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# The Role of Prostaglandins in Reproduction

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## 1. INTRODUCTION

It was not until 1968 that prostaglandins were considered as a potent mediator for physiological process, although they were first discovered from the sheep seminal vesicle in 1934 by von Euler.[1] Karim[2] and Wiqvist et al.[3] simultaneously reported the action of prostaglandins on the pregnant uterus and suggested a potential use of these for regulation of fertility. Other areas of research have also been stimulated, but the field of reproductive physiology was most significantly influenced by prostaglandins which were recognized as a possible regulator for cellular processes.

This review is mainly concerned with the studies which have been conducted to demonstrate that prostaglandins play a role in regulating many processes in reproduction, -including especially ovulation, function of corpus luteum and motility of oviduct and uterus.

## 2. PROSTAGLANDINS AND OVARIAN FUNTION

### (1) Ovulation:

The processes of follicular growth, maturation and ovulation are governed by anterior pituitary gland under the influence of hypothalamus. Prostaglandins have been postulated to play an important role in the hypothalamo-pituitary control of gonadotropin secretion. $PGE_2$ stimulates the release of LH[4-8] and FSH.[4,6,9] Evidences suggest that $PGE_2$ may stimulate the hypothalamus to secrete LH-RH resulting in LH release: however, other evidence indicates that the release of gonadotropin is due in part to direct action of prostaglandin on the pituitary gland. Harms et al.[4,6] have demonstrated that intraventricularly administered $PGE_2$ can elevate plasma LH levels, whereas the same amount of $PGE_2$ injected into the pituitary gland was less effective in releasing LH. $PGE_2$, when infused into a lateral ventricle, evoked an increase in the concentration of LH-RH in portal plasma, indicating that the increase of LH release might be mediated by an increased secretion of LH-RH.[10] The results of Koch et al.[11] indirectly support this assumption. They found that antiserum to LH-RH blocked $PGE_2$-induced release of LH in immature male and female rats. However, Dowd et al.,[12] using superfusion system, have reported that $PGE_2$ directly stimulated the release of LH in a dose related fashion. In addition, Sato et al.[18] have shown that $PGE_2$ can stimulate the release of LH from rat pituitary halves in vitro although others[11,13] have failed to find the direct effect of $PGE_2$ on the pituitary gland.

Indomethacin, an inhibitor of prostaglandin synthesis,[15-17] has shown to be capable of interfering with the process of ovulation. Behrman et al.[18] found that neither LH nor LH-RH could overcome the block of ovulation caused by indomethacin, suggesting that release of LH is not affected in indomethacin-treated

rats and indomethacin exerts its ovulation inhibiting action at the ovary.[18~20] The histological findings in indomethacin-treated rabbits and rats showed a driect effect of indomethacin on the follicles. Luteinization of the follicles was evident after at least two days following the expected time of ovulation, but in every ovary examined the egg was found to be retained within grossly hemorrhagenic follicles.[17] Plasma progesterone levels in indomethacin-treated rabbits were not significantly different from control.[20] This suggests that the action of LH on steroidogenesis was not blocked, and that role of LH to cause expulsion of the egg might be mediated by prostaglandins. $PGF_{2\alpha}$ not only initiated ovarian contraction but also led to an increase in amplitude and frequency.[21,22] This supports a possible role for prostaglandins in the ovulatory process on a local level. Recent studies, however, indicate that indomethacin acts on the hypothalamo-pituitary axis. Indomethacin inhibits plasma LH when injected into the 3rd ventricle or implanted into the medial basal hypothalamus.[14] More definite evidence was provided by the failure of indomethacin to prevent LH release induced by exogenous administration of LH-RH to ovariectomized rats.[14]

Therefore, it might be stated that prostaglandins play a physiological role in the control of gonadotropin and this is due to a direct effect of the prostaglandin on the hypothalamus. However, altered prostaglandin content in or prostaglandin release from the hypothalamus in situation which LH-RH levels are changed should be demonstrated to clarify such a role of prostaglandin.

(2) **Corpus Luteum:**

The cyclic regression of corpus luteum in mammals is thought to be under pituitary control since a basal level of LH and probably prolactin play an important role in maintaining luteal function and the withdrawal of these hormones induces luteal regression. However, measurable quantities of gonadotropins are present in peripheral plasma of rodents and primates at the time of luteal regression. Thus, it appears that complete withdrawal of pituitary gonadotropin from the circulating blood is unlikely to be a general mechanism for the induction of luteal regression.

In addition to the pituitary gland, the uterus plays an important role in the control of corpus luteum function in mammals, with the exceptions of primates.[23,24] Hysterectomy during the luteal phase of estrous cycle in sheep and cow [25] or pseudopregnancy in rat and rabbit[26,27] was able to lengthen corpus luteum life span. These results suggest that the uterus produces a luteolytic substance to regress corpus luteum in some species. By definition a luteolysin is a substance which decreases progesterone secretion from the corpus luteum or shortens its life span. In contrast, a luteotropin is a substance which increases progesterone secretion by the corpus luteum or prolongs its life span. Pharriss and Wyngarden[28] proposed that since $PGF_{2\alpha}$ was abundant in uterus, $PGF_{2\alpha}$ might be a luteolytic factor from the uterus. They showed that $PGF_{2\alpha}$ caused luteal regression when administered during pseudopregnancy in rat. When $PGF_{2\alpha}$ was infused into the arterial supply of the autotransplanted ovary of the sheep, $PGF_{2\alpha}$ exactly mimicked the luteolytic factor.[25,29] The level of $PGF_{2\alpha}$ in the peripheral circulation of the sheep is highest just at the time of luteal regression.[25] Evidence for the role of $PGF_{2\alpha}$ as a luteolysin is also provided by studies in rabbit in which luteal regression at the end of pseudopregnancy was prevented either by administering indomethacin or by actively immunizing rabbit against $PGF_{2\alpha}$ with

$PGF_{2\alpha}$ conjugated bovine serum albumin.[30] Unlike primate, most species in which an effect of hysterectomy has been demonstrated have a bicornuate uterus. Furthermore, many of these animals show an unilateral effect of hysterectomy, i.e., removal of one uterine horn causes maintenance of the corpus luteum in the adjacent ovary but not in the opposite ovary connected to the remaining uterine horn as in sheep.[25,26] The vascular connections between uterus and ovary have to be maintained for normal luteal regression to occur in several species including sheep.[25,26,29] Most of ovarian artery in sheep runs over the surface of the utero-ovarian vein befcre entering the hilus of the ovary, and it is considered that substances might diffuse from the vein to the artery and pass directly into the ovary. When $^3H$-labeled $PGF_{2\alpha}$ was infused into the uterine vein, the amount of radioactivity associated with $PGF_{2\alpha}$ in ovarian arterial blood was higher than in iliac arterial blcod, indicating that transport of $PGF_{2\alpha}$ via a counter current mechanism could occur.

Since endometrium of the uterus contains PGs,[29,31] it seems likely that $PGF_{2\alpha}$ might indeed be a luteolytic factor in sheep. $PGF_{2\alpha}$ was identified and measured in uterine vein blood of sheep using mass spectrometry.[32] At the time of luteal regression the concentration of $PGF_{2\alpha}$ in uterine venous plasma increased by 10 fold. Infusion of $PGF_{2\alpha}$ into uterine vein in situ consistently induced premature luteal regression in the adjacent ovary. No effect was seen when $PGF_{2\alpha}$ was infused into the systemic circulation.[29] These studies confirmed not only the importance of the counter current mechanism but also the role of $PGF_{2\alpha}$ as a luteolytic hormone in sheep.

The situation in primate is clearly different since hysterectomy in monkey and human has no effect on corpus luteum function. Whether PGs play a luteolytic role in human and subhuman primate is still controversial. In non-pregnant woman, infusions of $PGF_{2\alpha}$ have had either no effect or only a transient effect in reducing circulating progesterone levels.[33,36] In monkey, subcutaneous injection of $PGF_{2\alpha}$ during luteal phase reduced cycle length and decreased progestin concentration in peripheral serum[37] whereas indomethacin treatment did not prolong a functional life span of the corpus luteum.[38] The inability to demonstrate unequivocal luteolytic effects in woman may be due to the side effects of $PGF_{2\alpha}$ prohibiting use of a concentration sufficient to induce luteolysis. Since neither hysterectomy [37] nor intrauterine administration of $PGF_{2\alpha}$[38] alters ovarian cyclicity and normal luteal function in rhesus monkey and woman, $PGF_{2\alpha}$ must come from an extrauterine source if endogenous $PGF_{2\alpha}$ is important in luteolysis. This is strongly supported by the observation that prostaglandins are synthesized by human oviduct, probably by oviductal mucosa and $PGF_{2\alpha}$ moves from the surface of the tubal mucosa to the lamina propria after ovulation, suggesting a possible mechanism for local delivery of $PGF_{2\alpha}$ to the ovary.[39]

The normal triggering mechanism fcr the release of $PGF_{2\alpha}$ from the uterus is not fully documented. It is known, however, that estrogen secretion increases concomitantly with the release of $PGF_{2\alpha}$ from the uterus of sheep [25] and that exogenous estrogen in the guinea pig releases $PGF_{2\alpha}$ from the uterus.[40] It thus seems likely that follicular development occurred at the time of luteal regression in sheep results in a surge of estradiol followed by a luteolytic release of $PGF_{2\alpha}$ which initiates a new ovarian cycle.[41]

In conclusion, it can be stated that $PGF_{2\alpha}$ is most likely luteolytic in all species, and is the "uterine luteolytic factor" responsible for regulating a functional life span of corpora lutea in most non-primate mammalian species. Whether or not this activity of $PGF_{2\alpha}$ may be put to practical use in human as a contraceptive device remains to be established. However, pharmacological approaches using this knowledge may be fundamental to the development of an effective "once a-month" pill.

## 3. PROSTAGLANDINS AND REPRODUCTIVE TRACTS

### (1) Oviduct:

Motility of mammalian oviduct is important in regulating the timely entry of developing embryo into the uterus. The pattern of oviduct motility is changed at various stages of menstrual cycle in human[42,43] and rhesus monkey.[44,45]

Spontaneous activity during the follicular phase of the menstrual cycle was characterized by high frequency-low amplitude contraction. During the ovulatory phase, ampullary activity was at its highest amplitude and lowest frequency. The rhythmic contractions observed at this time may be essential to allow close association of the fimbria with the ovary at the time of follicular rupture. The high frequency and amplitude during a few days after ovulation could be important physiologically in keeping the ova at the ampullary-isthmic junction without transporting them through the oviduct prematually. Low frequency and high amplitude contractions observed after ovulation may also be a prerequisite for efficient ovum pick up and transport into the oviduct by ciliary action. Motility then decreased and remained low through duration of the cycle. It has been recognized that prostaglandins play a major role in the regulation of egg transport in mammals. In the oviduct, ovarian steroids, adrenergic compounds and prostaglandins may interact to synchronize developmental changes of embryos with those of uterus. Simultaneous determination of the location of eggs and the concentration of prostaglandins in oviductal tissue have revealed that eggs are transported to the uterus when tissue levels of $PGF_{2\alpha}$ fall.[46] It has been suggested that preovulatory ovarian hormones stimulate $PGF_{2\alpha}$ synthesis in the isthmus of oviduct and that postovulatory increase of progesterone reduces tissue concentration of $PGF_{2\alpha}$ and allows progressive movement of the uterus.[47]

Prostaglandin E and F series are known to be mutually antagonistic in their effects on spontaneous muscle activity of oviduct. $PGE_2$ inhibits and $PGF_{2\alpha}$ stimulates oviductal motility of rabbit,[48~50] monkey[44,45] and woman.[51] Postovulatory subcutaneous injection of large doses of $PGF_{2\alpha}$ is effective in modifying oviductal motility and in accelerating egg transport.[49,52] In this way prostaglandins can interfere with the normal process of implantation by altering the precise timing of the arrival of the blastocyst into the uterine lumen. When prostaglandins are administered systemically in therapeutically effective dose levels, unpleasant side effects are reported in woman. Such effects have limitted the use of prostaglandins as contraceptives. Therefore, it has been hoped that local administration of this compound might reduce dosage, limit side effects and increase contraceptive efficacy of prostaglandins. Fortunately recent report shows that vaginal administration of silastic suppositories containing small doses of $PGF_{2\alpha}$ is effective in modifying egg transport and implantation in rabbit.[50]

### (2) Uterus:

The action of prostaglandins on the uterus

when tested in vitro and in vivo is controversial. Further confusion also results from the discrepancy in action when prostaglandins were applied to non-pregnant or pregnant uterus. However, it has been suggested that the predominant influence of all prostaglandins tested in vivo in pregnant or cycling woman is stimulation of myometrial activity.

Uterine contractions in sheep are thought to be a consequence of release of $PGF_{2\alpha}$ since elevated levels of $PGF_{2\alpha}$ are found in uterine vein before the onset of uterine activity.[53] Liggins et al.[54,55] have shown that the intra-aortic infusion of $PGF_{2\alpha}$ causes uterine contractions. Unlike normal term labor, however, no changes occurred in the levels of maternal estrogen and progesterone. In pregnant sheep, administration of stilbestrol caused the threshold dose of oxytocin to fall by about 90% after 24 hours though peripheral or uterine progesterone levels were not changed.[54,55] Both exogenous estradiol-17$\beta$ and stilbestrol caused an increase in maternal placental, myometrial and uterine venous plasma levels of $PGF_{2\alpha}$ within 24 hours of administration, but pharmacological amounts of progesterone, which were sufficient to block normal parturition, prevented estrogen stimulated release of $PGF_{2\alpha}$ into the uterine vein.[56] These data suggest that in sheep, estrogen induces $PGF_{2\alpha}$ production in the myometrium and the maternal cotyledons. Progesterone appears to inhibit the release of $PGE_2$, but not the response of the myometrium to $PGF_{2\alpha}$ which is thought to be an increase in myometrial sensitivity to oxytocin. Therefore, it might be stated that estradiol promotes the synthesis of $PGF_{2\alpha}$ and increases the sensitivity of myometrium to oxytocin, without any change in plasma or myometrial progesterone concentration[56].

Indomethacin has been known to block spontaneous contractions of the uterus in rat and myometrial contractions in response to oxytocin in rat[57] and rabbit[58] at term when the endogenous progesterone level is low.

These studies support the concept that the "intrinsic uterine stimulant" may be $PGF_{2\alpha}$.[59] In rat and rabbit, the myometrium is intrinsically active, but this activity is normally blocked by progesterone. Myometrial action begins when progesterone level is reduced below the level which normally suppresses intrinsic activity. Naproxen, an inhibitor of prostaglandin synthesis, delays the onset of parturition in rats for at least 24 hours.[60] Ovariectomized pregnant rat treated with estradiol-17 $\beta$ deliver 96% of the fetuses prematurely.[61] Daily treatment with naproxen reduced this prematurity to 50% in estradiol-treated, ovariectomized animals. Whether the fact that prostaglandins are the "intrinsic myometrial stimulant" whose activity can be modified by progesterone[59] can be applied to other animals is not certain. Liggins et al. have demonstrated that in sheep estradiol or $PGF_{2\alpha}$ administered in physiological amounts stimulates uterine activity and markedly lowers the threshold to oxytocin without fall in either the plasma levels or placental secretion of progesterone.[55] In addition, administration of physiological amounts of exogenous progesterone did not interfere with the initiation of parturition.

In woman, the uterine endometrial content of $PGF_{2\alpha}$ was found to be five to ten times higher during the secretory phase of the menstrual cycle than during the proliferative phase or in noncycling woman with atrophic endometrium.[62,63] The major urinary metabolite of $PGF_{2\alpha}$ increases 2~5 fold and $PGF_{2\alpha}$ production gradually increases during human gestation although previous measurements[65,66] of circulating $PGF_{2\alpha}$ levels failed to demonstrate this pattern. Reports using bioassay[2] and radio-

immunoasssay[67] indicated that high concentrations of PGE and $PGF_{2\alpha}$ were present in the antecubital vein plasma of women in active labor and Karim[2] suggested that prostaglandins might be responsible for the initiation of uterine activity at term. The highest $PGF_{2\alpha}$ concentrations in antecubital vein plasma are found 15~45 seconds after the peak of uterine contraction, indicating that prostaglandins are released into the circulation after the onset of uterine contraction.[68] Other workers have measured much lower levels of peripheral plasma $PGF_{2\alpha}$ in women during labor[69,70] although qualitative pattern of higher antecubital vein plasma $PGF_{2\alpha}$ levels 30~45 secods after a peak uterine contraction has been confirmed.[69] Low levels of uterine prostaglandins in early pregnancy may be necessary to prevent spontaneous abortion which has been shown to be associated with elevated levels of prostaglandins in amniotic fluid.[71]

## 4. CELLULAR MECHANISM OF PROSTAGLANDIN ACTION

Since prostaglandins seem to be active in all endocrine systems, it is believed that they act as intracellular messenger. This assumption is supported by their ability to cause an alteration of intracellular cAMP levels, a response which probably explains their non-specificity of target organ action in the various endocrine systems. Kuehl and Humes[72] suggested that the action of LH on the ovary is mediated at the cellular level by the ability of prostaglandins to increase cAMP. The interaction among LH, PGs and cAMP to regulate steroidogenesis in the corpus luteum can be summarized as follows. The hormone (LH), the first messenger, interacts with a receptor in the plasma membrane. This hormone-receptor interaction results in a stimulation of the enzyme adenyl cyclase which converts ATP to cAMP, the second messenger. cAMP thus generated acts to stimulate progesterone secretion in the corpus luteum. cAMP stimulates the conversion of cholesterol to pregnenolone, the rate limiting reaction in the synthesis of progesterone in the corpus luteum. The intracellular site of action of cAMP is not known with certainty and may involve:

1) stimulation of protein kinase enzymes[73] with a resultant phosphorylation of certain protein called histone. This can then change their interaction with DNA so that the end result is an increased transcription of mRNA molecules for new enzymes. 2) stimulation of ribosomal activity resulting in an increase of enzyme synthesis at the translational level.[74] The locus of action of the PGs is not known. Kuehl et al.[75] suggested that PGs were an essential inermediate in LH action since inhibitor of prostaglandin action blocked the action of LH upon incorporation of adenine into cAMP in mouse ovaries. Thus, PGs themselves can stimulate adenyl cyclase which then acts within the cell to stimulate steroidogenesis. However, the mechanism by which PGs exerts its effects on the luteolysis remains obscure. The luteolysin may act directly on the cell and thereby inhibit steroidogenesis or it may exert its effect indirectly by reducing blood flow to the secretory tissue.

Pharriss et al.[76] initially proposed that $PGF_{2\alpha}$ may induce luteolysis by constricting the flow of blood in the utero-ovarain vein and thus, decreasing blood flow to the ovaries. The administration of $PGF_{2\alpha}$ results in a redistribution of blood flow from the corpora lutea to the interstitial tissue in rabbit ovary.[77] A significant correlation between blood flow to the luteal ovary and levels of progesterone in the circulation was observed.[78] It is suggested

that alterations in blood flow may be an integral part of the overall mechanism regulating luteal function in ewe. Morphological changes in the vasculature of corpora lutea removed from sheep after treatment with $PGF_{2\alpha}$ appeared to be associated with changes in blood flow to the luteal ovary and secretion of progesterone.[79] The most rapid changes in the vascular compartment appeared to be a swelling of the endothelial cells and a decrease in perfusion, evidenced by a decrese in percent volume of red blood cells within the corpus luteum. Moreover after the infusion of $PGF_{2\alpha}$ in sheep, an abrupt decrease in peripheral progesterone level was accompanied by cessation of granule secretion thought to contain progesterone by luteal cells.[79,80] Lipid droplets were accumulated and progression of these structural changes led to cellular shrinkage and disorganization culminating in regression of the corpus luteum.[80] However there are evidences that luteolysis may be induced by a mechanism completely independent from any vascular effects. A direct luteolytic action of $PGF_{2\alpha}$ on ovarian tissue in vitro has been reported: decreased synthesis of progesterone occurred when luteal cells[81,82] and slices of luteal tissue[83] were treated with $PGF_{2\alpha}$. An alternate possibility for the mechanism of luteolysis induced by $PGF_{2\alpha}$ is an attenuation of gonadotropin through complex interrelationship of hormones with $PGF_{2\alpha}$. In rat both LH and prolactin are necessary for continued function of the corpus luteum. The action of LH was shown to cause an acute increase in progesterone biosynthesis[84] and prolactin has been shown to maintain the ability of the corpus luteum to secrete progesterone.[85] An early action of LH on corpus luteum in rat is an activation of cholesterol ester hydrolase, thereby providing a source of cholesterol for conversion to progesterone.[86] The synthesis of cholesterol ester is catalysed within the corpus luteum by cholesterol ester synthetase, an enzyme which is specifically maintained by prolactin[85]. Thus, the active turnover of cholesterol ester appears to be regulated by both gonadotropins, a process which is fundamentally linked to steroidogenesis. Pharriss[87] demonstrated that in hypophysectomized rat $PGF_{2\alpha}$ prevented maintenance of the corpus luteum by prolactin. Behrman et al.[88] showed that $PGF_{2\alpha}$ prevented tropic expression of prolactin to maintain the enzymes required for cholesterol ester turnover with a resultant loss in progesterone biosynthesis and suggested that the action of $PGF_{2\alpha}$ may be to neutralise gonadotropin action.

The regulation of myometrial activity by prostaglandins involves interaction with adenyl cyclase, cAMP and calcium. $PGE_2$ and $PGF_{2\alpha}$ decrease ATP dependent calcium binding to muscle cell components, specifically the sarcoplasmic reticulum[89] and the mitochondria[90] while biologically inactive $PGF_1$ has no effect. Carsten[89,91] has suggested that the decrease of ATP-dependent calcium binding caused by $PGE_2$ and $PGF_{2\alpha}$ may increase the release of calcium from the sarcoplasmic reticulum. Since calcium is required for maximal smooth muscle contractions, the regulation of its intracellular concentration could be the basis for the effects of prostaglandins on uterine contractility. In the bovine sarcoplasmic reticulum preparation described by Carsten, the efficacy of $PGE_2$ and $PGF_{2\alpha}$ was greater than that of oxytocin in inhibiting cacium binding[91]. The increase of myometrial cAMP, which suppresses myometrial activity and is brought about by $\beta$-adrenergic agents, is inhibited by prostaglandins and by oxytocin.

Evidence is now accumulating to suggest that prostaglandins may mediate effects of oxytocin which result in decreasing intracellular cAMP,

membrane depolarization and enhanced myometial contractility.[92]

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