production by granulosa cells, indicating that oxytocin, which is produced by the LH/FSH surge, may play a role in the upregulation of PGs. In addition, the temporal complexity of the expression of mRNA for PG receptors offers evidence that both follicular cell types are targets for both PGE_2 and $PGF_{2\alpha}$, and it indicates that a wide range of well controlled activities are taking place. As a result of the differential impact of PGE_2 on progesterone synthesis by granulosa versus theca cells of periovulatory follicles, the notion of cell specificity of PG actions during the periovulatory phase has been supported. The presence of PG transporter mRNA in both theca and granulosa cells as well as its regulation during the periovulatory period suggests, for the first time, a mechanism that can control the movement and location of PGs within the periovulatory follicle [94].

It is possible that both PGE_2 and $PGF_{2\alpha}$ have numerous, cell-specific functions throughout the processes of ovulation and luteinization, as shown by the temporal and cell-specific variations ((Bridges and Fortune, 2007) in the production of mRNA for their receptors during these processes.

FOLLICULAR FUNCTIONS AND PROSTAGLANDINS

(A) Ovulation

Prostaglandins (PGs) were initially implicated in the control of ovarian follicular activity when it was shown that inhibitors of prostaglandin production, such as aspirin and indomethacin, may prevent ovulation in rats [115], mice [116], rabbits [107-114].

The inhibitor was effective when administered locally to the follicle in rabbits and goldfishes, suggesting that the blockage was mediated directly on the follicle rather than via some indirect mechanism, such as suppression of gonadotrophin production. The findings that intrafollicular levels of prostaglandins of both the E and F series increased markedly in several of these species shortly before ovulation provided further evidence of a role for prostaglandins at the follicular level [117-123] Antiserum against PGs was shown to inhibit LH-induced ovulation in oestrous rabbits, whether given systemically [124] or intrafollicularly [15]. This gave credence to the idea that prostaglandins play a role in ovulation. In these

trials, antiserum to $PGF_{2\alpha}$ was more efficient than antiserum to PGE_2 indicating that $PGF_{2\alpha}$ was the more important prostaglandin in ovulation.

(B) Luteinization

Several investigations suggested that E-series prostaglandins may be involved in additional follicular activities. Yang et al. (1974) reported that in rabbit, PGE levels remained high somewhat longer after ovulation; although $PGF_{2\alpha}$ may be most essential for follicular rupture, PGEs may play a part in the luteinization process that usually follows ovulation. The demonstration in vivo that intrafollicular injection of PGE_2 induces luteinization of rabbit follicles [125], as well as reports of the effects of PGE_2 on progesterone production by follicles or granulosa cells undergoing 'luteinization' in culture, provided further support for this theory [126-130]. Surprisingly, indomethacin-induced ovulation blockage did not seem to be accompanied by a blockade of progesterone secretion or corpus luteum formation [131, 132], even when the indomethacin therapy was maintained far beyond the period of ovulation [133]. Furthermore, indomethacin did not seem to affect the usual preovulatory LH surge. The discovery that ovulation could be blocked without affecting gonadotrophin or steroid secretion sparked hopes that a new class of anti-fertility drugs could be developed with the desired anti-ovulatory effect but none of the side effects associated with steroidal contraceptives more general endocrine disturbances.

(C) Human follicles produce prostaglandins

Before starting on a broad search for anti-prostaglandin drugs that are more acceptable than indomethacin for use as ovulation inhibitors in women, it seemed prudent to investigate whether the ideas established in the above-mentioned research in experimental animals might be applied to women. The addition of gonadotropins (human menopausal gonadotrophin and human chorionic gonadotrophin, hCG) to the culture medium promoted substantial synthesis of prostaglandin F in cultured human follicle wall tissue (theca and granulosa cells) [134]. In vitro studies with isolated follicle cell types have shown that both the theca and granulosa cells may generate significant quantities of prostaglandins.

PROSTAGLANDINS AND STEROIDOGENESIS

(A) Biosynthesis of Androgens

Granulosa cells produce no androgens in the absence of FSH, hCG, or PGE_2, as well as in the presence of these hormones. This is similar with results in most other species, and it explains why granulosa cells seem to lack the 17α-hydroxylase and $C_{17,\,20}$-lyase enzymes [135]. As previously stated, the generation of estradiol by the thecal preparations was very low and of questionable relevance. Tsang et al. [112] revealed that the thecal preparations generate a huge amount of androgens. The hCG increases androgen production (testosterone + DHT) in a dose-dependent manner. FSH fails to induce androgen synthesis in theca cells, confirming that theca cells lack substantial amounts of FSH receptors [136]. The hCG, but not FSH, increases cAMP synthesis by human thecal preparations across a dose range that was similar to that needed for androgen stimulation [137]. PGE_2's capacity to promote both cAMP and androgen production on isolated thecal preparations may be compared to that of hCG [113]. The capacity of exogenous cAMP (in the form of its dibutyryl derivative) to increase androgen synthesis by theca preparations adds to the growing body of data indicating cAMP is involved in the stimulatory effects of PGE_2 and hCG [112].

The findings of these investigations are consistent with theories suggested for other animal species to explain cellular and gonadotrophic interactions in follicular steroid biosynthetic control [138]. These studies support that granulosa cells' main function is estradiol synthesis and theca cells' take part in androgen production (Fig 2.6 and Fig 2.7). Furthermore, Leung and Armstrong [115] showed that FSH is the more important gonadotrophin in controlling granulosa cell activities (oestrogen and progesterone production) during the stage of follicle growth studied, whereas LH is more significant in regulating theca cell functions (secretion of androgens). Channing et al. [117] reported substantial estrogen production by human theca tissues. Rhesus monkeys [140], sheep [139], and pigs [140] have all shown increased thecal estrogen production as follicles mature.

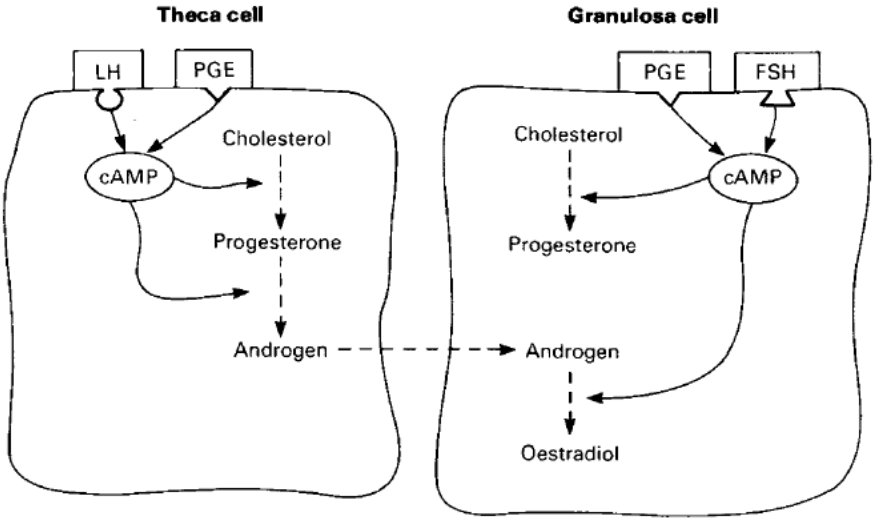

Figure 4:*The control of steroid production by cells of developing preantral and early antral follicles is influenced by cellular and hormonal interactions. Theca cells have receptors for LH and PGE (but not FSH) and react to them by producing more androgen but little or no estradiol. Granulosa cells have receptors for FSH and PGE (but not LH) and react to them by increasing the conversion of androgen generated by theca cells to oestradiol and the conversion of endogenous sterol to progesterone (Armstrong, 1981).*

Prostaglandins are widely known to have a role in the ovulation process, as discussed before. The fact that prostaglandin E_2 can mimic the action of FSH on human granulosa cells and LH on theca cells at early stages of follicular development, as well as the fact that follicular tissues (both granulosa and theca cells) are capable of producing significant amounts of prostaglandin PGE_2. Because inhibitors of prostaglandin synthesis do not interfere with LH's capacity to promote steroidogenesis by preovulatory follicles, luteinization, or oocyte maturation, the need for such activities has been questioned [141-144]. However, speculation about additional potential functions of follicular prostaglandins in ovarian control is intriguing. It is impossible to exclude the notion that they are important at very early stages of follicular differentiation, before the development of pituitary hormone receptors.

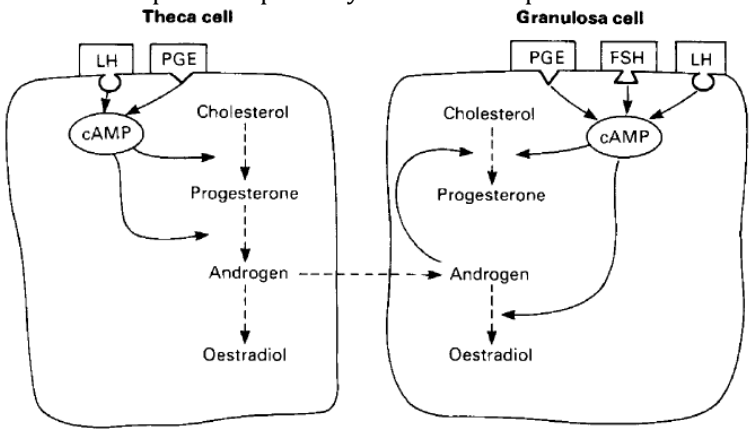

Figure 5:*Cellular and hormonal interactions in the control of steroid production by cells of mature follicles nearing the preovulatory stage. Theca cells become capable of producing large quantities of estradiol after increasing their rate of androgen synthesis. The enhanced rate of progesterone synthesis by the granulosa cells is caused by androgen, which acts synergistically with gonadotrophins. Granulosa cells develop LH receptors and responsiveness (Armstrong, 1981).*

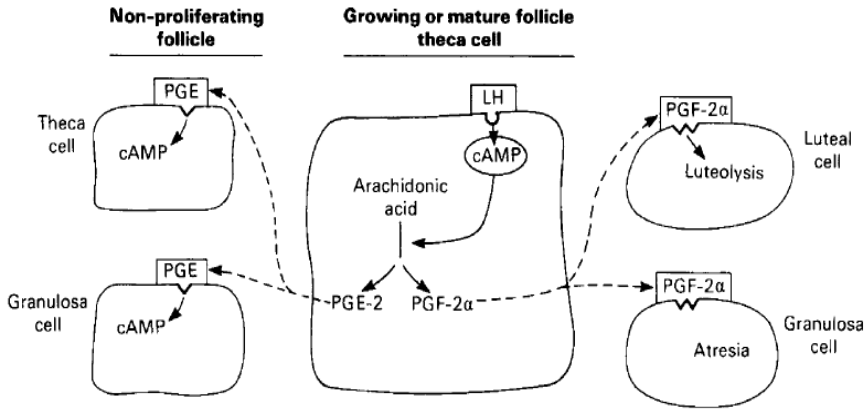

Figure 6:*Prostaglandins may have certain potential functions in ovarian follicular control. PGE_2 is produced by theca cells in developing follicles, and it may promote cAMP synthesis in both theca and granulosa cells. By exerting gonadotrophin-like effects on granulosa and theca cells that do not yet have receptors for pituitary gonadotrophins; this may provide the ovarian stimulation necessary for the start of development of non-proliferating follicles. Through contact with particular receptors on luteal and granulosa cells, follicular prostaglandin $PGF_{2\alpha}$ may start or otherwise contribute to the processes of luteolysis and atresia (Armstrong, 1981).*

PGE_2 generated by theca cells, for example, may aid in the activation of FSH receptors and therefore FSH responsiveness of granulosa cells in immature follicles through diffusion through the basement membrane. Prostaglandins may also diffuse short distances across the ovarian stroma to neighbouring follicles, acting on theca cells in an LH-like way, perhaps aiding in the start of non-proliferating pool follicle growth. Prostaglandins may be worth considering as intra-ovarian follicular factors, as proposed by Peters [120], in the regulation of non-proliferating follicle development, with pituitary gonadotrophins being the main regulatory agents after growth has started and they have gained FSH and LH receptors (Fig 2.8). Lamprecht et al. [121] found that PGE_2 stimulates adenylate cyclase activity in foetal and neonatal rat ovaries, while LH is ineffective until the second week of life, supporting this theory. In several animal species, uterine-derived $PGF_{2\alpha}$ has been generally recognised as a luteolytic agent [145-150].

$PGF_{2\alpha}$ receptors have been found in human corpus luteum tissues [151-155]. Follicular-derived $PGF_{2\alpha}$ may also play a role in the luteolytic process, although to a lesser extent in species to this luteolytic mechanism, but to a greater extent in women who lack such a component. $PGF_{2\alpha}$ capacity to suppress progesterone synthesis by cultured human granulosa cells [125] supports this theory; conversely, this inhibitory action may indicate a function for $PGF_{2\alpha}$ in follicular atresia.

Whether mechanism similar to luteolysis or luteotrophic exists in atretic granulosa cells or not need to be explored further.

CONCLUSION

As evident from the review of literature, various studies showed that prostaglandins have vast physiological roles. The significance of the afore mentioned functions of prostaglandins in ovarian follicular control requires further research, especially using tissues taken from follicles at a broader range of differentiation stages and at more precisely timed phases. The creation of appropriate animal models will be critical in gaining a better understanding of the function and significance of prostaglandins in follicular control; most of the earlier studies have been carried out on rat, mice and pigs. Yet only fragmentary information is available on small ruminants.

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Author Contributions

Dr. R.K. Sharma created the layout and contributed intellectually to the manuscript. Dr. A.K. Sharma and Dr. Manju Bala Sharma gathered relevant literature, completed the write-up, and edited the various parts of the manuscript proposal. All the authors approved the final manuscript.

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