2nd Asian Symposium on Prostaglandins and Sulprostone

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Prostaglandins in obstetrics and gynaecology

J. HERCZEG

Department of Obstetrics and Gynecology, WHO Collaborative Centre in Clinical Research on Human Reproduction, University Medical School of Szeged, Szeged, Hungary

INTRODUCTION

Our universe in which we reside could have originated – according to quantum physicists – from an indefinitely small volume, which is continuously expanding and contracting in a pulsatile manner. In a classical universe at the moment of maximum expansion it implies a boundary condition which is unusual, because it lies in our future.[1]

The physical, atomic and molecular biology world seems to show an analogy to the whole universe, and it is reasonable to assume that bioregulation processes at the subcellular level follow a similar cyclical pattern.

The rapidly expanding prostaglandin (PG) research has become an integral part of reproductive physiology with a promisingly bright future.

The primary, naturally occurring PGs were isolated and their chemical structure was determined in the late 1950s, and the findings, that they were biosynthesized from unsaturated fatty acids, provided the foundation for the explosive research on prostanoids and related compounds during the last two decades.[2-5]

From the early controversies – arising from the therapeutic limitations of the naturally occurring PGs – a great amount of progress has been made since the new synthetic analogues have been developed. The role of PGs in reproductive bioregulation, and their recent and developing clinical application is reviewed in this paper.

REPRODUCTIVE PG BIOCHEMISTRY

The PG family called prostanoids has its origin in the polyunsaturated

fatty acids such as arachidonic acid (AA). The successive biochemical steps are called the arachidonic acid cascade (AAC). They start from the liberation of AA from esterified phospholipids by phospholipases found in large quantities in lysosomes; progress to generation of cyclic endoperoxides by the cyclo-oxygenase enzyme; and, through separately and independently controlled pathways, lead to the formation of the classical prostaglandins ($PGF_{2\alpha}$, PGD_2, PGE_2) and thromboxane (TXA_2) and prostacyclin (PGI_2).

The cyclo-oxygenase enzyme is a 'burning-out' type: addition of fresh enzyme allows the 'burned-out' reaction system to proceed once again. This microsome-bound intracellular regulator-forming system – which is also controlled by the availability of precursors (AA) – ensures a finite, limited response that does not depend on the diffusion of some distant product back to a regulatory site, as seems common with soluble, cytoplasmic feedback systems.[6]

In pregnant tissues AA is mostly stored in esterified form in the glycerophospholipids and released from this store by the phospholipase A_2 found in decidual lysosomes and fetal membranes.[7]

The smooth muscle cells like the myometrium have a calcium signaling system. Calcium is also required to remove AA from phospholipids. Subsequently, AAC products could exert stimulatory or inhibitory influences on the calcium signaling system. It has been proposed that the ignition of the AAC could be regarded as a basic cellular signaling system by initiating successive intracellular signals through receptors, thus taking part in translating external stimuli into internal messengers.[8]

In reproductive physiology one of the basic features of PG action is their capacity to elicit myometrial contractions throughout gestation. It is generally accepted that contraction of smooth muscle is regulated mainly by phosphorylation of myosin light chains. The initiating signal for contractions is the influx of Ca^{2+} through the cell membrane or by the release of Ca^{2+} from intracellular storage sites.

The intracellular Ca^{2+} release induced by agonists, such as PGs, probably originates from the endoplasmic reticulum. The removal of Ca^{2+} from the cytoplasm occurs by extrusion across the plasmalemma and by reaccumulation in the endoplasmic reticulum.[9]

BLOCKING THE ENZYMATIC DEGRADATION OF PGs

The primary PGs are rapidly metabolized when introduced into the circulation, especially in the lungs, which contain 15PGDH in large quantities. Therefore, if systemic administration is desired, the primary

prostaglandins have to be infused continuously.[10]

The introduction of the 15(S)15methyl group into the $PGF_{2\alpha}$ molecule blocks the enzymatic reactions, which are attacking the molecule at C15 leading to rapid enzymatic degradation and loss of activity in the case of the naturally occurring PGs.

Later developments resulted in new analogues and further significant improvement in clinical effectiveness and acceptability. The positioning of two methyl groups at C16 resulted in the development of 16,16-dimethyl-PGE-analogues.

Two of them have proved to be clinically useful. The only problem with these 16,16dimethyl analogues is the fact that the ring structure of the PGE molecule is easily dehydrated, which leads to the formation of inactive PGAs and PGBs. To prevent this dehydration, 9deoxo16, 16dime9methylenePGE_2 was synthesized; this proved to be more stable and clinically feasible.[11]

The development of the analogues has opened up new avenues in their use for human reproduction-related purposes. One of the main advantages of the analogues over the primary PGs (besides their altered and slowed metabolism) is that they can be administered intramuscularly, because they are free of the very intense local reaction at the injection site with intense pain characteristic of the parent compounds. With these new analogues non-invasive treatment has become possible, when the drug is given intramuscularly, and the intra-amniotic or extra-ovular space of the uterus is not entered. This route is very convenient, allows repeated administration and eliminates the risk of drug-instillation-related intra-uterine infection. Some of the newest analogues possess a very low gastro-intestinal side-effect rate, such as the multisubstituted 16phenoxyE_2 molecule which displays tissue selectivity and can be administered without preventive medication for vomiting and diarrhoea.[12]

PGs IN THE OVARIAN – TUBAL – ENDOMETRIAL CYCLE

Prostaglandins have been associated with ovarian functions such as follicular growth, rupture, oocyte formation, corpus luteum (CL) physiology and luteolysis. The role of PGs in ovulation has been demonstrated in animal experiments. Systemic or local administration of PG synthetase inhibitors (PGSI) or intrafollicular injections of a PGF antibody inhibit ovulation.[13]

The role of prostaglandins is probably largely confined to follicular rupture, since the effect of luteinizing hormone on the ovum maturation, CAMP and progesterone production is not influenced during the

inhibitions of PG synthesis.[14] In particular, PGE may have a physiological role in luteinization and CL maintenance by modulating the effects of gonadotropins. $PGF_{2\alpha}$ is essential for luteolysis in several species.

Luteolysis

The importance of $PGF_{2\alpha}$ in luteolysis in the human subject is not yet proven, but there are data supporting its role at least in vitro. The age of the CL is of particular importance in this regard, since $PGF_{2\alpha}$ is luteolytic only for CL of a critical age (in the human, seven to 11 days following ovulation).[15]

During luteolysis in sheep $PGF_{2\alpha}$ is released from the uterus as a series of pulses each lasting about one hour at a frequency of about six hours. This relatively short pulse frequency is a minimal requirement for regression of the CL in sheep. The crucial part of this pulsatile $PGF_{2\alpha}$ release system working during luteolysis in sheep, is the oxytocin-receptor interaction which reinforces the secretion of $PGF_{2\alpha}$ but at the same time downregulates its own receptor resulting in hour-long episodes of $PGF_{2\alpha}$ release at six-hourly intervals, which is the regeneration time of oxytocin receptors by oestradiol.[16]

What controls the human and primate CL is poorly understood. Circulating levels of human chorionic gonadotropin (HCG) are essential in rescuing a functional CL during early pregnancy.[17]

The administration of increasing doses of exogenous HCG, mimicking the pattern of secretion of chorionic gonadotropin in early pregnancy, prevented increased in vitro production and the characteristic increase in the ratio of PGF:PGE production by CL.[18]

Luteolytic doses of oestrogen induce increases in the ratio of PGF:PGE production and HCG rescue of the CL is associated with a marked decrease in the ratio of PGF:PGE in rhesus monkey CL.[19] The ratio of production of PGF:PGE by the CL may play a role in the control of its lifespan and steroidogenic capacity in the rhesus monkey.[20] Therefore, pharmacologic doses of HCG during early pregnancy could be of clinical value in preventing spontaneous abortions.

Egg transport and its disorder: ectopic pregnancy

PGs are also intimately involved in tubal motility and egg transport. Administration of various PGs in vitro induce marked and differentiated changes of the activity of muscle strips from different tubal segments. In the ampullary-isthmic junction (AIJ) PGE_1 and PGE_2 exert a clear-cut inhibition of circular muscle layers and a biphasic

response to longitudinal muscle preparations, whereas $PGF_{2\alpha}$ stimulates both layers of AIJ. In circular preparations simultaneous administration of PGE and PGF causes 'E-type' effects.[21]

Indomethacin reduces spontaneous activity in a dose-dependent manner in all muscle layers of the oviduct, and initial activity is restored by exogenous $PGF_{2\alpha}$ indicating the significance of endogenous PG production for spontaneous activity of the oviduct.[22]

Recent interest in the implication of PGs in tubal motility was prompted by the growing awareness of a steady increase in the absolute number and relative frequency of ectopic pregnancies.[23] The alarming increase in the number of emergency laparotomies for tubal pregnancies is reaching the magnitude of a new surgical epidemic. Prompted by the possible catastrophic nature of the condition, research has recently been aimed at early diagnosis and exploring why the ectopic sac is not aborted.[24]

Recent analysis[25] suggests that PGs have some form of therapeutic effect in eradicating extra-uterine pregnancy by nonoperative means. This is based on a survey of reported menstrual induction cases (early pregnancies treated by PGs) in the English literature between 1970 and 1982. In this pool of patients there were only two ectopic gestations (an incidence 0.067%, or 1 in 1,483). The generally accepted frequency among adult women is 0.50-0.25% (one per 200-400 pregnancies) during the time period of the survey. Thus, the expected ectopic pregnancy rate is 3.7-7.4 times greater than found among the study cases.

If the recently documented increase in frequency of ectopic gestations is taken into account, the low rate among PG-treated cases shows a difference of more that 10-fold.

Acceleration or delay of the egg transport in the tube has been raised as a possible explanation for tubal pregnancy.[26] It has been shown that intraluminal tubal pressure increases in response to the administration of PG.[27] The possibility of a direct effect of PGs on the tubal musculature resulting in tubal spasm and expulsion of the ectopic sac is raised.[25] However, this seems improbable since the ectopic sac grows not in the lumen but in the wall of the tube. An indirect effect (as suggested) on the ovary seems more likely, accelerating the reduction in the function of the CL (luteolysis). If CL is removed during early gestation abortion will ensue.[28]

However, Wentz and Jones failed to induce menstruation by administering PG to patients who received HCG to induce pseudopregnancy.[29] The CL continues to offer itself as a suspected target of PGs during extra-uterine pregnancies.

When a high dose of $15mePGF_{2\alpha}$ (5ng/min) was infused for 6 hours a sustained luteolytic response in eight out of 10 patients was observed

in the mid-luteal phase.[30] HCG has a luteotropic effect on the CL thus reducing the luteolytic effect of $PGF_{2\alpha}$ in ewes.[31]

During ectopic gestation the circulating HCG levels are sometimes very low, as supported by clinical findings, providing an opportunity for prostaglandins to attack the ectopic sac probably through exercising a stronger luteolytic effect on the relatively unprotected CL.

PGs in endometrial haemostasis

PGs also have a role in the haemostatic events of the endometrium.

The PGF levels in the proliferative phase are significantly correlated with the oestradiol levels in plasma. PGF concentration in endometria of pill users was found to be higher than during the normal cycle. Pretreatment with clomiphene results in lower levels of both PGF and PGE.[32]

Release of PGs from granulocytes in intra-uterine device (IUD) users may contribute to the rise in the concentration of PGs in the endometrium.[33] An effective decrease in menstrual blood loss in IUD users has been reported by PGSI treatment.[34] If used for this purpose (for instance, in IUD users), low doses should not be employed, since with intermittent administration they would shift the TXA_2:PGI_2 balance favouring PGI_2 production and might elicit an undesirable effect: an increase in bleeding tendency.

The vessel wall converts AA (or prostaglandin endoperoxides) almost exclusively into PGI_2 (prostacyclin).[35] Prostacyclin opposes the action of TXA_2; it relaxes vessel walls and inhibits, and even reverses, platelet aggregation.[36]

The recently available non-selective inhibitors of the PG-synthetase, in spite of their unselective blockade of both the TXA_2 and PGI_2 pathways, offer some possibility for therapeutic manipulation of the AAC. PGSI inhibits the platelet cyclo-oxygenase irreversibly, but the vascular endothelium recovers in a few hours, synthesizing new enzyme protein.

Following ingestion of PGSI, the bleeding time increases, since the vessel wall completely recovers from inhibition producing PGI_2, thus pushing the balance towards bleeding tendency.[37]

In clinical practice, these characteristics of the TXA_2:PGI_2 synthesis in platelets and in the vessel walls bear important therapeutic consequences.[37] When treatment of bleeding tendencies (menorrhagia) is aimed low, intermittent doses should be avoided in contrast to treatment situations of thrombotic tendencies (i.e. prophylaxis by PGSI of thrombo-embolism during pregnancy or post-partum thrombophlebitis), when PGSI should be used in low doses and with long (two days)

intervals[37] capitalizing on the PGI_2 production of the vessel walls, which swiftly recover from inhibition.

PG-OPERATED BIOLOGICAL CLOCK IN THE CONCEPTUS. 'FREE-RUNS' OF THE CLOCK: PRETERM LABOUR, PREGNANCY-INDUCED HYPERTENSION

The rhythmic nature of biological systems can be considered as a basic principle.

Available evidence, to date, strongly suggests a PG-related timing mechanism 'hiding somewhere' in the pregnant uterus.[38] The pregnant intra-uterine tissues are evidently well poised to be a site for housing such a timing mechanism. However, it is suspected that this 'internal clock' is not quite accurate, sometimes it has 'free-runs' with subsequent premature uterine activity, or other imbalances.

PGs in gap junctions and biorhythm

PGs are closely involved in one of the basic intercellular communication systems, i.e. in the regulation and formation of gap junctions and their gating between the myometrial cells. Gap junction development between myometrial cells plays a significant role in transforming the relatively quiescent pregnant uterus into a reactive organ. Gap junctions between myometrial cells are composed of symmetric portions of the plasma membranes from two apposing cells.[39] Gap junctions are believed to play a role in the passage of current (electrical, ionic coupling) or metabolites (metabolic coupling).[40, 41]

AA products, perhaps the endoperoxides or thromboxane, are involved in regulating gap junctions. PGs directly influence gap junction formation in the myometrium.[42] Gap junction formation could be prevented by PG-synthetase inhibitors.[43] In another study in peripartal sheep, the area of gap junctions at delivery was found to be twice that present before and after labour.[44]

The phenomenon of recurring variation in contractile pattern is characteristic of the spontaneous activity of the uterine muscle. In primates, existence of uterine biorhythms has been demonstrated. In the human, systematic modulation of peak pressure has been noted during contractions before onset of labour.[45] The implication of PGs in maintenance of rhythmic myometrial contractility is well documented.[46–49]

Premature labour

Studies have revealed that the phospholipids in the preterm amnion are loaded with the same high concentrations of AA as are those of the chorion and amnion at term. This suggests that from early gestation there is enough precursor of the PGs in amnion to initiate premature labour at any time if prompted by an adequate stimulus.[50]

Micro-organisms with phospholipase A_2 activity from endocervical contamination or infection could constitute such a stimulus, producing deacylation of AA from amniotic phospholipids leading to increased concentrations of AA with subsequent increased PG synthesis.[51]

Following synthesis and release, human decidual prolactin is transported across the intact fetal membranes into the amniotic fluid. The loss of cellular contact between the amnion and chorion impairs transport of newly synthesized human decidual prolactin to the amniotic sac. If prolactin transport from the decidua is blocked, then prolactin can no longer exert its suppression on PGE_2 production of the amnion. The released $PGF_{2\alpha}$ synthesis will lead to preterm labour.[52]

During β-mimetic treatment of premature uterine activity AAC products theoretically can induce β-adrenoceptor desensitization. In particular, the cyclo-oxygenase products may interfere with the coupling of the adenylate-cyclase moiety, an early event which leads to β-receptor down-regulation.[53] This may help to understand the occurrence of relapses during prolonged exposure to β-agonists of tocolytic treatment for preterm labour.

Feto-placental circulation, pre-eclampsia

PG production by the feto-placental vessels is involved in controlling blood flow through this vascular bed. $PGF_{2\alpha}$ and PGE_2 contract the fetal vessels in the placenta, whereas PGI_2 relaxes them.[54]

The patency of the fetal ductus arteriosus is actively maintained by continuously produced PGs (PGE_1, PGE_2) providing a basis for pharmacologic manipulation of the ductus by continuous infusion of PGE_1 or PGE_2 in newborns with ductus-dependent congenital heart malformations.[55, 56]

Release of PGs into the fetal circulation may also elicit systemic effects within the fetus contributing to the low vascular resistance of the fetal circulation.[57]

In vitro perfused human cotyledons react to injection of angiotensin II into the fetal circulation by stimulated PGE and 6-oxo-$PGF_{1\alpha}$ (without TXB_2, and $PGF_{2\alpha}$) release into the fetal circulation without an effect on the maternal side.[57] Angiotensin II plays an important role

in the maintenance of uterine blood flow which is seen to decrease when conversion of angiotensin I to II is blocked by an inhibitor of the angiotensin-coverting enzyme, captopril.[57] Control of uterine blood flow may involve PGE_2 since angiotensin II increases the production of PGE_2 in the pregnant uterus.[58, 59] It has been proposed that angiotensin II stimulated release of PGE and 6-oxo-$PGF_{1\alpha}$ may serve to modulate the vaso-active acions of angiotensin II on the fetal vasculature.[57] During angiotensin II induced systemic vasoconstriction in near-term sheep, prostacyclin – a potent vasodilator – has a paradoxical effect in the placental circulation, i.e. it further constricts the placental vessels.[60]

In the pathomechanism of pregnancy-induced hypertension PGs certainly play a profound role.[61] It has been suggested that prostacyclin deficiency is a specific feature of pre-eclampsia.[62] Pre-eclampsia is characterized by increased vasoconstriction, frequently associated with increased platelet aggregation, reduced uteroplacental blood flow and intra-uterine growth retardation or premature delivery. During pre-eclamptic pregnancy, the placenta produces seven times more thromboxane than its opponent prostacyclin, therefore creating an imbalance.[63, 64]

PGs IN CERVICAL BIODYNAMICS AND TISSUE BIOCHEMISTRY

The longstanding view of the cervix playing only a passive role during human pregnancy has been successfully challenged by recent advancements in connective tissue biochemistry. From studies in pregnant sheep, where the cervix has been surgically separated from the corpus, it is evident that the cervix undergoes structural remodelling and softening after its separation from the influence of uterine contractions.[65]

Some years ago, several studies – claiming a direct PG effect on the cervix – faded into obscurity, because investigators thought that the dilatation during PG treatment was a byproduct of subclinical uterine contractions. It has been well established that PG analogues are capable of dilating the cervix in a matter of hours.[66]

Progress in this field has been speeded up by recent understanding of cervical biochemistry. The first claim that the cervix in the human subject is predominantly a fibrous tissue made up from collagen fibres and basic substance constituents – such as proteoglycans containing glycosaminoglycans (GAGs, previously known as acid mucopolysaccharides) connected to the protein core – surfaced not long ago. The

distal portion of the cervix contains only 6% muscular tissue (29% in the upper region).[67]

From studies by Danforth it became patently clear that cervical function and questions related to the cervical sphincter action should be answered in terms of connective tissue biochemistry instead of smooth muscle physiology, since the human cervix is a fibrous tissue covered by only a thin layer of smooth muscle.[68, 69]

The basic molecule of the cervical connective tissue is collagen (70% type 1 and 30% type 3).[70] The collagen microfibrils are interconnected by cross-links, forming larger fibres. Recent studies have demonstrated that this main extracellular constituent of the cervical tissue, the collagen, is peculiar in several respects. It is the only protein that undergoes several changes following translation of all the information stored in the mRNA.

In the human uterine cervix, there are such swift and voluminous changes in protein restructuring, that it seems possible that the expressional programme (DNA to RNA transcription changes) of the protein biosynthesis is dictated by local temporal signals. PGs with a reputation of local tissue hormones can not be ruled out from the activation process of collagenase or other enzyme genes which initiate the production of mRNA coding for cervical proteins during translation.

In the human non-pregnant cervix, it has been demonstrated that PGs have a marked effect on protein synthesis in the cervical slices. During the follicular phase both $PGF_{2\alpha}$ and PGE_2 decreased net synthesis of collagen and the opposite effect was found in the luteal phase.[71]

The cervix is undergoing a continuous remodelling process during gestation which starts in early pregnancy. This pregnancy-initiated remodelling ensures that mature collagen with many non-breakable cross-links (characteristic to non-pregnant women) starts to break down at the beginning of the pregnancy and will be replaced by extractable collagen. This implies that catabolism as well as synthesis of collagen is high during pregnancy, providing a total remodelling of the organ.[72] This remodelling, is nearly complete before the onset of labour.

The basic substance is a gel-like interstitial matrix, which is responsible for incorporating water, which – during mechanical dilatation – has nowhere to go. The collagen network and the matrix will determine the biochemical characteristics of the cervix.[73]

PGE_2 has been shown to regulate the cAMP level in the target cell. $PGF_{2\alpha}$ enhances the activity of hyaluronic acid synthetase within half an hour by enzymatic induction. Both mechanisms can be important in the induction of cervical ripening by PGs. They modulate the synthe-

sis of collagen, proteoglycans, hyaluronic acid and perhaps other connective tissue components.[72]

The work of Christensen and Bygdeman raised the possibility that the influence on the biochemistry of cervical tissue induced by PGE_2, and 9methylenePGE_2, is mediated via the endogenous AAC towards non-PG compounds.[74]

The prostacyclin synthesizing activity in the human ripening (at the time of delivery) cervix was found to be six times higher than in the non-pregnant cervix.[75] Explants of human non-pregnant cervix produce collagenolytic enzymes which degrade collagen over a 10-day period in culture. This is enhanced by the presence of very low concentrations of AA. It has been suggested that remodelling of the structure of the cervix depends upon AA or one of its cyclo-oxygenase or lipoxygenase derived products.[76]

PG-RELATED PHARMACOLOGY OF CERVICAL RIPENING

Spontaneous cervical ripening at term is recognized as softening, effacement resulting in remodelling of the cervix and dilatation. The ripeness of the cervix is an important clinical indication of the nearing to the end of gestation. If the cervix remains long, firm and closed, two of the possible clinical interventions, labour induction by oxytocin or caesarean section are still controversial, since the first possibility forecasts a protracted labour and the second might mean possibly unavoidable major maternal surgery.

Now prostaglandins offer fresh hope by providing a realistic new possibility through combination of intracervical PG pre-induction ripening and waiting for a limited period of time, then inducing labour by conventional means. This approach is also very promising in managing non-operatively and successfully one of the greatest enigmas of obstetrics, the premature rupture of membranes (PROM) in the case of the unfavourable cervix.

It is well documented that the cervix is capable of producing both PGE_2 and $PGF_{2\alpha}$. Ellwood et al. studied the production of PGs by the perfused pregnant human cervix. PGE, PGF, 13, 14dihydro15keto-$PGF_{2\alpha}$ and 6keto$PGF_{1\alpha}$ were produced at rates approximately 1.5-4 ng/g dry weight/min while TXB_2 production was virtually undetectable.[77]

In a controlled study, 87.5% of the patients receiving intracervically PGE_2 3 or 5 mg in gel experienced uterine contractions, which poses the danger of *unmonitored labour in high-risk patients* during the night before induction.[78] The logical requirement that cervix ripening under the influence of a PG preparation should precede the development of uterine contractions seems to be fulfilled by other studies where only

37% of the gel-treated patients experienced labour prior to receiving oxytocin.[79] Pharmacologically induced ripening mostly occurs over a relatively short time-period.[80]

Even $PGF_{2\alpha}$ can be successfully used to prime the cervix prior to therapeutic interruption of pregnancy, when 5 mg $PGF_{2\alpha}$ is applied intracervically in 5% Tylose gel resulting in dilatation up to Hegar 8 in 99 out of 100 patients in their seventh to 12th week of gestation.[81]

However, the use of $PGF_{2\alpha}$ is somewhat contradictory to available data, since earlier studies revealed that PGE_2 occurred earlier and was followed by a surge of $PGF_{2\alpha}$ during the course of labour, suggesting that PGE_2 might be more intimately involved in the subtle changes during the month-long prelabour preparation of the corpus and the cervix.[82, 83]

Another reason why most studies favoured the use of PGE_2 is the fact that $PGF_{2\alpha}$ exerts a stimulatory action on the sparse cervical muscle fibres, in contrast to the relaxing effect of PGE_2.[84-86] Further support for the priority of PGE_2 in the cervical ripening process came from a clinical study where β-mimetic drugs were administered orally 30 minutes before endocervical PGE_2 application to suppress undesirable uterine contractions during the ripening process. This prevented the increase in uterine contractility, but cervical ripening proceeded at a similar rate to that in the controls. It was noted that patients with premature rupture of the membranes needed further treatment to induce cervical ripening although they had higher transient $PGF_{2\alpha}$ metabolite (13, 14dihydro15keto) levels indicating increased $PGF_{2\alpha}$ production. It was concluded that cervical ripening depends on PGE_2 and not $PGF_{2\alpha}$.[87]

Oral administration of PGE_2 is an effective, clinically established therapy for labour induction. The best results have been reported in parous women with a favourable cervix, combined with early artificial rupture of the membranes.[88, 89]

When intravenous oxytocin and vaginal PGE_2 gel was compared in women with unripe cervixes and PROM, both obstetrical and perinatal outcome of the E_2 gel proved to be superior for labour induction in term pregnant patients with premature rupture of the membranes.[90]

PRE-OPERATIVE CERVIX DILATATION/MYOMETRIAL MOTOR ACTIVATION BY PG ANALOGUES (SULPROSTONE) IN CLINICAL TRIALS AT THE DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, UNIVERSITY MEDICAL SCHOOL OF SZEGED, HUNGARY

'Fast PG abortions' – which prompted widespread enthusiasm at the beginning of the PG era – could do more harm than good to the

cervix by fast conversion of the refractory uterus into a reactive, motorically active organ, which suddenly starts to work against the unyielding, tight, long cervix, absolutely unprepared for effacement and dilatation. This controversy posed a real challenge to the medical profession to find ways for quick pharmacological evacuation of the uterus within a reasonable time (clinically acceptable if 90% of the cases were completed within 24 hours) without harming the structural integrity of the cervix.

The initial euphoria over the natural PGs used by invasive routes was followed by a period of dissatisfaction, in spite of the fact that induction-abortion time (IAT) was markedly reduced from the 31 hours of saline to 18 hours.[91] The transverse rupture of the posterior cervical wall was established as a typical complication of natural PG-induced abortions.[92]

Developing new PG analogues became an important pathway for full realization of therapeutic usefulnes of PGs. The search (using systemic structure-activity studies) for structurally modified analogues, which are more tissue selective and exhibit enhanced resistance to metabolic inactivation, led to the design of the PGE_2-derivate, sulprostone.[93] This new PGE_2 analogue could be administered through a non-invasive route (intramuscularly) and has very few gastro-intestinal (GI) side-effects as a sign of apparently enhanced tissue selectivity. Comparing its clinical effectiveness in the second trimester to the 15 me$F_{2\alpha}$ analogue following laminaria predilatation, the E_2-derivative proved to be superior: 75% of the cases aborted within 10 hours/14 hours with 15meF.

This combined semi-invasive treatment (laminaria plus sulprostone) is especially advantageous in primigravidae with a long, uneffaced, tight cervix.

IAT was further shortened from approximately 15 hours to around 11 hours if laminaria predilatation was followed by sulprostone (or 15me$F_{2\alpha}$) treatment. The GI side-effects were very few – as few as with saline when sulprostone was used. Their incidence was also somewhat lower in cases of 15me$F_{2\alpha}$ analogue which could be explained by the fact that laminaria, by reducing IAT, also reduced the necessary amount of PG.

PGE_2 is capable of influencing the collagen metabolism of the cervix leading to the loosening of the cross-links between collagen fibres.[94] Sulprostone might well possess this special effect.

In the first trimester a two-stage method was employed. The 15me$F_{2\alpha}$ meEster in a single dose as a vaginal suppository up to the 12th week induced sufficient dilatation permitting uterine evacuation, while any subsequent dilatation became easy.[95] In 90% of the cases 10 mm or more cervix dilatation was achieved.