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Prostaglandin in Obstetrics and Gynecology: Physiology, Pharmacology, and Clinical Applications

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Abstract:

Background: Postpartum hemorrhage remains an important obstetric emergency and may occur when effective uterine contraction is not achieved following placental delivery. Prostaglandins are potent locally acting lipid mediators involved in reproductive physiology, cervical ripening, labor initiation, and regulation of uterine contractility. Their effects are mediated through distinct prostanoid receptors located in the myometrium, cervix, trophoblast, and fetal membranes. Prostaglandin F2 alpha primarily acts through the FP receptor and activates the phospholipase C–inositol triphosphate–calcium pathway, producing powerful myometrial contraction. Carboprost, a prostaglandin F2 alpha analogue, is therefore used as an effective uterotonic agent, particularly when conventional uterotonics are inadequate. Prostaglandin E1 analogues, especially misoprostol, also enhance uterine contraction and offer practical advantages, including ease of administration, stability, and availability through oral, sublingual, buccal, rectal, and vaginal routes. However, the two prostaglandin classes differ in potency, safety, tolerability, and clinical contraindications. Comparing their effectiveness and adverse effects is clinically relevant for selecting an appropriate prophylactic uterotonic agent during elective cesarean section.

Keywords: Prostaglandin F2 alpha; Prostaglandin E1; Carboprost; Misoprostol; Postpartum hemorrhage; Elective cesarean section; Uterotonics; Uterine contractility.

Introduction:

Natural prostaglandins (PGs) are metabolites derived from polyunsaturated fatty acid metabolism, specifically focusing on arachidonic acid (AA). This precursor is liberated from membrane phospholipids by phospholipase A_2 in response to various physical, chemical, and neurohormonal stimuli. Following its release, AA is swiftly converted into oxygenated metabolites via two separate enzymatic pathways: cyclooxygenase and lipoxygenase. The intermediate cyclooxygenase products are subsequently transformed into primary prostaglandins, whereas the lipoxygenase pathway yields leukotrienes. Notably, the production of specific cyclooxygenase products varies significantly across different tissue types **(1,2).**

Cardiovascular and Renal Regulation by Endothelial Prostaglandins.

Within the cardiovascular and renal systems, prostaglandins of the E series and prostacyclin (PGI_2) play critical regulatory roles. These autacoids are produced by the endothelium and the vascular wall to sustain microcirculation and to mitigate the vasoconstrictive and proaggregatory effects of thromboxane A_2 (TXA_2). Furthermore, prostaglandins E and I_2 enhance renal blood flow and induce diuresis and natriuresis, mechanisms that are mediated partially through their influence on the renin-angiotensin-aldosterone system **(1,2).**

Smooth Muscle Contractility and Uterotonic Effects

The physiological effects of prostaglandins on smooth muscle tissue are highly type-specific and frequently antagonistic. For instance, prostaglandin F (PGF) induces the contraction of bronchial and gastrointestinal smooth muscle, whereas prostaglandin E (PGE) and PGI_2 generally exert opposing actions. In the respiratory tract, PGE relaxes bronchial muscle, while PGF induces bronchoconstriction; consequently, dysregulation of these pathways may exacerbate elevated bronchial tone in conditions such as bronchial asthma. Conversely, in reproductive physiology, both PGEs and PGFs—excluding PGI_2—induce significant contraction of the uterine muscle, which accounts for their characteristic uterotonic effects **(1,2).**

Gastrointestinal Mucosal Protection and Cytoprotection

In the gastrointestinal tract, prostaglandins of the E and I series, alongside TXA_2, are synthesized by the mucosa and released into the lumen in response to neurological or hormonal stimulation. These molecules contribute fundamentally to the preservation of mucosal integrity and local microcirculation. Parallel to these endogenous mechanisms, all proton pump inhibitors, including variants that do not directly inhibit gastric acid secretion, exhibit distinct cytoprotective properties against various ulcerogenic and necrotizing agents **(1,2).**

Emerging Perspectives on Eicosanoid Pathophysiology

Ultimately, traditional prostaglandins represent merely a minor portion of the biologically active derivatives originating from arachidonic acid metabolism. Recent investigations into lipoxygenase products increasingly highlight their profound biological significance and complex roles in various pathological conditions, underscoring the need for continued expansion of the current eicosanoid paradigm **(1,2).**

The reproductive system has always been acknowledged as the primary producer of prostaglandins. The initial finding of PGs was attributed to their elevated content in seminal fluid. PGs are found in human semen at concentrations of several hundred micrograms per milliliter, exceeding values in other biological fluids by at least a million times. The elevated concentration of prostaglandins (PGs) in semen, along with their substantial absorption from the vagina, has prompted the hypothesis that PGs introduced during copulation may enhance the movement of semen inside the uterus and fallopian tubes, thereby aiding in the fertilization of the ovum. A lack of prostaglandins in semen has been asserted to cause male infertility. Elevated prostaglandin synthesis in the endometrium has been associated with the pathophysiology of dysmenorrhea, as treatment with cyclooxygenase inhibitors is recognized to alleviate the pain associated with this condition. Prostaglandin levels in the blood and amniotic fluid of pregnant women often rise during labor and are consequently linked to the onset and sustenance of uterine contractions throughout this process. These data strongly indicate the significant function of PGs in both the female and male reproductive systems **(3)**.

Pharmacological Role of PGs in the Uterus:

PGs are a series of metabolites formed from arachidonic acid, which are mainly produced by cyclooxygenase. PGs were originally thought to activate membrane receptors near their formation site. Their different biological activities and generation of second messengers (cyclic AMP [cAMP], inositol phosphates, and Ca2+[IP3/Ca2+]) suggested that PGs interact with distinct receptors, and different receptors correspond with different PGs (**4)**.

It was determined that prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), prostacyclin I2 (PGI2), and thromboxane A2 (TXA2) exert their biological function by interactions with their respective receptors – the DP, EP, FP, IP, and TP receptors (Coleman, 1994). Four subtypes of EP receptor have been identified (EP1–EP4). PG receptors are located in the myometrium, trophoblast cells, amnion, and cervix, and all belong to the G-protein-coupled superfamily, incorporating 7 transmembrane domains. The PGs produced in the human endometrium are mainly those of the E and F series, while PGD2, PGI2, and TXA2 occur less frequently **(3).**

PGF2α action is mediated by the FP receptor, increasing the intracellular calcium concentration ([Ca2+]i) via the PLC-IP3-Ca2+ pathway. PGE2 acts differently through 4 subtypes (EP1–EP4) in human myometrium: its interaction with EP1 receptors elevates [Ca2+]i via the PLC-IP3-Ca2+ pathway, while EP2 and EP4 receptor signals stimulate the production of adenylyl cyclase. Overall, differences in biological functions of the PG receptors reveal 3 subclusters. The first of these subclusters consists of receptors TP, FP, and EP1, which increase [Ca2+]i and constitute a group of "contractile" receptors because they cause smooth muscle contraction. The second group consists of receptors IP, DP, EP2, and EP4, which increase the concentration of intracellular cAMP via Gs protein and are defined as "relaxant" receptors because they induce smooth muscle relaxation. Finally, the third group consists only of EP3 and is generally associated with a decline in cAMP. The "inhibitory" receptor generally causes smooth muscle contraction, depending on the cell type; however, the EP3 receptor can also increase intracellular cAMP and induce [Ca2+]i **(5).**

PGs in Pregnancy and Birth:

Interestingly, the nonpregnant human uterus contracts in the presence of PGF2α and TXA2 but relaxes in the presence of PGE **(6)**. Uterine strips isolated from pregnant women contract with PGF2α and low concentrations of PGE2, while PGI2 and high concentrations of PGE2 induce relaxation **(6)**.

One possible explanation for this is that PG receptor expression varies considerably from the nonpregnant state through pregnancy to birth, and the relative level or type of receptors may dictate the degree of uterine quiescence or contractility. For example, the uterine FP mRNA expression level has been found to decline significantly with gestational age in patients not in labor and then at term increase significantly with labor. Thus, in the initiation of parturition, myometrial active quiescence may change to an active contractile state due to an upregulation of contractile receptors and down regulation of relaxatory receptors **(7)**.

Moreover, the additional control for the onset of labor is built into the increased synthesis of endogenous PGs of the E and F series in the uterine compartment **(8)**.

The intra-amniotic, intravenous, or vaginal administration of exogenous PGs can initiate labor at any stage of gestation and in all mammalian species. For pregnant women in labor and placental delivery, PGE or PGF2α produces a dose-dependent increase in the frequency and intensity of uterine contractions. Additionally, PGE2 appears to play a more important role in cervical ripening and rupture of the fetal membranes than in uterine contractility **(3)**.

PG Analogs for PPH:

In the prevention and treatment of PPH, the PG agents that are frequently used in clinical practice include carboprost, sulprostone, and misoprostol, representing the analogs of PGF2α, PGE2, and PGE1, respectively **(9).**

Pharmacological Effects of Prostaglandins:

Cardiovascular System:

- **PGF2α:** Potent vasoconstrictor for large arteries and veins. It has little effect on BP, heart rate, cardiac contractility or capillary permeability. It is not a smooth muscle cell mitogen
- **PGI2:** It is uniformly vasodilator and is more potent hypotensive than PGE2. It keeps the patency of ductus arteriosus **(3).**

Platelets:

- **PGI2,** effectively inhibits platelet aggregation.
- **PGI2,** it maintains the integrity of the vascular endothelium, preventing platelets to aggregate and stick to the arteriolar walls. Because platelets lack nuclei (and hence DNA), they cannot continually synthesize COX-1 and therefore a limited amount of COX-1 and TXA2 persists only up to the lifetime of platelet (approx. 7 days). This contrasts with the vascular endothelial cells, which have nuclei and therefore can produce new COX-1 (and therefore PGI2) on a regular basis. This property of platelets has been exploited by using low doses of aspirin for the prevention of coronary thrombosis) **(10**).

Uterus:

Both PGE2 and PGF2α uniformly contract pregnant as well as nonpregnant uterus in vivo, but PGF2α is 20 times more potent than PGE2. In vitro, however, PGE2 relaxes nonpregnant but contracts the pregnant uterus while PGF2α consistently contracts both. At term, PGs, in low doses, soften the cervix and make it more yielding. PGs produced by the fetus, at term, may be involved in the initiation and progression of labour. Primary dysmenorrhea is attributable to the increased endometrial synthesis of PGE2 and PGF2α during menstruation, with uterine contractions which lead to ischemic pain. Aspirin group of drugs, therefore, are highly effective in relieving dysmenorrhea in most women **(11).**

Bronchial Muscle:

PGE2 and PGI2α cause relaxation of bronchial smooth muscle. PGF2α and TXA2 (also PGD2 through a TP receptor) induce contractions of respiratory muscles. Asthma may also be attributed to an imbalance between bronchoconstrictor PGs (PGF2α, TXA, and LTs) on one hand and bronchodilator PGs (PGE2, PGI2 and PGE1) on the other. The dilator PGs also inhibit histamine release. In some individuals, aspirin induces asthma because of the shift in arachidonic acid metabolism from the COXpathway (blocked by aspirin) to the leukotriene pathway. Leukotrienes are very powerful broncho- constrictors **(12)**.

Gastrointestinal Tract:

PGE2 markedly reduces acid secretion in the stomach. PGI2 also inhibits acid secretion but to a lesser extent. Both PGE2 and PGI2 also increase mucus production and mucosal blood flow, i.e., PGE2 and PGI2 are antiulcerogenic. The ulcerogenic action of the aspirin group of drugs is probably due to the loss of this cytoprotective influence.

The longitudinal muscle of the gut is contracted by PGE2 (via EP3 effect) and by PGF2α (via FP effect). PGE2 also increases water and electrolyte secretions in the intestines. Hence colic with watery diarrhea are important side effects of PGE2. PGI2 opposes the propulsive activity of PGE2 and does not produce diarrhea. PGs seem to play some important role in colonic cancer and regular intake of aspirin, therefore, reduces the risk of colonic cancer **(13).**

Kidney:

The renal medulla produces substantially more PGS compared to the renal cortex. Both PGE2 and PGI2 cause natriuresis and renal vasodilatation and inhibit ADH action to promote water clearance. In addition, PGE2 decreases Cl reabsorption. Both facilitate ß1 adrenoceptor stimulated renin release. TXA2, however, causes renal vasoconstriction, and perhaps an ADH-like effect (but kidneys synthesize very little TXA2). Loop diuretics, e.g., furosemide, produce a part of their effect through stimulation of COX activity to produce vasodilator PGE2 and PGI2. That is why, the patient's response to a loop diuretic diminishes if a COX-inhibitor like indomethacin is administered concurrently **(14).**

Male Reproductive System:

There is about 20 times more PGE (PGE1 and PGE2) than PGF2α in fertile semen. TXA2 and LTS are not found in semen. Testosterone promotes prostaglandin production while large doses of aspirin decrease PG contents of seminal fluid. PGE2, due to its smooth muscle relaxing effect, enhances penile erection. It increases sperm motility from the vagina to uterus **(14).**

Central Nervous System:

No clear cut physiological role of PGs in CNS has yet been established. Nonetheless, PGE1 and PGE2 are pyrogenic (via EP3 receptor action). Their synthesis is blocked by aspirin. In some animal species, PGD2 induces sleep. PGF2α is not pyrogenic (unless given exogenously). PGD2 and TXA2 are also not pyrogenic. PGs probably function as neuro-modulators in the brain as they inhibit the release of NE from postganglionic sympathetic nerve endings **(15).**

Peripheral Nerve Endings:

Both PGE2 and PGI2 sensitise pain receptors at afferent nerve endings to mediators of pain (histamine, 5-HT and bradykinins) at the inflammatory site and amplify algesia **(16).**

Endocrine System:

PGE2 facilitates the release of growth hormone, TSH, ACTH, FSH, LH and prolactin. However, PGE2 analogues, per se have no significant effect on the release of these hormones. It also has insulin-like effects on carbohydrate metabolism **(17)**.

Bone Metabolism:

PGE2 plays some role in osteoporosis that occurs at menopause as it stimulates bone resorption. PGE2 plays an important role in osteoporosis which occurs at menopause as it stimulates bone resorption. PGE2 secreted by osteoblasts increases when bone density decreases. It has been seen in various studies that the use of NSAIDs contributes like ibuprofen treatment being able to improve trabecular bone quality by Inhibition of prostaglandin synthesis contributing to the limitation of pathological bone growth and the formation of heterotopic ossification reducing osteoclasts and bone inflammatory cytokines (IL-1β and TNF-α) **(18).**

Eye:

PGF2α (via FP receptor action) and PGE2 lower the intraocular pressure by increasing the outflow of aqueous humour from the anterior chamber via the uveoscleral pathway **(19).**

Cancer:

PGE2 is considered to be the principal pro-oncogenic prostanoid, which promotes polyp formation (colon carcinogenic). TXA2 is another likely pro-carcinogenic mediator **(20).**

Therapeutic Uses of Prostaglandins:

Abortion:

PGE2 and PGF2α and their analogues are used to terminate pregnancy and to induce cervical ripening in pregnancy. These prostaglandins are used for first and second-trimester abortion and appear to soften the cervix, before abortion, by increasing proteoglycan content and changing the collagen characteristics (**21**).

Misoprostol: It is a PGE1 derivative which is given orally for abortifacient purposes. It is used with mifepristone to induce abortion in the first few weeks of pregnancy. Vaginal, route of administration is associated with increased incidence of sepsis **(22).**

FIGO Misoprostol-Only Dosing Chart **(23):**

For use ONLY when mifepristone is not available

Abbreviations & Routes of Administration

- **BU:** Buccal
- **SL:** Sublingual
- **PV:** Per Vagina
- **PO:** Per Oral

1. Gestational Age: \le 12 Weeks

- **Induced Abortion:** Misoprostol 800µg BU/SL/PV every 3 hours until expulsion.
- **Missed Abortion / Anembryonic Pregnancy:** Misoprostol 800µg BU/SL/PV every 3 hours until expulsion.
- **Incomplete Abortion:** Misoprostol 400µg SL \times 1, OR 600µg PO \times 1, OR 800µg BU \times 1 dose.
- **Cervical Preparation before Aspiration:** Not required.

2. Gestational Age: 13–17 Weeks

- **Induced Abortion:** Misoprostol 400µg every 3 hours BU/SL/PV until expulsion.
- **Missed Abortion:** Misoprostol 400µg every 3 hours BU/SL/PV until expulsion.
- **Incomplete Abortion:** Misoprostol 400µg every 3 hours BU/SL.
- **Cervical Preparation Before Aspiration:** Misoprostol 400µg 1–2 hours BU/SL/PV before the procedure.

3. Gestational Age: 18–24 Weeks

- **Induced Abortion:** Misoprostol 400µg every 3 hours BU/SL/PV until expulsion.
- **Fetal Demise:** Misoprostol 400µg every 3 hours BU/SL/PV until expulsion.
- **Incomplete Abortion:** Misoprostol 400µg every 3 hours BU/SL.
- **Cervical Preparation before D&E (Use of multiple modalities is recommended):** Osmotic Dilators 1–2 days before and Misoprostol 400µg BU/SL/PV 1–2 hours before the procedure.

4. Gestational Age: 25–27 Weeks

- **Induced Abortion:** Misoprostol 200µg every 4 hours BU/SL/PV until expulsion.
- **Fetal Demise:** Misoprostol 200µg every 4 hours BU/SL/PV until expulsion.

- **Induction of Labor:** Misoprostol 25–50µg every 4 hours PV, OR Misoprostol 25–50µg every 2 hours PO.

5. Gestational Age: ≥ 28 Weeks

- **Induced Abortion:** Misoprostol 25–50µg every 4 hours PV, OR Misoprostol 50–100µg every 2 hours PO.
- **Fetal Demise:** Misoprostol 25–50µg every 4 hours PV, OR Misoprostol 50–100µg every 2 hours PO.
- **Induction of Labor:** Misoprostol 25–50µg every 4 hours PV, OR Misoprostol 25–50µg every 2 hours PO.

6. Postpartum Applications

- **Prophylaxis of Postpartum Hemorrhage (PPH):** Misoprostol 600µg SL \times 1.
- **Treatment of Postpartum Hemorrhage (PPH):** Misoprostol 800µg SL \times 1.

Footnotes & Clinical Notes

- **Route Associations:** SL/PO routes are associated with more side effects.
- **Vaginal Bleeding:** Avoid the vaginal route if there is vaginal bleeding.
- **Prior Cesarean Delivery:** Misoprostol is safe below 26 weeks, EVEN with a history of Cesarean Delivery. Misoprostol is not recommended in women ≥ 28 weeks gestational age with a prior Cesarean Delivery.
- **Maximum Dosing:** There is NO Maximum dose of misoprostol. If an abortion is not complete after 5 doses, options include continuing additional doses or resting for 12 hours and starting again.
- **Contraindications:** Misoprostol is not contraindicated in grand multiparas.
- **Aspiration:** Routine aspiration after medication abortion is not required or recommended.
- **Viable Pregnancies:** Buccal and Sublingual Misoprostol is not recommended for induction of labor with viable pregnancies; it is associated with hyperstimulation and fetal distress.
- **Fetal Viability:** Induced fetal cardioplegia should be considered for induced abortion after fetal viability.

Carboprost: It is a PGF2α derivative which is usually administered by intra-amniotic injection for inducing second-trimester abortions. The drug is now least preferred because of its serious toxicity such as cardiovascular collapse, chances of anaphylactic shock and pulmonary hypertension.

Facilitation of labour, cervical priming and postpartum haemorrhage. Dinoprostone (PGE2 derivative), however, is less effective than oxytocin as it is for vaginal administration. Vaginal PGE2 or dinoprostone can also be used to soften the cervix before inducing labour. Oral PGF2α causes more GIT toxicity than PGE2. Though clinical benefits have not been documented, PGs can be preferred over oxytocin for inducing labour in women with preeclampsia, eclampsia or cardiac or renal disease as they have diuretic and natriuretic effects. In intrauterine foetal death, PGE2 alone or with oxytocin seems to cause evacuation effectively **(24).**

Carboprost (PGF2α derivative) has been successfully used to control postpartum haemorrhage when oxytocin or methyl ergonovine is not available **(25).**

Healing of peptic ulcer

PGE1 and PGE2 are used for healing peptic ulcers in patients with NSAID-induced ulcers or in persons who are chronic heavy smokers **(26).**

To prevent platelet aggregation:

TXA2 promotes platelet aggregation and PGI2 inhibits it. PGI2 derivative (epoprostenol) can be used to prevent platelet aggregation in extra-corporeal circulation such as renal dialysis and cardiopulmonary bypass. PGE1 and PGI2, in smaller amounts, can also be used for storage of platelets for transfusion **(27).**

To treat pulmonary hypertension:

A longer-acting PGI2 analogue, treprostinil has been approved for use in pulmonary hypertension by I.V, S.C and inhalation route **(28).**

For patency of ductus arteriosus:

Both PGE2 and PGI2 are responsible for maintaining the patency of foetal ductus arteriosus. **(29).**

Peripheral vascular disease:

PGE1 or PGI2 infused I. V. can promote ulcer healing in acute intermittent claudication. Beraprost is a stable oral PGI2 derivative which is given thrice a day for treating peripheral vascular disease **(30).**

For treating glaucoma:

Ocular drops of latanoprost (a stable, long-acting PGF2α derivative) have shown efficacy similar to 20 timolol in reducing intraocular pressure (via FP receptor action).Prostaglandin analogues are the frontline medications for the treatment of glaucoma. **(31).**

Adverse effects of PGs:

The best-known side effect of PGs includes mild GI disturbances including nausea, dyspepsia, heartburn, and abdominal pain or cramps. **(32).**

Renal vasodilator prostaglandins, among other effects, maintain renal blood flow and glomerular filtration rates. This effect is mainly exerted by them relaxing preglomerular resistance and acting as angiotensin II and norepinephrine antagonists. Therefore, their increase might lead to renal dysfunction, ranging from a reversible impairment of glomerular filtration rate to irreversible renal damage. **(32).**

Renal prostaglandins also affect the systemic vascular resistance. The result from this effect is an elevation in blood pressure that can be as high as 6 mm Hg. **(32).**

PG use is also associated with cardiovascular (CV) adverse events. Although the exact mechanism is not fully understood, it seems to be linked to the relative imbalance in PGI2 and TXA2 production, resulting in a prothrombotic state. Upper and lower airway eosinophil infiltration is a key feature in PGs use as they might lead to bronchospasm. Fatal episodes have also been reported **(32).**

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