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A Risk-Benefit Assessment of Oxytocics in Obstetric Practice

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Abstract

Substances that stimulate contractions of the myometrium have found wide applications in present day obstetrics. Above all, fully synthetic, uterus-selective prostaglandin analogues are used for preoperative priming of the cervix for termination of pregnancies in the first trimester as well as for the induction of abortions in the second trimester and have proved to have a much higher efficacy than oxytocin. Because of the pharmacological synergism of their cervix ripening and myometrium stimulating activities, the local use of natural prostaglandin E_2 preparations (used intracervically as a gel or vaginally as a gel or as a tablet) is unequivocally superior to use of oxytocin with its almost exclusive contraction stimulating activity for induction of labour, especially for women with an unripe cervix. In women with a ripe cervix, oxytocin and prostaglandins are equally

effective with oxytocin having the major advantage of its better controllability on continuous intravenous infusion (plasma elimination half-life of 10 minutes).

Over the past 50 years, the use of oxytocin and ergot alkaloids preparations as prophylaxis against postpartum atonia has led to a marked reduction in maternal deaths. The same is true to a major extent for therapy for uterine atonia where the intravenous infusion of dinoprost is an indispensable and life-saving procedure after the failure of systemic administration of oxytocin or ergot alkaloid preparations.

On the other hand, the administration of oxytocics can be accompanied by a wide range of adverse systemic and uterine effects and complications ranging from severe cardiovascular incidents with a fatal outcome through to the threat of uterine hyperstimulation with fetal asphyxia to uterine rupture. For these reasons, an adequate knowledge of the pharmacokinetics as well as the systemic and uterine activities and adverse effects of these substances is an essential prerequisite for every physician in evaluating differential indications for their use and adequate monitoring for mother and infant.

Of particular importance is the use of prostaglandins for cervical priming prior to termination of pregnancies in the first and second trimesters and the use of native prostaglandin and oxytocin for inducing delivery in cases of fetal deaths as well as vital infants. Both substances play a decisive role at the beginning of delivery. Cervical priming and induction of contractions would not be conceivable without prostaglandin and oxytocin. The pharmacological properties of the 2 substances can be used in different ways for the induction of delivery. Oxytocin, ergot alkaloids and prostaglandin are essential for the management of postpartum uterine atonia where their use often represents a decisive, life-saving intervention.

1. Prostaglandins

1.1 Structure

Naturally occurring prostaglandins are cyclic unsaturated C_{20} fatty acids (fig. 1). According to the substitution on the cyclopentane ring, they are divided into subgroups (prostaglandin A, B, C, etc.) Prostaglandins of the F group bear 2 hydroxy groups on the cyclopentane ring, those of the E group 1 keto and 1 hydroxy group.

1.2 Naturally Occurring Prostaglandins

1.2.1 Synthesis and Occurrence

Prostaglandins are not stored in tissue but are newly synthesised under the action of microsomal enzymes, for example cyclo-oxygenase, from the ubiquitous arachidonic acid as a response to a mechanical or bacterial stimulus. As locally acting hormones, prostaglandins influence numerous physiological processes.

Among the prostanoids formed, prostaglandin E_2 (dinoprostone), prostaglandin E_1 (alprostadil) and prostaglandin $F_{2\alpha}$ (dinoprost), which lead to myometrial contractions and cervical ripening, are of obstetric relevance (table I). It should be mentioned that the latter is merely the reduced form of prostaglandin E_2 and that a spontaneous conversion of prostaglandin E_2 to prostaglandin $F_{2\alpha}$ occurs *in vivo*.[1] Prostaglandins occur in all organs and tissue fluids and are also produced by all intrauterine tissues. During pregnancy the synthesis of prostaglandins in the amnion, chorion and placenta increases, thus leading to significantly elevated prostaglandin levels in the amniotic fluid and maternal blood.[2]

1.3 Semisynthetic and Fully Synthetic Prostaglandins

The short duration of action and the associated need for repeated administration as well as the high incidence of adverse effects on systemic adminis-

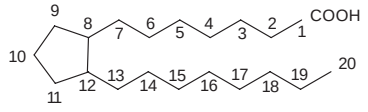


Fig. 1. The molecular skeleton of the prostaglandins.

tration of naturally occurring prostaglandins prompted the development of methylated prostaglandin derivatives. However, these prostaglandins of the so-called second generation (see table I) also exhibited a high incidence of adverse effects. The introduction of completely synthetic prostaglandin E_1 and prostaglandin E_2 analogues (see table I) with activities limited mainly to the uterus as the target organ finally resulted in a marked reduction of the substance-specific risks. The advantages of these compounds of the so-called third generation are the 10- to 30-fold higher potential to induce abortion, a 10-fold lower stimulating effect on intestinal musculature and a reduced influence on bronchial and vascular musculature. The elimination half-lives of synthetic prostaglandins are considerably longer (e.g. the elimination half-life for sulprostone is approximately 24 minutes) than those of the naturally occurring prostaglandins.

1.4 Activities of Prostaglandins

Because of their short elimination half-life times (the elimination half-life for dinoprost is 20 seconds), the duration of action of naturally occurring prostaglandin ranges from a few seconds to a few minutes. They are inactivated by prostaglandin-specific dehydrogenases present in the tissues. The principle sites of metabolism are the lungs, which are able to deactivate prostaglandin in the circulation to an extent of more than 90% after 1 or at the most 2 passages.[3]

Dinoprostone and dinoprost apparently cause an increase in the permeability of cell membranes for calcium and thus an elevated intracellular calcium ion level which causes contraction of the myometrium.[4] They also participate in the process of cervical ripening.[5] Their action is modulated by specific receptors on the membrane of the target cells.[6] Furthermore, prostaglandins induce the formation of gap junctions which improve the transmission of signals in the myometrium and promote the formation of oxytocin receptors in the uterus.[7]

Local administration of prostaglandin leads to a pronounced, multifocal loosening of connective tissue with 'active' fibroblasts which are characterised by a fine-grained loosening of the cytoplasm, enlarged mitochondria with a vacuolarised appearance, and an increased number of vesicular systems in the cell periphery (fig. 2).[8] At the same time, collagenase activity is doubled, elastase activity is increased by about 7-fold and a significant increase in the level of hyaluronate occurs; these factors play a major role in the softening of the cervix.[5,9] The collagenases mainly originate from neutrophilic granulocytes[10] which, similar to a normal birth at term, also accumulate in increasing

Table I. Prostaglandins and prostaglandin derivatives used in gynecology and obstetrics

Prostaglandins and prostaglandin derivatives	Characteristics
Prostaglandins	
First generation	Short half-life time, high substance-specific risk
Dinoprost [prostaglandin (PG) $F_{2\alpha}$]	
Dinoprostone (prostaglandin PGE_2)	
Derivatives	
Second generation	Longer half-life time
15-methyl-$PGF_{2\alpha}$ (tromethamol salt)	
15-methyl-$PGF_{2\alpha}$ methyl ester	
16,16-dimethyl-PGE_2	
Third generation	Low substance-specific risk
Gemeprost (16,16-dimethyl-trans-Δ^2-PGE_1 methyl ester)	
Misoprostol [(±)-methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate]	
Sulprostone (16-phenoxy-ω-tetranor-PGE_2 methylsulfonylamide)	
Meteneprost (9-deoxo-16,16-dimethyl-9-methylene-PGE_2)	

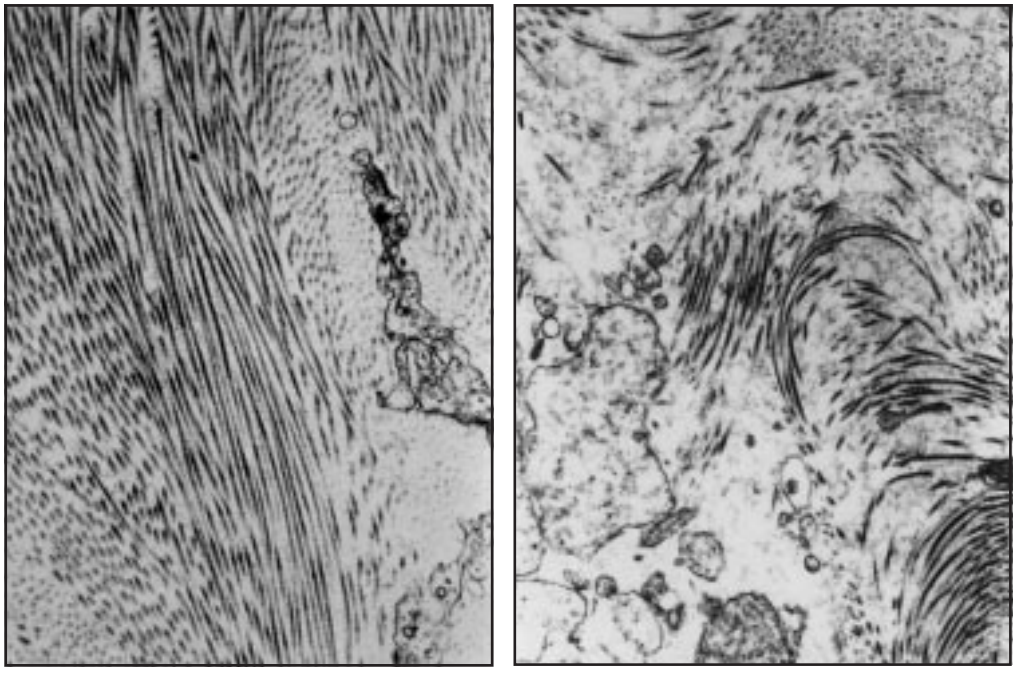


Fig. 2. Collagen fibres in the human cervix before (left) and after (right) administration of prostaglandin. Apart from relatively dense collagen fibre strands, features that are conspicuous after the administration of prostaglandin are: large, focal tissue loosening with widely spaced collagen fibres with, in part, disordered, vortex-like fibre courses.

amount in cervical stroma after administration of prostaglandin (fig. 3).[11]

Thus, on the one hand, prostaglandins lead to cervical ripening and, on the other hand, to the induction of labour. Both effects are exploited in therapy.

On the basis of knowledge about the distribution of prostaglandin receptors in the uterus, prostaglandins of the E group represent the substances of choice for drug-induced cervical ripening while dinoprost should no longer be employed to induce labour because of its low potential for cervical ripening and the risk of sustained contractions. The indication for the use of dinoprost comprises the treatment of postpartum atonia where its rapid and highly potent tonicising action on the uterus is exploited.

1.5 Systemic Effects of Prostaglandins

Systemic adverse effects of prostaglandins are mainly attributable to their influence on the smooth musculature of various organs (table II). The most prominent systemic adverse effects for the patient are gastrointestinal complaints such as nausea, vomiting and diarrhoea.

Differing effects of the prostaglandins on blood pressure are possible. For example, dinoprost causes an increase in vasotonia and thus an elevated blood pressure whereas dinoprostone leads to a decrease in vasotonia and a lowered blood pressure. Bronchoconstriction and increases in intraocular pressure are exclusively effects of dinoprost and occur as a result of the endogenous conversion of prostaglandin E_2 to prostaglandin $F_{2\alpha}$.[1,3] Prostaglandin-induced systemic effects do not usually constitute a risk for the healthy pregnant woman; however, contraindications should be excluded by a thorough case history and clinical examination (table II). Furthermore, prostaglandins should not be administered in women with acute infections (e.g. clinical chorioamnionitis,

clinical pronounced cervicitis) since, in cases of pathogenic colonisation of the birth canal, the biosynthesis of prostaglandin will be stimulated by the action of bacterial mediators[12] and an additional administration of exogenous prostaglandin may lead to dangerous hyperstimulations.

2. Use of Prostaglandins in Obstetrics

The uses of prostaglandins in obstetrics range from the initiation of an early abortion (< seventh week of pregnancy) and priming the cervix in the first trimester through to induction of abortions in disturbed and vital pregnancies in the second trimester, induction of labour in normal pregnancies and in instances of intrauterine fetal death in the third trimester, to the treatment of postpartum atonia (table III). A clinically less relevant indication is, for example, the treatment of ectopic pregnancies.[13]

2.1 Administration of Prostaglandins in the First Trimester

2.1.1 Menstrual Regulation

Although prostaglandins do not exhibit a direct action on the corpus luteum, they have been used with success for the induction of menstruation within the first 7 weeks of amenorrhoea. Here, the strong uterine contractions induced by prostaglandins result in detachment and expulsion of the freshly implanted blastocyte.[14] With repeated intramuscular injections of sulprostone 500µg, this method was successful in 87 to 98% of patients.[15] However, the required high doses of prostaglandin are accompanied by an unacceptable high incidence of adverse effects (e.g. nausea and vomiting in almost 25% of patients) with the result that this procedure has not become established for inducing abortion.

2.1.2 Termination of Pregnancy in the First Trimester

According to World Health Organization data, about 30 million abruptions in the first trimester are performed worldwide each year. In addition, through improved ultrasound diagnostic methods, physicians are frequently confronted by the problem of the early termination of disordered pregnancies (abortive ovum, missed abortion) with clinically still latent symptomatology. In these situations, the local administration of prostaglandin serves principally for the preoperative softening of the cervix prior to performance of curettage; this results in a reduced incidence of traumatic cervical lesions caused by mechanical dilation (from 2.5 to 0.5%), a reduced occurrence of uterine perforations (from 0.8 to 0.1%), and a lower rate of late complications such as cervical insufficiency, late abortion and premature birth in subsequent pregnancies.[16]

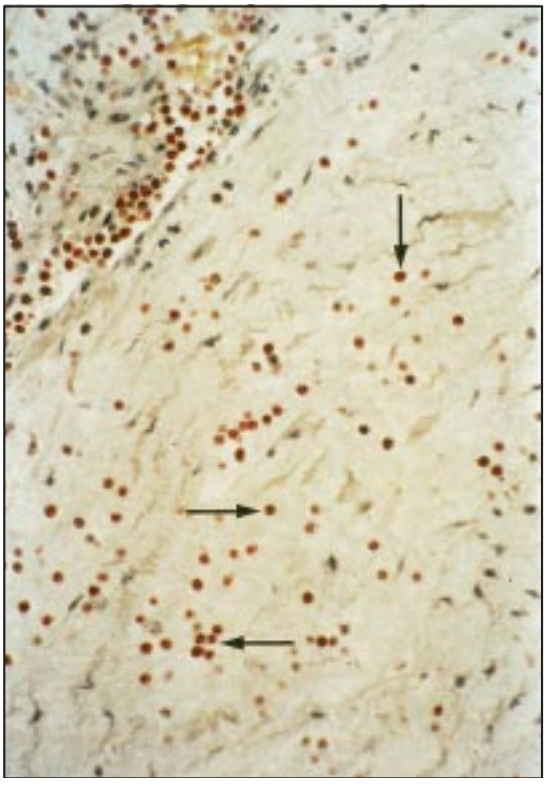


Fig. 3. Accumulation of neutrophilic granulocytes in a cervical capillary and in the cervical stroma (arrows) for a cervix width of more than 6cm.

In our opinion, the vaginal administration of gemeprost 1mg represents the current method of choice for preoperative priming of the cervix for termination of pregnancy in the first trimester.

Thus, 3 hours after vaginal administration of gemeprost 1mg, an opening of the cervical canal of on average 7 to 10mm can be detected. In 85% of patients, a dilation of the cervical canal of up to >8mm without resistance is observed. In placebo-controlled, double-blind investigations after tonometric objectivisation, free patencies (required force <2.95N) of the cervical canal of on average 6.4 to 7.4mm in unigravida and 9.4 to 9.8mm in multigravida were observed.[17-19] With this method uterine contraction pain occurred in 24 to 47.3% of the patients and gastrointestinal adverse effects were reported by up to 10% of the patients.[19-22] Since not only the priming effect but also the incidence of systemic adverse effects increases with time,[23] an interval 3 hours or less should pass between the administration of gemesprost vaginal suppositories and curettage. Intracervical administration of dinoprostone 500µg gel (administration interval: 6 to 8 hours) is an alternative method for preoperative cervical priming in the first trimester.

2.2 Abortion Induction in the Second Trimester

Today, administration of prostaglandin represents the method of choice for inducing abortion in the second trimester; administration can be by intravenous, oral, vaginal, intra- and extra-amniotic or intracervical routes. Because of their higher abortive action, longer elimination half-life lives and the lower incidence of undesired systemic effects, fully synthetic, uterus-selective prostaglandin analogues are preferred today over the naturally occurring compounds (table IV).

Table II. Adverse effects and contraindications for prostaglandins used in obstetrics

Adverse effect	Dinoprostone	Dinoprost	Contraindications
Heart rate	↑	↑	
Blood pressure	↓	↑	
Bronchoconstriction	↓↑	↑	Chronic obstructive pulmonary disease, asthma bronchiale
Body temperature	↑	↑	Thyreotoxicosis, infections
Tremor, hot flushes	↑	↑	
Nausea, vomiting, diarrhoea	↑	↑	Colitis ulcerosa, Crohn's disease
Intraocular pressure	↑	↑	Glaucoma

Table III. Uses of prostaglandins in obstetrics

Inducing an early abortion (menstrual induction, < seventh week of pregnancy)
Preoperative cervical dilation prior to termination of pregnancy in first trimester (abruptio, disturbed early pregnancy)
Abortion induction in second trimester in vital or disturbed pregnancies (e.g. missed abortion, hydatiforme mole)
Cervical ripening and induction of labour in third trimester (vital pregnancy and intrauterine fetal death)
Postpartum uterine tonicisation (prophylaxis and therapy for postpartum uterine atonia)
Treatment of tubal pregnancy

In practical use, the stage of the pregnancy and the distinction between termination of a vital or still pregnancy (missed abortion) should be taken into account when calculating the necessary for the doses to be used. Since the sensitivity of the myometrium towards prostaglandin increases with the approach of term,[14] lower doses of prostaglandin are required for abortion induction with increasing duration of the pregnancy. In addition, appreciably lower amounts of prostaglandin are sufficient to terminate the pregnancy in the case of a dead fetus than for a vital gravidity.[24]

Before the current standard administration procedures of prostaglandin for inducing abortions in the second trimester can be evaluated, the objectives of the process must be defined (table V). In every case, the severe physical and psychological stress for the patient in such a situation must be taken into account and adequate analgesic and antiemetic therapy must be ensured.

2.2.1 Prostaglandin E_2 Analogues

The intravenous administration of sulprostone (1 to 8.3 µg/min) leads within 24 hours to successful abortion in 67 to 96% of patients. The average induction-to-abortion interval is between 12 and 18 hours.[25] The advantages of the high efficacy and

good controllability of the method must be weighed against the stress for the patient of immobilisation with, in some patients the need for longer duration infusions, the high incidence of infusion phlebitis at the instillation site and the possible dys-synergy between labour and cervical ripening leading to the necessity for operative termination in some patients. In these patients, the strong labour activity in the first hours after starting the infusion often meets a considerable cervical resistance. After a latent time of varying length, a balloon-like distention of the cervix with subsequent, sudden expulsion of the fetus is observed. This means that the systemic administration of prostaglandin apparently results in cervical dilation through a primary induction of contractile activity and not through an induction of cervical ripening and dilation. Possible sequelae are, in addition to the long and for the patient stressful induction-to-abortion interval, unsuccessful attempts at induction and, above all, severe complications such as uterine rupture and cervical tears.[26]

Furthermore, the frequency of undesired systemic effects in up to 60% of patients has hindered the acceptance of this method.

The extra-amniotic administration of sulprostone (25 to 100μg) or of dinoprostone (100 to 200μg) in aqueous solution has not become widely accepted in clinical practice because of the tedious mode of administration and, in comparison to systemic administration of sulprostone, lower efficacy.

Table IV. Uses of prostaglandins for abortion induction in the second trimester

Administration mode	Preparation
Intravenous	Dinoprostone 0.25-5 μg/min
	Sulprostone 1-8.3 μg/min
Extra-amniotic	Dinoprostone 100-200μg
	Sulprostone 25-100μg
Vaginal	Gemeprost 1mg every 3 hours (up to 5 times)
	Misoprostol 200μg (2 × 100μg) at 12-hourly intervals

Table V. Objectives of abortion induction in the second trimester

Short administration-to-abortion interval
Avoidance of cervical and uterine lesions
Avoidance of failed abortion inductions with the necessity for surgical interventions to terminate the pregnancy
Low rate of systemic adverse effects
As complete as possible expulsion of fetus and placenta

The intramuscular administration form of sulprostone 500μg was withdrawn by the manufacturer in April 1992. This action was based on the occurrence worldwide of severe drug reactions in 23 women where pulmonary oedema, heart attacks, bradycardia, sudden blood pressure losses, shock, and death (n = 4) were linked with intramuscular administration of sulprostone. However, most of these women had other medical problems prior to this therapy. It is possible that short term high drug concentrations with consecutive vasospasms played a part in the causal pathogenesis.

2.2.2 Prostaglandin E_1 Analogues

After administration of a gemeprost 1mg vaginal suppository the principle action in the initial phase is that of cervical ripening followed, on average 2.6 to 3.9 hours after administration, by uterine contractions.[27,28]

A clinically detectable effect on cervical ripening can be expected after 3 to 4 hours in 51 to 64% and after 6 hours in 82% of patients.[23,28]

For induction of abortions in the second trimester, vaginal administration of gemeprost at 3 to 6 hour intervals up to a total of 5 suppositories per 24 hours is recommended; 9 hours later (i.e. 24 hours after the first administration) a second therapy cycle may be commenced.

In nulliparous women and abruptions between the 18th and 22nd weeks of pregnancy, a single administration of gemeprost leads to a successful induction of abortion in 58.9% of patients.[29] The abortion rate over 24 hours for this method is between 81 and 90%.[24,27,30] The average induction-to-abortion interval is reported to be 12.9 to 15.9 hours,[30,31] with an average of 3 to 4 administrations being needed.[24] If the pregnancy is not ter-

Table VI. Use of gemeprost[a] 1mg vaginal suppositories for abortion induction in the second trimester (from Winkler et al.,[32] with permission)

Abortion rate in the first 24 hours	81-88%[b]
Average induction-to-abortion interval	12.9-15.9h
Average number of administrations	3-4
Failure rate after a maximum of 10 administrations	4%[b]
Complete abortions	24-48%[b]
Pain requiring analgesics	68-80%[b]
Gastrointestinal complaints	14-27%[b]

a Gemeprost was given every 3 hours for up to 5 administration per treatment cycle.

b Percentage of patients treated.

minated after 5 administrations of gemeprost, a cycle of a further 5 suppositories can be started and will lead to a success rate of 96%. In about 4% of patients additional oxytocin or sulprostone infusions will be needed to terminate the pregnancy[30,33] (table VI).

The incidence of pain requiring analgesics was 68 to 80%, that of gastrointestinal complaints between 14 and 27% for this method. Complete abortions were achieved in 24 to 48% of the patients; cervical lesions were observed in about 1%.[30] Haemorrhages requiring transfusion are rare with this therapy (0 to 1%) on account of the strong myometrium-stimulating action of prostaglandins.

After positive results had been obtained with the use of misoprostol, another synthetic prostaglandin E_1 analogue (table I), for inducing abortion in the first trimester,[34,35] this prostaglandin has also been used in the past few years for inducing abortion in the second trimester[36] and for the induction of birth in the third trimester[37,38] (see section 2.3.2) using both oral and vaginal routes of administration.

Upon oral administration, misoprostol is rapidly resorbed so that the maximum plasma concentrations of the biologically active metabolite (misoprostolic acid) are reached in less than 30 minutes.[39,40] No pharmacokinetic data are as yet available for the vaginal route of administration.

Undesired accompanying effects are very rare. Misoprostol has no significant effect on blood pressure up to an oral dose of 800µg.[41]

With vaginal administration of misoprostol 200µg every 12 hours, the abortion rate within the first 24 hours was 89%. In these women, the average induction-to-abortion interval was 12 hours. Complete abortion occurred in 43% of patients.[36]

2.2.3 Comparison of Methods

In a comparative investigation of intramuscular injection of sulprostone 500µg (table VII) and vaginal administration of gemeprost 1mg, the 2 treatments were found to be equally effective; however, systemic adverse effects after sulprostone (40%) were markedly more frequent than after gemeprost (22.5%).[31]

In comparison to the double or triple cervical priming by means of dinoprostone 3mg vaginal tablets and subsequent intravenous infusion of sulprostone 500µg, serial administration of gemeprost 1mg proved to be more effective (abortion rates in 24 hours were 79% for gemeprost and 62% for dinoprostone plus sulprostone). Gastrointestinal adverse effects in the gemeprost group were not significantly more frequent (33% compared with 18% after combined therapy) while the need for analgesics was the same.[42]

After administration of gemeprost alone, the induction-to-abortion interval was significantly shorter than after combined therapy.[43] Complications (e.g. local thrombophlebitis, bronchospasm) did not occur after serial administration of gemeprost alone, in contrast to combinations of local and systemic administration of prostaglandin (4 of 38 women).[43]

The comparison of combined use of dinoprostone 500µg gel intracervically plus intravenous sulprostone 1 to 8.3 µg/min with the serial administration of gemeprost 1mg revealed an unequivocal superiority of gemeprost with regard to efficacy; the abortion rate over 24 hours with gemeprost was 75%, which is significantly higher than the rate of 22% in the group receiving dinoprostone. The need for analgesics was about the same in both groups [on average about 90mg pethidine (meperidine) was required after gemeprost and 145mg after dinoprostone].[44]

Table VII. Comparison of the vaginal administration of gemeprost (every 3 to 6 hours) with other procedures for prostaglandin-induced abortion in second trimester

Alternative procedure	Author	Results
IM sulprostone 500μg	Di Lieto et al.[31]	Abortion/24h: 82.5 *vs* 85% Adverse effects: 22.5 *vs* 40%
Dinoprostone 2-3 × 3mg vaginal tablet + IV sulprostone 1-8.3 μg/min	Ranta et al.[42]	Abortion/24h: 79 *vs* 62%
Dinoprostone 3mg vaginal tablet + IV sulprostone 1-8.3 μg/min	Müller et al.[43]	Abortion/24h: 52 *vs* 13% Induction-to-abortion interval: 23 *vs* 33h
Intracervical dinoprostone gel 500μg + IV sulprostone 1-8.3 μg/min	Mink et al.[44]	Abortion/24h: 75 *vs* 22%
Intracervical dinoprostone gel 500μg every 4h	Kjolhede et al.[45]	Abortion/48h: 95 *vs* 75% No difference in rate of adverse effects

IM = intramuscular; **IV** = intravenous.

As shown in a Scandinavian randomised study,[45] the administration of gemeprost 1mg is also clearly superior to the repeated intracervical administration of dinoprostone 500μg gel (success rate of 95 *vs* 75% after 48 hours). No differences were observed with regard to the average need for pethidine (125 *vs* 150mg) and the incidence of gastrointestinal adverse effects.

On the whole, therefore, all previous comparative studies on abortion induction in the second trimester demonstrate a higher efficacy and a similar or lower incidence of undesired adverse effects for the use of gemeprost than for the other methods.

Vaginal administration of misoprostol 200μg at 12-hour intervals for abortion induction in the second trimester exhibits the same efficiency as the 3-hourly vaginal administration of dinoprostone 20mg vaginal suppositories. Adverse effects such as fever (11 *vs* 63%), nausea (4 *vs* 33%), and diarrhoea (4 *vs* 33%) after misoprostol were significantly less frequent and the costs were significantly lower ($US00.97 *vs* $US315.30) [1994 values].[36]

Although severe adverse effects of the local administration of dinoprostone are extremely rare, life-threatening complications (e.g. myocardial infarction, amniotic fluid embolism) have been described in individuals, especially in medically stressed women (e.g. patients with chronic hypertension) and with the use of relatively high doses (i.e. dinoprostone 20mg as vaginal suppository).[46,47]

Thus, in our opinion, the vaginal administration of the prostaglandin E_1 analogue gemeprost is currently the method of choice for inducing abortion in the second trimester.

2.3 Labour Induction in the Third Trimester

The principle objective of the obstetrician for inducing labour artificially is to achieve a better perinatal result for both mother and infant, after consideration of the underlying pathology and the possible drug-induced adverse effects, than would result from a wait-and-see policy. In other words, the induction of labour must have recognisable benefits for both mother and infant. Accordingly, clear indications (table VIII) and a clear impression as to the point in time at which labour should be induced in consideration of the urgency of the indications are essential.[48]

A limiting factor for every birth induction is the state of ripeness of the uterine cervix which can be objectivised by means of the Bishop score[49] (table IX). In women with a Bishop score of >8, an intravenous oxytocin infusion in combination with

Table VIII. Indications for induction of labour in the third trimester[48]

Exceeding term by ≥10 days
Premature rupture of membranes
Pathological cardiotocogram
Pregnancy-induced hypertension
Chronic placental insufficiency with intrauterine growth retardation of ≥2 weeks (normal non–stress test)
Diabetes mellitus
Rhesus incompatibility

Table IX. Bishop score for cervical evaluation before induction of labour[49]

Cervical status	Score			
	0	1	2	3
Dilation (cm)	0	1-2	3-4	>5
Effacement (%)	0-30	40-50	60-70	80
Station	–3	–2	–1/0	+1 or +2
Cervical consistency	Firm	Medium	Soft	
Position	Posterior	Mid	Anterior	

amniotomy still retains its value as an effective and well controllable method for the induction of labour (see section 4.1).

However, in women with an unripe cervix (Bishop score <5), this method is characterised by unsuccessful labour induction in up to 60% of patients and the necessity for a caesarean section in 30% of patients.[50]

Thus, the unripe cervix constitutes the domain of prostaglandin administration. Prostaglandin for induction of labour can be given orally, intravenously, extra-amniotically, intracervically, or vaginally. Because of their rapid metabolisation and the necessity for frequent repeat doses, oral administration of prostaglandins for inducing labour is no longer practised.[51]

In spite of the good controllability, intravenous infusions of dinoprost or dinoprostone for inducing birth of a vital fetus are no longer recommended on account of the disadvantages of immobilisation of the patient, the danger of infusion phlebitis (4 to 10%), and a dose-dependent, varyingly high frequency of systemic and, above all, gastrointestinal adverse effects (22 to 54%).

Extra-amniotic instillation of prostaglandin via a catheter is often reported by the patient to be unpleasant, favours ascending infections and is accompanied by the risk of prostaglandin resorption that is not constant with time.[52]

Because of the mentioned disadvantages, local or locosystemic forms of administration, e.g. intracervical or vaginal, are preferred today (table X). This is also valid for treatment of intrauterine fetal death.

Table X. Administration routes of prostaglandins for inducing birth

Active principle	Route of administration	Dosage
Dinoprostone	Intravenous	0.2-1.5 μg/min
Dinoprostone	Intracervical	0.5mg (possible repeat after 6h)
Dinoprostone	Vaginal	3mg (possible repeat after 6h)
Dinoprostone	Vaginal	1-2mg (possible repeat after 6h)
Alprostadil	Vaginal	25-50μg (possible repeat after 2-4h)

2.3.1 Dinoprostone in Labour Induction in the Third Trimester

Intracervical Administration

In women with an unripe cervix (Bishop score <5) intracervical administration of dinoprostone 0.5mg, dissolved in 2 to 3ml of gel (triacetin or polydextrin as carrier base) is currently the most frequently used method to induce labour. In patients where there is an inadequate effect (e.g. improvement of the Bishop score of <3 points), the treatment should be repeated after 6 to 8 hours. In over 80% of the patients, this method leads to an increase in the Bishop score by at least 3 points within this period of time. Depending on the parity of the patient and the degree of ripeness of the cervix before commencement of treatment, a vaginal delivery can be expected within 24 hours in 64 to 86% of patients.[53]

A meta-analysis of prospective studies[54] clearly showed the advantages of intracervical administration of prostaglandin in comparison with oxytocin: with low Bishop scores (<5) vaginal delivery followed within the first 24 hours after start of labour induction in only 36% of the patients treated with oxytocin as compared with 64% of patients treated with intracervical dinoprostone gel. The frequency of transvaginal surgical interventions after dinoprostone was also lower. In women with premature amniorrhexis, a caesarean

section frequency of 11.7% was observed for the sole use of oxytocin as compared with only 4% with intracervical dinoprostone administration.[55]

According to a more recent Canadian multicentre study, labour induction by up to 3 doses of a dinoprostone 0.5mg intracervical gel in uncomplicated pregnancies after completion of the 41st week of pregnancy had no advantages with regard to perinatal mortality and neonatal morbidity in comparison to a group managed by a wait-and-see policy. However, the treatment costs for the latter group were significantly higher.[56]

Monitoring and Adverse Effects

The galenics-dependent liberation of prostaglandin from the carrier medium is decisive for risk evaluation. A uterine reaction can occur within 20 minutes after administration because of the rapid release of prostaglandin from the gel. The spectrum of uterine reactions ranges from irregular contractions, which can develop into a regular labour activity after 2 hours, through tachy-frequent contraction patterns with an increase in uterine basal tone, to a rapid elevation of intrauterine pressure and the occurrence of sustained contractions.[57] Hence, cardiotocographic monitoring should be started immediately after administration of the gel and should be continued for a period of at least 2 hours.

When repeat administration of the gel is necessary because of an absent or insufficient cervical ripening response, adverse uterine effects increase significantly. This also applies when the administration interval is reduced to less than 6 hours.

Overall, uterine hyperstimulations (polysystoles and sustained contractions) occur in up to 13.9% of patients receiving intracervical dinoprostone gel.[44,58-60] In this situation, immediate emergency tocolysis (e.g. intravenous fenoterol 20μg) with subsequent a fenoterol infusion (2 to 4 μg/min) can prevent intrauterine hypoxia in the fetus. The frequency of pathological fetal heart rate patterns in connection with prostaglandin-induced hyperstimulation is less than 1%, emergency caesarean sections for this indication are thus extremely rare (less than 0.5%).[61]

Maternal adverse effects are also rare; however, gastrointestinal complaints must be expected in up to 5% of patients.[62] More severe complications following intracervical administration of dinoprostone occur only in a few women. The risk of uterine rupture may occur when an excessively high dose of dinoprostone (e.g. 1.5 to 6mg) has been administered intracervically or the induced labour activity has been augmented too soon (<6 hours) and with an excessively high dose of oxytocin.[63-65] Uterine rupture after intracervical use of dinoprostone gel has only been reported in isolated instances.[64,66]

Vaginal Administration: Tablets

In women with of a ripe cervix (Bishop score >5), depending on the patient's parity and the degree of ripeness of the cervix prior to treatment, administration of a dinoprostone 3mg vaginal tablet can induce vaginal delivery within 24 hours in 80 to 96% of patients.[67,68] In women with an unripe cervix (Bishop score <5) treatment with a dinoprostone vaginal tablet is inferior to intracervical gel administration.[54] The frequency of a vaginal delivery within 24 hours of commencement of therapy with vaginal tablets is between 55 and 60% as compared with 64 to 86% with intracervical gel. Here a significant increase in fetal acidosis morbidity (up to 22%) in comparison with administration in women with a ripe cervix (9%) must be expected.[59,69]

With the use of dinoprostone 3mg vaginal tablets, 6-fold higher doses of the active principle are required in comparison with intracervically administered dinoprostone gel – a fact that can be explained by the delayed and target-distant liberation of the active substance.[70-72] This is a locosystemic form of administration in which, depending on the vaginal environment and cervical secretion, an incalculable amount of active substance can enter the circulation through vaginal resorption in an unpredictable period of time. Elevated plasma concentrations of dinoprostone metabolites after intracervical administration of dinoprostone 0.5mg as gel or intravaginal administration of dinoprostone 3mg as tablet have not been observed.[73]

The start of the effect can only be estimated with difficulty: more or less regular contractions only occur after 3 to 4 hours and latency times between 8 and 12 hours are not uncommon. In the latter instances, the start of labour activity is often sudden and strong. Thus, women should be carefully monitored in the delivery room.

Monitoring and Adverse Effects of Tablets

Because of the latency period, cardiotocographic monitoring should commence 2 hours after administration and be continued intermittently depending on the labour activity. Fetal acidosis (pH <7.20) in a patient with an uncomplicated pregnancy exceeding term and a ripe cervix (Bishop score >4) after induction of labour with dinoprostone vaginal tablets is not more frequent than in control women with spontaneous onset of labour (2.5 *vs* 1.3%).[67]

In a risk group, fetal acidosis was observed after induction with dinoprostone vaginal tablets only in 2.8% of patients (there was no instance of an umbilical artery pH value of <7.10) and the 1- or 5-minute Apgar score was <7 in only 5.5 or 4%, respectively, of patients.

Maternal adverse effects, consisting mainly of gastrointestinal complaints, may occur in 1 to 4% of the patients.[59]

A shortening of the administration interval (<6 hours) as well as an increase in dose or intracervical administration in the case of a wrongly assumed insufficient effect of the vaginal table are strongly discouraged since they may lead to the induction of dangerous hyperstimulation of the uterus with the threat of fetal hypoxia.[16,65]

With correct usage, the incidence of hyperstimulation is between 1 and 3%.[69] In women where hyperstimulation occurs, the remains of the tablet should immediately be removed from the vagina and intravenous tocolysis should be initiated.

As a result of the poor controllability both after intracervical administration of prostaglandin gel and after administration of dinoprostone vaginal tablets uterine hyperstimulations are more difficult to control than those occurring with intravenous administration of oxytocin.

The problems of both methods of dinoprostone administration are listed in table XI.

Vaginal Administration: Gel

In the light of these problems, administration of a dinoprostone vaginal gel (dinoprostone 1 or 2mg in 2.5ml triacetin gel) represents an alternative that can be recommended for a Bishop score ≥4. From the pharmacokinetic point of view there are similarities between the vaginal and intracervical routes of administration of the gel: the prostaglandin E metabolite concentrations in plasma increase rapidly within 20 to 30 minutes and remain constantly high for more than 4 hours.[75] In contrast to dinoprostone 3mg vaginal tablets, the maximum prostaglandin E metabolite concentration correlates with the cervical ripening effect after administration of vaginal dinoprostone gel.[74]

In nulliparous women with an unripe cervix a single administration of a vaginal gel containing dinoprostone 2mg can lead to contractions and birth in 63% of patients with an average induction-to-birth interval of 13 hours and a caesarean section frequency of 7%.[76]

Table XI. Problems with the use of dinoprostone intracervical gel and vaginal tablets

Intracervical gel	Vaginal tablets
Tedious and uncomfortable mode of administration	Incalculable liberation of active substance → incalculable length of latency period, short active phase, problems in monitoring
Technical difficulties in placing the gel: in part intravaginal administration	
Uncertain placement in dependence on take-up capacity of cervical canal (in the unripe cervix about 0.6ml[74]):	Poor controllability → risk of uterine hyperstimulation
flow off of gel into vagina → unsatisfactory efficiency	
extra-amniotic instillation → uterine hyperstimulation	
Artificial rupture of membranes	

With an unripe cervix and a dose of 2.5mg, a better priming effect and regular contractions are achieved significantly more frequently than after intracervical administration of dinoprostone 0.5mg gel.[77] In addition, there are appreciable advantages with regard to induction-to-birth interval and caesarean section frequency in comparison with dinoprostone vaginal tablets.[78] Of relevance for patient monitoring is the observation that regular contractions can take place as early as 20 minutes after administration of the gel.[77] At Bishop scores of 4 to 7, administration of dinoprostone 1mg vaginal gel did not produce any clinically significant differences to dinoprostone vaginal tablets; however, use of the dinoprostone vaginal gels did result in shorter induction-to-birth intervals (9 *vs* 10.4 hours).[79]

Monitoring and Adverse Effects: Gel

Since bioavailability and liberation of dinoprostone with the vaginal gel are comparable with those of intracervical administration[74] and contractions often start as soon as 20 minutes after administration,[77] cardiotocographic monitoring should be started immediately following vaginal administration of the dinoprostone gel. With regard to monitoring modalities, the better definable start of action of the dinoprostone vaginal gels offers a higher safety in comparison with dinoprostone vaginal tablets.

After use of dinoprostone 2.5mg vaginal gel, uterine hyperstimulations are about 6 times more frequent (2.9%) than with intracervical administration of 0.5mg dinoprostone gel (0.5%), probably because of the partial systemic effects.[58] The frequency of gastrointestinal complaints is about the same (4.2 *vs* 3.8%).[77] On the other hand, hyperstimulations after administration of the vaginal gel are considerably less frequent than after use of dinoprostone 3mg vaginal tablets.

Of comparable efficiency to the above-mentioned dinoprostone formulations are pessaries containing dinoprostone carried in a polymer for vaginal administration which give up the dinoprostone continuously.[80,81] By this means a slower increase in the concentration of prostaglandin E metabolites in the peripheral circulation is achieved than with, for example, dinoprostone vaginal gel;[82,83] this should lead to a lower incidence of uterine hyperactivity. The pessary carries a thread which permits its rapid removal from the vagina in case of hyperstimulation. In spite of these apparent advantages, uterine hyperstimulations (10%) and problems with removal of the pessary from the vagina have been reported.[84,85]

Use after Previous Caesarean Section

Because of the risk of rupture of the uterus, a history of previous caesarean section is a relative contradiction or at least a limitation for the use of prostaglandins to induce labour. On the other hand, it is just this situation, especially when the cervix is unripe, that represents a special problem since contractions of the uterus against the resistance of a rigid cervix increase the risk of uterine rupture. The cervical resistance can be reduced by the local administration of prostaglandin and thus risk of the rupture is lowered. In contrast, administration of oxytocin with an unripe cervix carries the danger of overdosage with subsequent uterine hyperstimulations and, therefore, considerably reduced chances of a successful vaginal delivery.[59,86]

Induction of labour by prostaglandin or other oxytocic agents should not be employed after a longitudinal uterine incision, instead a caesarean section should be performed, otherwise a uterine rupture may be expected in up to 20% of these patients.[87] In controlled studies of women who had previously undergone a caesarean section via an isthmic transverse incision, uterine ruptures were only observed in a few women after induction of labour by: intracervical administration of dinoprostone (0 out of 30 patients[86] to 0 out of 161 patients[87]); vaginal administration of dinoprostone 2.5 or 5mg in a viscous cellulose gel or dinoprostone 2.5mg as a glyceride pessary (0 out of 143 patients[88]); after intracervical or intravaginal administration of dinoprostone, depending on cervical status (0 out of 60 patients[89]); or by means of oxytocin infusion (0 out of 21 patients[90]). Thus, the occurrence of uterine rupture is not more frequent than after spontaneous onset

of labour (less than 1%) or augmentation of labour with oxytocin (0.4%).[91]

However, induction of labour should only be performed under continuous cardiotocographic control and intensive monitoring of the patient with all prerequisites for an immediate caesarean section. Hyperstimulations of the uterus must be avoided and means for emergency tocolysis must be at hand (e.g. fenoterol 20μg).

Use In Grand Multiparas

Only limited experience is available concerning induction of labour in women who are grand multiparas (para of 5 and more) who are common in Third World countries. The problems in induction of labour in these women are considerable, and complications may include uterine rupture, precipitate labour and postpartum haemorrhage. In a prospective controlled study[92] in 150 grand multipara women at term with induction of labour by intracervical application of a 0.5mg dinoprostone tablet, labour was successfully induced in 98% of the women, of whom 96.5% delivered vaginally. In comparison with control participants who went into labour spontaneously, the mean duration of the active phase of labour as well as of the second and third stage was shorter in the study group. Operative deliveries were 2 to 3 times more frequent among control participants, as were complications in the second and third stages (for example postpartum haemorrhage).

2.3.2 Prostaglandin E_1 for Labour Induction in the Third Trimester

In women with an unripe cervix (Bishop score <5) in the third trimester, vaginal administration of misoprostol at a dose of 25μg (a quarter of a 100μg tablet placed in the posterior fundus of the vagina) at 3-hourly intervals produces a similarly good induction as observed for the intracervical administration of dinoprostone 0.5mg.[93] In contrast to a previous study[94] using misoprostol 50μg every 3 hours, complications such as tachysystoles (17.4%) and meconium-stained amniotic fluid (17.4%) were, with the reduced dose of misoprostol, not significantly more frequent than in the dinoprostone group (10.2 and 13.9%). Sanchez-Ramos et al.[95] observed a significantly shortened induction-to-birth interval (11 hours as compared with 18 hours) with an intravaginal dose of misoprostol 50μg, and a higher incidence of uterine tachysystoles (34.4%), in comparison to a group undergoing induction with dinoprostone and oxytocin (13.8%); however, the hyperstimulations after misoprostol were not more frequent (10.9% with misoprostol and 4.6% with oxytocin), while the rates of caesarean sections were equally high (21.9% with misoprostol and 21.5% with oxytocin).

These results were confirmed in a meta-analysis of 8 randomised, controlled studies performed over the period of 1993 to 1995 in which the courses of birth and the babies' progress after vaginal administration of misoprostol 25 to 100μg were compared with the results of other methods of birth induction (controls). The frequency of pathological 5-minute Apgar values (misoprostol recipients: 0 to 2.6%, control individuals: 0 to 1.5%) as well as the number of babies requiring neonatal intensive care (misoprostol recipients: 0 to 19.1%, control individuals: 0 to 16.8%) were similar in both groups.[38] A recently published meta-analysis[96] of more than 20 randomised trials showed that misoprostol was more effective than oxytocin for labour induction. Uterine hyperstimulation was more common both with and without associated fetal heart rate changes. There were no statistically significant differences in perinatal and maternal outcomes. In comparison to dinoprostone, the failure to achieve vaginal delivery within 24 hours with misoprostol was reduced. Uterine hyperstimulation without fetal heart rate changes was more common with misoprostol. Overall, there was a reduction in instrumental deliveries with misoprostol.

In all studies the costs of the misoprostol treatment were only a fraction (1/200 to 1/300) of those for the use of dinoprostone.[36,93]

2.4 Use of Prostaglandins in the Postpartum Period

2.4.1 Dinoprost in Postpartum Uterine Atonia

Over 75% of all postpartum haemorrhages are caused by uterine atonia. If, on administration of

oxytocin and ergot alkaloids, an immediate uterine tonicisation is not successful after expression and curettage, the use of prostaglandins is indicated (rapid infusion of dinoprost 5µg in 1L of Ringer's solution). With this dilution, a maximal dose of 150 µg/min[97] will not be exceeded even with very rapid instillation; no prostaglandin-induced bronchoconstrictions have as yet been observed.[98] An alternative is the intravenous administration of sulprostone (500µg in 0.25L of Ringer's solution, 8 to 16 µg/min for about 2 hours).[99]

In therapy-resistant patients, a dinoprost tamponade should be used (the tamponade should be soaked with a solution of dinoprost 5mg in 19ml distilled water).[100]

Another method ensuring a rapid and reliable start of action is the intramyometrial injection of dinoprost, by which a solution of dinoprost 0.2 to 2mg (or sulprostone 250µg) is transabdominally placed in the anterior wall of the uterus. During caesarean section, administration in the fundus of the uterus can be visually controlled. However, this method has the disadvantages of an incalculable resorption of prostaglandin and the possibility of an accidental intravasal injection with the risk of severe complications[101-103] and dinoprost is not used intravenously or intracavitary in all countries (i.e. the US). Our therapeutic procedure in Germany for postpartum uterine atonia is summarised in figure 4.

On the whole, the success rate for the use of prostaglandin as a treatment for postpartum atonia is between 85 and 98%.[101,104] Failure of therapy can at least in part be attributed to the delayed administration of prostaglandin after coagulation disorders have already occurred or to a manifest uterine infection.[105] The frequency of systemic adverse effects is 6 to 15% and thus of minor clinical significance in the light of the high maternal risks.

2.4.2 Prostaglandin E_1 in the Postpartum Period

The routine oral administration of misoprostol in the postpartum period has been the subject of some recent discussion not only for cost reasons but also because of the simple storage and transport

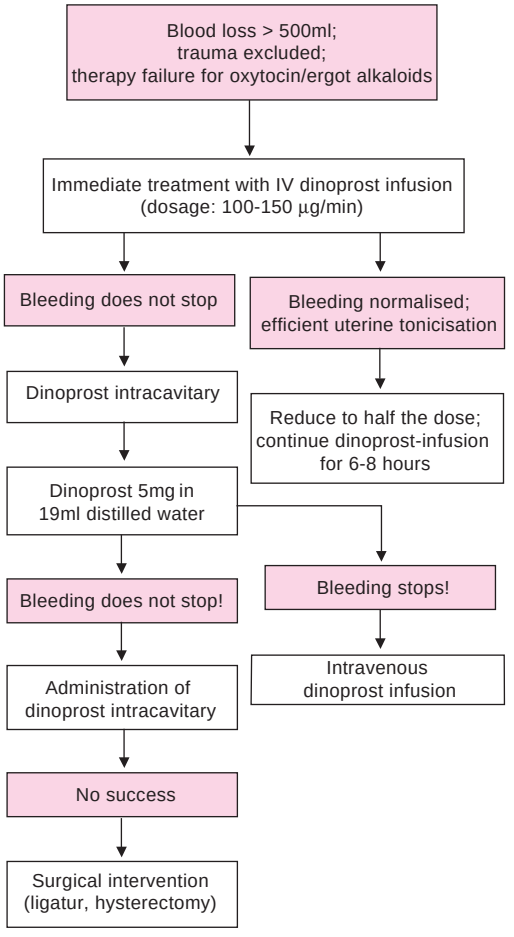


Fig. 4. Practical procedure for the management of atonic postpartum haemorrhage.[100] **IV** = intravenous.

of the substance (in contrast, oxytocin and dinoprost require cooling and have a limited storage life[106]). In a comparative study, no differences with regard to the frequency of postpartum bleeding, the additional need for a uterine tonic, and the duration of the placental period were found between patients receiving a single administration of misoprostol 600µg given orally and those treated with oxytocin 5IU and methylergometrine 0.5mg.[107]

In summary, it can be stated that the use of prostaglandin is today is a firmly established treatment modality in obstetric practice. In spite of the high

efficacy and the ever increasing experience with these substances, each and every use requires a clearly defined and critically considered indication.

3. Oxytocin

3.1 Structure

Oxytocin is a peptide hormone composed of 9 amino acids (fig. 5),[108] that is produced by neurons of the posterior lobe of the hypophysis and pulsatively released into the periphery. Its structure was elucidated in 1951 and its synthesis then became possible.

3.2 Activity in Uterus

Above all, oxytocin has a stimulating effect on the myometrium. The sensitivity of the uterus to this peptide hormone depends on the density of oxytocin receptors in the target organ. In the course of pregnancy the number of oxytocin receptors in the myometrium, decidua and especially corpus of the uterus increases;[109,110] thus, with increasing duration of pregnancy decreasing doses are needed for stimulation. Because of the wide variations in the sensitivity of the myometrium towards oxytocin and the individually differing plasma clearance rates, patients exhibit very different uterine sensitivities to intravenously administered oxytocin.

The elimination half-life time of oxytocin in the blood circulation varies between 2 and 10 minutes and this is the reason for the good controllability

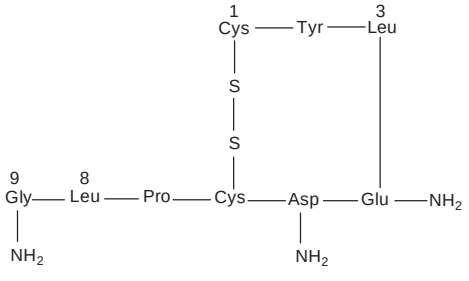


Fig. 5. The structure of oxytocin. **Asp** = asparagine; **Cys** = cysteine; **Glu** = glutamine; **Gly** = glycine; **Leu** = leucine; **Pro** = proline; **Tyr** = tyrosine.

of labour induction with this hormone. However, it should be noted that about half of the plasma oxytocin concentration is cleared within 1 minute because of the high plasma clearance rate of 23.1 ± 8.2 ml/kg/min,[111] and accordingly, relatively long infusion times are necessary (40 to 60 minutes) in order to reach a steady state plasma concentration.[112]

This also means, however, that a pronounced decrease in labour activity must be expected within 15 to 20 minutes after termination of the oxytocin infusion.[113]

4. Use of Oxytocin in Obstetrics

4.1 Labour Induction and Augmentation of Contractions

At present oxytocin is used to induce labour or to augment contractions in women with secondary uterine inertia, which occurs in 15 to 30% of all births in the western industrialised countries.[113] Oxytocin is used to induce contractions or to improve the quality of contractions in order to achieve a vaginal delivery without risk to mother and baby.

As with every induction of birth, the degree of ripeness of the cervix (e.g. by determination of the Bishop score) must be ascertained before administration of this drug. Here, women with a ripe cervix (a Bishop score of >8) constitute the domain of oxytocin-induced delivery. This method has equal efficiency but superior controllability when compared with the administration of prostaglandin.

Oxytocin should not be used to induce or augment contractions in women with an unripe cervix.[114] Our procedures for the induction of labour with prostaglandin and oxytocin are summarised in figure 6.[54]

Although the intravenous administration of synthetic oxytocin has been clinically established for many years, even today there is no consensus on the optimal dose. At present, initial dosages of 0.5 to 6 mU/min and intervals between increases of 20 to 60 minutes are recommended.[113,115]

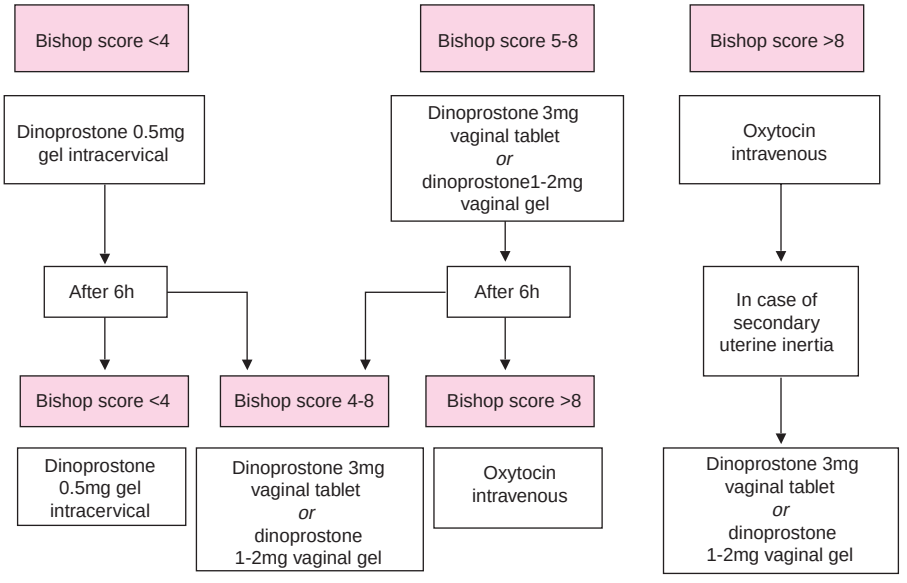


Fig. 6. Stepwise treatment algorithm for induction of labour in the third trimester with oxytocics in relation to cervical status (from Schneider et al.,[54] with permission).

Monitoring and Adverse Effects

The following prerequisites should be fulfilled for oxytocin administration:

- intravenous administration via an infusion pump
- cardiotocographic monitoring
- presence of qualified personnel
- immediate availability of an obstetrician in case of complications.

The most dangerous complication of labour induction by means of oxytocin is uterine hyperstimulation through to sustained contractions with the threat of fetal hypoxia. Because of the already mentioned good controllability of this method, these situations can mostly be managed by interruption of the oxytocin infusion and immediate emergency tocolysis, thus avoiding the necessity for surgical intervention. The danger of uterine rupture from oxytocin stimulation is particularly large when previous operations have been performed on the uterus. This applies particularly to multiparous women although the triggering factor is not always an excessive dosage of oxytocin.[116] For women who were grand multiparas, a 45 minute incremental regimen resulted in less precipitate labour, less uterine hyperstimulation and reduced length of hospital stay, but in longer induction-delivery intervals (median 2 hours) compared with a 15 minutes incremental regimen.[117]

In contrast to the continuous process, pulsatile administration of oxytocin can result in a reduction of the required oxytocin dose.[118] However, this mode of administration has not been accepted generally.

4.2 Prophylaxis and Therapy for Postpartum Uterine Atonia

The intravenous bolus administration of oxytocin 3 to 6IU immediately after delivery of the baby serves as prophylaxis for postpartum uterine atonia. This significantly reduce blood loss and shortens the postpartum period.[119]

Intravenous bolus administration of oxytocin 3 to 6IU accompanied by an infusion of 500ml of electrolyte solution with oxytocin 10IU is the primary medical therapy for postpartum uterine atonia.

Higher doses of oxytocin (>6IU) should not be administered as an intravenous bolus but rather as infusion since in individual patients, dramatic hypotension has been observed after high dose intravenous bolus administration of oxytocin.[113] However, it must be considered that, because of the structural similarities between oxytocin and vasopressin (the 2 molecules differ only in 2 amino acids), higher doses of oxytocin (>20 mU/min) can lead to vasopressin-like reactions (e.g. hypernatraemia, confusion, cramps, coma, heart failure) and hence to water intoxication. These complications must be expected, particularly when oxytocin is administered together with large amounts of physiological saline within a short time. Thus, administration should be performed in Ringer's lactate solution by means of an infusion pump.[113]

5. Ergot Alkaloids

5.1 Structure and Activity

Ergot alkaloids that are used in obstetrics (ergometrine and methylergometrine) are amine derivatives of lysergic acid (fig. 7) which principally excite the smooth musculature of the uterus and vessels. At the doses used for an effect on the uterus (0.2 to 0.5mg), the vasoconstricting actions of both substances are low.

5.2 Activity in Uterus

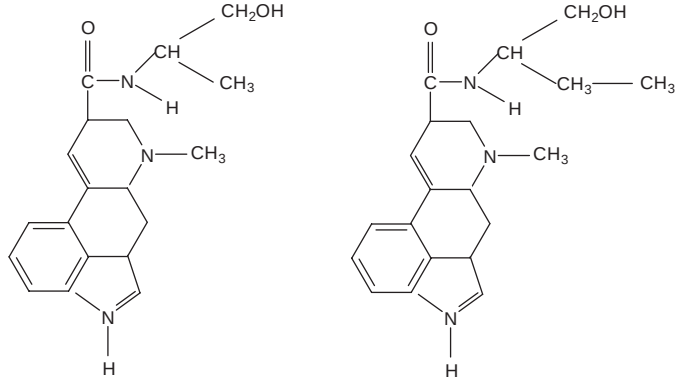
At low concentrations all ergot alkaloids cause, or increase the frequency, of rhythmic contractions of the uterus; at higher concentrations they effect a continuous contraction of the uterine musculature.

6. Use of Ergot Alkaloids in Obstetrics

Ergot alkaloids are currently used as prophylaxis for postpartum bleeding disorders and therapy for postpartum atonia. Because of their strong myometrium-stimulating activity they are contraindicated during pregnancy.

The introduction of these, and other, substances into obstetric practice has made it possible to reduce maternal mortality caused by postpartum bleeding from about 0.3 out of 1000 births in the 1930s to 0.06 out of 1000 in 1952.[97]

The action of intravenous methylergometrine at a dose of 0.5mg is comparable with that of oxytocin, except that cervical spasms are observed somewhat more frequently after methylergometrine. Adverse effects such as headaches, nausea, vomiting and the danger of an increase in blood pressure are more pronounced.[120] In this context, particular caution is required for women with pre-eclampsia and heart diseases during pregnancy. Severe cardiovascular complications[121] and postpartum eclampsia[122] have been observed in individual pa-



Ergometrine Methylergometrine

Fig. 7. Structures of ergometrine and methylergometrine.

tients after administration of ergot alkaloids for improvement of uterine tone.

The combination of methylergometrine and oxytocin has proved more effective for the prevention of postpartum bleeding than therapy with oxytocin alone. A recent meta-analysis suggested a reduction in the risk of postpartum haemorrhage (defined as blood loss of ≥500ml) for women receiving the combination drug methylergometrine and oxytocin when compared with oxytocin 5IU.[123] The advantage was smaller but still significant for the lower postpartum haemorrhage range (blood loss of up to 500ml) for those receiving a higher oxytocin dose of 10IU. There was no difference seen between the groups using either oxytocin 5IU or 10IU in terms of blood loss equal to or greater than 1000ml.[123]

However, since adverse effects and, especially the risk of elevated blood pressure, are more frequent with the combination of methylergometrine and oxytocin[120] the use of this combination as a routine prophylaxis for postpartum uterine atonia is not recommended.[119] Furthermore, it has been observed that the combination of methylergometrine and oxytocin, presumably because of its methylergometrine content, reduces the mother's serum prolactin level and may thus have adverse effects for breast feeding.[124]

The undesired adverse effects can be reduced by lowering the methylergometrine content of the combination from 0.5 to 0.25mg. This is not accompanied by a reduction in the myometrium-stimulating activity.[125]

7. Conclusions

As a result of the wide use in the past years of drugs that increase the contractile activity of the myometrium, induction of abortion in the first and second trimester have become more favourable for the patients through the use of prostaglandin to achieve shorter induction-to-birth intervals. Methods for inducing delivery and supporting contractions in the third trimester can now be individualised by adaptations in the mode of administration of prostaglandin and/or oxytocin to the status of the cervix. In addition, maternal mortality resulting from postpartum bleeding complications has been drastically reduced. At the same time, the frequency of operative interventions after unsuccessful delivery or abortion inductions as well as the incidence of cervical and uterine lesions have been lowered markedly. When dosage recommendations are followed, patients with risk factors for severe adverse effects are identified in advance and a close control of both mother and baby is applied, complications are rare or, when they do occur, they can be managed.

References

1. Bygdeman M, Berger GS, Keith LG. Prostaglandins and their inhibitors in clinical obstetrics and gynaecology. Lancaster: MTP Press, 1986
2. Egarter C, Husslein P. Biochemistry of myometrial contractility. Baillieres Clin Obstet Gynaecol 1992; 4: 755-69
3. Samuelson B, Goldyne M, Gangström E, et al. Prostaglandins and thromboxanes. Ann Rev Biochem 1987; 47: 997-1029
4. Carsten ME. Prostaglandins and cellular calcium transport in the pregnant human uterus. Am J Obstet Gynecol 1973; 117: 824-32
5. Rath W, Osmers R, Adelmann-Grill BC, et al. Biochemical changes in human cervical connective tissue after intracervical application of prostaglandin E_2. Prostaglandins 1993; 45: 375-84
6. Wakeling AE, Wyngarden LJ. Prostaglandin receptors in the human, monkey and hamster uterus. Endocrinology 1974; 95: 55-64
7. Chan WY, Berezin I, Daniel EE. Effects of inhibition of prostaglandin synthesis on uterine oxytocin receptor concentration and myometrial gap junction density in parturient rats. Biol Reprod 1988; 39: 1117-28
8. Theobald PW, Rath W, Kuhnle H, et al. Histological and electron-microscopic examinations of collagenous connective tissue of the non-pregnant cervix, the pregnant cervix, and the pregnant prostaglandin-treated cervix. Arch Gynecol 1982; 231: 241-5
9. Rath W, Osmers R, Adelmann-Grill BC, et al. Grundlagen der physiologischen und medikamentös induzierten Zervixreifung – Neuere morphologische und biochemische Befunde. Geburtshilfe Frauenheilkd 1990; 50: 657-64
10. Osmers R, Rath W, Adelmann-Grill BC, et al. Origin of cervical collagenase during parturition. Am J Obstet Gynecol 1992; 166: 1455-60
11. Junqueira LC, Zugaib M, Montes GS, et al. Morphologic and histochemical evidence for the occurrence of collagenolysis and for the role of neutrophilic polymorphonuclear leukocytes during cervical dilatation. Am J Obstet Gynecol 1980; 138: 272-81
12. Platz-Christensen JJ, Brandberg A, Wiquist N. Increased prostaglandin concentrations in the cervical mucus of pregnant

women with bacterial vaginosis. Prostaglandins 1992; 43: 122-30
13. Lindblom B, Kallfelt B, Hahlin M, et al. Local prostaglandin F_2 alpha injection for termination of ectopic pregnancy. Lancet 1987; I: 776-7
14. Karim SMM. Clinical applications of prostaglandins in obstetrics and gynaecology. Ann Acad Med Singapore 1982; 11: 493-502
15. Schmidt-Gollwitzer K. Medikamentös induzierter Frühabort: Zyklus post abortum. In: Hepp H, Schüssler B, editors. Prostaglandine in Gynäkologie und Geburtshilfe. Berlin: Springer, 1981: 199-208
16. Rath W, Kuhn W. Prostaglandinen in Gynäkologie und Geburtshilfe. Arzneimitteltherapie 1988; 6: 111-21
17. Chen JK, Elder MG. Preoperative cervical dilatation by vaginal pessaries containing prostaglandin E_1 analogue. Obstet Gynecol 1983; 62: 339-42
18. Welch C, Elder MG. Cervical dilatation with 16.16-Dimethyltrans-prostaglandin E_1 methylester pessaries before surgical treatment of first trimester pregnancies. Br J Obstet Gynaecol 1982; 89: 849-52
19. Kulenkampff D, Rath W, Kuhn W. Gemeprost Vaginal-Suppositorien versus intrazervikale Sulproston-Gel-Applikation zum Zervixpriming im I. Trimenon. Geburtshilfe Frauenheilkd 1994; 54: 174-8
20. Rabe T, Helk J, Kiesel L, et al. Anwendung eines neuen Scheidenzäpfchens: Prostaglandin-E_1-Analog Gemeprost zur Zervixreifung vor Schwangerschaftsabbrüchen im ersten Trimester. Geburtshilfe Frauenheilkd 1985; 45: 393-401
21. Christensen NJ, Bygdeman M, Green K. Comparison of different prostaglandin analogues and laminaria for preoperative dilatation of the cervix in late first trimester abortion. Contraception 1983; 27: 51-61
22. Kajanoja P, Mandelin M, Mäkilä UM, et. al. A gemeprost vaginal suppository for cervical priming prior to termination of first trimester pregnancy. Contraception 1984; 29: 251-60
23. Kajanoja P. Is preoperative cervical softening necessary in termination of pregnancy in nulliparous women? Zentralbl Gynakol 1990; 112: 589-91
24. Krauß T, Rath W, Cunze T. Schwangerschaftsbeendigung im II. Trimenon durch serielle Applikation von Gemeprost-Vaginalsuppositorien. Geburtshilfe Frauenheilkd 1994; 54: 623-6
25. Rath W, Krauß T, Kuhn W. Abortinduktion bei fortgeschrittenen Schwangerschaften. In: Künzel W, Kirschbaum M, editors. Gießener Gynäkologische Fortbildung. Berlin, Heidelberg, New York: Springer, 1993: 166-75
26. Rath W. Die Anwendung von Prostaglandinen zur Schwangerschaftsbeendigung im I. und II. Trimenon. Wien Klin Wochenschr 1987; 99: 741-51
27. Andersen LF, Poulsen HK, Sorensen SS, et al. Termination of second trimester pregnancy with gemeprost vaginal pessaries and intraamniotic $PGF_{2\alpha}$. Eur J Obstet Gynecol Reprod Biol 1989; 31: 1-7
28. Sakomoto S, Satoh K, Nishiya I, et al. Abortifacient effect and uterine cervix-dilating action of 16,16-dimethyl-trans-delta 2 PGE_1-methyl ester (ONO 802) in the form of a vaginal suppository (a randomized, double-blind controlled study in the second trimester of pregnancy). Prostaglandins Leukot Med 1982; 9: 349-59
29. Querido L, Haspels AA. Late second trimester abortion with 16,16-dimethyl-trans-delta 2-PGE_1 methyl ester (Gemeprost). Contraception 1990; 42: 43-9
30. Thong KJ, Baird DT. An open study comparing two regimens of gemeprost for the termination of pregnancy in the second trimester. Acta Obstet Gynecol Scand 1992; 71: 191-6
31. Di Lieto A, Catalano D, Albano G, et al. Uterine motility and cervical ripening in second trimester elective abortion by two different PGE analogues. Clin Exp Obstet Gynecol 1991; 18: 251-9
32. Winkler M, Rath W. Aktuelles Vorgehen bei der vorzeitigen Schwangerschaftsbeendigung mit Prostaglandinen im II. und III. Trimenon. Z Geburtshilfe Neonatol 1997; 201: 39-43
33. Cameron IT, Michie AF, Baird DT. Prostaglandin-induced pregnancy termination: further studies using gemeprost vaginal pessaries in the early second trimester. Prostaglandins 1987; 34: 111-7
34. Rabe T, Basse H, Thuro H, et al. Effect of PGE_1 methyl analog misoprostol on the pregnant uterus in the first trimester. Geburtshilfe Frauenheilkd 1987; 47: 324-31
35. Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. Lancet 1991; 338: 1233-6
36. Jan JK, Missile DR. A comparison of intravaginal misoprostol with prostaglandin E_2 for termination of second-trimester pregnancy. N Engl J Med 1994; 331: 290-3
37. Windrow R, Beneath K, Muddle W, et al. Oral administration of misoprostol for labor induction: a randomized controlled trial. Obstet Gynecol 1997; 89: 392-7
38. Sanchez-Ramos L, Chintz AM, Wears AL, et al. Misoprostol for cervical ripening and labor induction: a meta-analysis. Obstet Gynecology 1997; 89: 633-42
39. Gars RE, Quirked CF. Misoprostol: a prostaglandin E_1 analogue. Clin Pharm 1989; 8: 627-44
40. Karim A. Antiulcer prostaglandin misoprostol: single and multiple dose pharmacokinetic profile. Prostaglandins 1987; 33 Suppl.: 40-50
41. El-Refaey H, Templeton A. Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and of their effect on blood pressure. Br J Obstet Gynaecol 1994; 101: 792-6
42. Ranta H, Tuimala R. Second trimester abortion with vaginal gemeprost or intravenous sulprostone. J Obstet Gynaecol 1991; 11: 227-8
43. Müller T, Backe J, Rempen A. Vorzeitige Schwangerschaftsbeendigung im II. und III. Trimenon. Geburtshilfe Frauenheilkd 1996; 56: 234-8
44. Mink D, Heiss C, Rothbrust S, et al. Vergleich von Dinoproston-Gel und Gemeproston-Suppositorien zur Abortinduktion im zweiten und dritten Trimenon. Zentralbl Gynakol 1995; 117: 263-8
45. Kjolhede P, Dahle LA, Matthiesen L, et al. An open prospective randomized study of dinoproston and gemeprost in second trimester legal abortions. Acta Obstet Gynecol Scand 1994; 73: 316-20

46. Guidotti RJ, Grimes DA, Cates W Jr. Fetal amniotic fluid embolism during legally induced abortion. Am J Obstet Gynecol 1981; 141: 257-61
47. Meyer WJ, Benton SL, Hoon TJ, et al. Acute myocardial infarction associated with prostaglandin E_2. Am J Obstet Gynecol 1991; 165: 359-60
48. Wischnik A, Rath W. Indikationen zur Geburtseinleitung unter besonderer Berücksichtigung der Prostaglandine. In: Rath W, editor. Fortschritte in der medikamentösen Geburtseinleitung. Mülheim: HUF-Verlag, 1996: 47-62
49. Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964; 24: 266-8
50. Goeschen K, Saling E. Induktion der Zervixreife mit Oxytocin- versus $PGF_{2\alpha}$-Infusion versus PGE_2-Gel intrazervikal bei Risikoschwangeren mit unreifer Zervix. Geburtshilfe Frauenheilkd 1982; 42: 810-6
51. Davies NJ, Martindale E, Haddad NG. Cervical ripening with oral prostaglandin E_2 tablets and the effect of the latent period in patients with premature rupture of the membranes at term. J Obstet Gynecol 1991; 11: 405-8
52. Keirse MJ. Therapeutic uses of prostaglandins. Baillieres Clin Obstet Gynaecol 1992; 6: 787-807
53. Kieback DG, Zahradnik H-P, Quass L, et al. Clinical evaluation of endocervical prostaglandin-E_2-triacetin-gel for preinduction cervical softening in pregnant women at term. Prostaglandins 1986; 32: 81-5
54. Schneider KTM, Lüftner D, Rath W. Geburtseinleitung mit Prostaglandinen - Nutzen und Risiken. In: Rath W, editor. Fortschritte in der medikamentösen Geburtseinleitung. Mülheim: HUF-Verlag, 1996: 63-83
55. Goeschen K, Mesrogli M, Rosswog V, et al. Vorzeitiger Blasensprung in Terminnähe: Abwarten oder Handeln? Z Geburtshilfe Perinatol 1989; 193: 16-21
56. Goeree R, Hannah M, Hewson S, et al. Cost-effectiveness of induction of labour versus serial antenatal monitoring in the Canadian multicentre postterm pregnancy trial. Can Med Assoc J 1995; 152: 1445-50
57. Dennemark N, Rath W. Lokale Prostaglandintherapie zur Geburtseinleitung bei Risikoschwangerschaften. Gynakol Prax 1985; 9: 657-67
58. Egarter C, Husslein PW, Rayburn WF. Uterine Hyperstimulation after low-dose prostaglandin E_2 therapy: tocolytic treatment in 181 cases. Am J Obstet Gynecol 1990; 163: 794-6
59. Schneider KTM, Lüftner D, Rath W. Die Geburtseinleitung mit Prostaglandinen - Nutzen und Risiken: In: Somville T, Rath W, editors. Prostaglandine. Aktualisierte Anwendung in Geburtshilfe und Gynäkologie. Gräfelfing: Socio-Medico-Verlag, 1993: 67-88
60. Rayburn WF. Prostaglandin E_2 gel for cervical ripening and induction of labor: a critical analysis. Am J Obstet Gynecol 1989; 160: 529-34
61. Noah NL, DeCoster JM, Fraser TJ, et al. Preinduction cervical softening with endocervical PGE_2 gel. Acta Obstet Gynecol Scand 1987; 66: 3-7
62. Osmers R, Rath W. Anwendung von Prostaglandinen zur Geburtseinleitung. Gynakol Prax 1986; 10: 621-31
63. Phuapradit W, Herabutya Y, Saropala. Uterine rupture and labor induction with prostaglandins. J Med Assoc Thai 1993; 76: 292-5
64. Maymon R, Haimovich L, Shulman A, et al. Third trimester uterine rupture after prostaglandin E_2 use for labor induction. J Reprod Med 1992; 37: 449-52
65. Azem F, Jaffa A, Lessing JB, et al. Uterine rupture with the use of a low-dose vaginal PGE_2 tablet. Acta Obstet Gynecol Scand 1993; 72: 316-7
66. Maymon R, Shulman A, Pomeranz M, et al. Uterine rupture at term pregnancy with the use of intracervical prostaglandin E_2 gel for induction of labor. Am J Obstet Gynecol 1991; 165: 368-70
67. Husslein P, Egarter C, Sevalda P, et al. Geburtseinleitung mit 3 mg Prostaglandin-E_2-Vaginaltabletten: Eine Renaissance der programmierten Geburt? Geburtshilfe Frauenheilkd 1986; 46: 83-7
68. Kofler E, Egarter C, Husslein P. Erfahrungen bei 2 149 Geburtseinleitungen mit 3 mg Prostaglandin-E_2-Vaginaltabletten. Geburtshilfe Frauenheilkd 1986; 46: 863-8
69. Dennemark N. Nicht selektive Geburtseinleitung mit Minprostin®-E_2-Vaginaltabletten. Med Report 1989; 1: 2-3
70. Bremme K, Eneroth P, Kindahl H. 15-Keto-13, 14-dihydro-prostaglandin $F_{2\alpha}$ and prolactin in maternal and cord blood during prostaglandin E_2 or oxytocin therapy for labor induction. J Perinat Med 1987; 15: 143-51
71. Fuchs AR, Goeschen K, Husslein P, et al. Oxytocin and the initiation of human parturition: III: plasma concentrations of oxytocin and 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ in spontaneous and oxytocin-induced labor at term. Am J Obstet Gynecol 1983; 147: 497-503
72. McLaren M, Greer IA, Smith JR, et al. Maternal plasma bicycling PGE_2 levels following vaginal administration of prostaglandin E_2 pessaries in full term pregnancies. Prog Clin Biol Res 1987; 242: 199-203
73. Reichel K, Husslein P, Goeschen K, et al. Untersuchungen zur Resorption von PGE_2 nach unterschiedlicher Applikation zur Zervixreifung und zur Geburtseinleitung. Wien Klin Wochenschr 1985; 97: 500-3
74. Lyndrup J. Induction of labour by PGE_2 and other local methods. Dan Med Bull 1995; 42: 227-43
75. Kimball FA, Ruppel PL, Noah ML, et al. The effect of endocervical PGE_2 gel (prepidil) on plasma levels of 13, 13-dihydro-15-keto PGE_2 in women at term. Prostaglandins 1986; 32: 527-37
76. Chin SC, Murray A, Maresh MJA, et al. The use of prostaglandin E_2 gel for induction of labour in nulliparous patients with a Bishop score of 4 or less. J Obstet Gynaecol 1989; 10: 103-5
77. Hales KA, Rayburn WF, Turnbull HD, et al. Double blind comparison of intracervical and intravaginal prostaglandin E_2 for cervical ripening and induction of labor. Am J Obstet Gynecol 1994; 171: 1087-91
78. Mahmood TA. A prospective comparative study on the use of prostaglandin E_2 gel (2mg) and prostaglandin E_2 tablet (3mg) for the induction of labour in primigravid women with unfavourable cervices. Eur J Obstet Gynecol Reprod Biol 1989; 33: 169-75

79. Greer IA, McLaren M, Calder AA. Vaginal administration of PGE_2 for induction of labour stimulates endogenous $PGF_{2\alpha}$ production. Acta Obstet Gynecol Scand 1990; 69: 621-5
80. Embrey MP, Graham NB, McNeill ME. Induction of labour with a sustained-release prostaglandin E_2 vaginal pessary. BMJ 1980; 281: 901-2
81. Embrey MP, MacKenzie IZ. Labour induction with a sustained release prostaglandin E_2 polymer vaginal pessary. J Obstet Gynaecol 1985; 6: 38-41
82. MacKenzie IZ, Castle B, Mountford L, et al. Prostaglandin release from preparations used vaginally for the induction of labour. Prostaglandins 1987; 34: 939-46
83. Taylor AVG, Boland J, MacKenzie IZ. The concurrent in vitro and in vivo release of PGE_2 from a controlled release hydrogel polymer pessary for cervical ripening. Prostaglandins 1990; 40: 89-98
84. Khouzam MN, Ledward RS. Difficulties with controlled release prostglandin E_2 pessaries. Lancet 1990; 336: 119
85. Bex P, Gunasekera PC, Phipps JH. Difficulties with controlled release prostglandin E_2 pessaries. Lancet 1990; 336: 119
86. Norman M, Ekman G. Preinductive cervical ripening with prostaglandin E_2 in women with one previous cesarean. Acta Obstet Gynecol Scand 1992; 71: 351-5
87. Behrens O, Goeschen K, Jakob H, et al. Geburtseinleitung mit Prostaglandin-E_2-Gel bei Zustand nach Sectio. Geburtshilfe Frauenheilkd 1994; 54: 144-50
88. MacKenzie IZ, Bradley S, Embrey MP. Vaginal prostaglandins and labour induction for patients previously delivered by caesarean section. Br J Obstet Gynaecol 1984; 91: 7-10
89. Schneider KTM, Lüftner D, Rath W, et al. Prostaglandin-Geburtseinleitung bei Zustand nach Sectio caesarea. Zentralbl Gynakol 1994; 116: 461-7
90. MacKenzie IZ. Prostaglandin induction and the scarred uterus. In: Keirse MJNC, Elder MG, editors. Induction of labour: special issues. 2nd European Congress on Prostaglandins in Reproduction. 1991 May 3, The Hague. Amsterdam: Excerpta Medica, 1991: 29-39
91. Flamm BL, Lim OW, Jones C, et al. Vaginal birth after cesarean section: results of a multicenter study. Am J Obstet Gynecol 1988; 158: 1079-84
92. Chattopadhyay SK, Sengupta BS, Edrees YB. Intracervical application of prostaglandin E_2 tablets for elective induction of labor in grand multiparae: a prospective controlled study. Eur J Obstet Gynaecol Reprod Biol 1986; 22: 7-15
93. Wing DA, Rahall A, Jones MM, et al. Misoprostol: an effective agent for cervical ripening and labor induction. Am J Obstet Gynecol 1995; 172: 1811-6
94. Wing DA, Jones MM, Rahall A, et al. A comparison of misoprostol and prostaglandin E_2 gel for preinduction cervical ripening and labor induction. Am J Obstet Gynecol 1995; 172: 1804-10
95. Sanchez-Ramos L, Kaunitz AM, Del Valle GO, et al. Labor induction with the prostaglandin E_1 methyl analogue misoprostol versus oxytocin: a randomized trial. Obstet Gynecol 1993; 81: 332-6
96. Hofmeyr GJ. Misoprostol administered vaginally for cervical ripening and labour induction with a viable fetus. The Cochrane Library 1998; 1
97. Prendiville W, Elbourne D, Chalmers I. The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1988; 95: 3-16
98. Zahradnik HP, Quaas L, Breckwoldt M. Uterusatonie - Wandel der Behandlungsmethoden in den letzten 20 Jahren. In: Haller U, Kubli F, Husslein P, editors. Prostaglandine in Geburtshilfe und Gynäkologie. Berlin: Springer, 1988: 220-9
99. Goedicke HD. Treatment of post partum atonic haemorrhage with the prostaglandin-E_2 derivative Nalador®: results of a multicentre trial. In: Egarter C, Husslein P, editors. Post partum uterine atonia. Vienna: Facultas, 1989: 41-9
100. Rath W. Therapeutisches Vorgehen bei atonischer Nachblutung. Kliniksarzt 1990; 19: 33-7
101. Heinzl S. Postpartale Uterusatonie und Prostaglandine. In: Haller U, Kubli F, Husslein P, editors. Prostaglandine in Geburtshilfe und Gynäkologie. Berlin: Springer, 1988: 207-15
102. Kilpatrick AW, Thorburn J. Severe hypotension due to intramyometrial injection of prostaglandin E_2. Anaesthesia 1990; 45: 848-9
103. Popat MT, Suppiah N, White JB. Cardiac arrest following intramyometrial injection of prostglandin E_2. Anaesthesia 1991; 46: 236
104. Litschgi M. Prostaglandins and post partum uterine atonia. In: Egarter C, Husslein P, editors. Post partum uterine atonia. Vienna: Facultas, 1989: 61-8
105. Keirse MJNC. Treatment of post partum uterine hypotonia with prostaglandins. In: Egarter C, Husslein P, editors. Post partum uterine atonia. Vienna: Facultas, 1989: 25-32
106. Hogerzeil HV, Walker GJA, de Goeje MJ. Stability of injectable oxytocics in tropic climates. Geneva: World Health Organisation, 1993
107. El-Refaey H, OBrien P, Morafa W, et al. Misoprostol for third stage of labour. Lancet 1996; 347: 1257
108. Zeeman GG, Khan-Dawood FS, Dawood MY. Oxytocin and its receptor in pregnancy and parturition: current concepts and clinical implications. Obstet Gynecol 1997; 89: 873-83
109. Fuchs A-R, Fuchs F, Husslein P, et al. Oxytocin receptors and human parturition: a dual role for oxytocin in the initiation of labor. Science 1982; 215: 1396-8
110. Fuchs A-R, Fuchs F, Husslein P, et al. Oxytocin receptors in the human uterus during pregnancy and parturition. Am J Obstet Gynecol 1984; 150: 734-41
111. Leake RD, Weitzman RE, Fisher DA. Pharmacokinetics of oxytocin in the human subject. Obstet Gynecol 1980; 56: 701-4
112. Seitchik J, Castillo M. Oxytocin augmentation of dysfunctional labor: II: uterine activity data. Am J Obstet Gynecol 1983; 145: 526-9
113. Kauffels W, Merrill DC, Nybiel J, et al. Die Geburtseinleitung mit Oxytozin-Nutzen und Risiken. In: Rath W, editor. Fortschritte in der medikamentösen Geburtseinleitung. Mülheim: HUF-Verlag, 1996: 85-96
114. Taylor RW, Taylor M. Misuse of oxytocin in labour. Lancet 1988; I: 352
115. ACOG technical bulletin: induction of labor. No. 217, Dec 1995. Int J Gynaecol Obstet 1996; 53: 65-72

116. Awais GM, Lebherz TB. Ruptured uterus, a complication of oxytocin induction and high parity. Obstet Gynecol 1970; 36: 465-72
117. Orhue AAE. A randomised trial of 45 minutes and 15 minutes incremental oxytocin infusion regimes for the induction of labour in women of high parity. Br J Obstet Gynaecol 1993; 100: 126-9
118. Cummiskey KC, Gall SA, Dawood MY. Pulsatile administration of oxytocin for augmentation of labor. Obstet Gynecol 1989; 74: 869-72
119. Kranzfelder D. Nachgeburtsperiode. In: Künzel W, Wulf K-H, editors. Klinik der Frauenheilkunde und Geburtshilfe. Munich: Urban & Schwarzenberg, 1996: 301-15
120. Elbourne D, Prendiville W, Chalmers I. Choice of oxytocic preparation for routine use in the management of the third stage of labour: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1988; 95: 17-30
121. Carey M. Adverse cardiovascular sequelae of ergometrine. Br J Obstet Gynaecol 1993; 100: 865
122. Dua JA. Postpartum eclampsia associated with ergometrine maleate administration. Br J Obstet Gynaecol 1994; 101: 72-3
123. McDonald S, Prendiville WJ, Elbourne D. Prophylactic syntometrine vs oxytocin in the third stage of labour. The Cochrane Library 1998; 1
124. Symes JB. A study on the effect of ergometrin on serum prolactin levels following delivery. J Obstet Gynaecol 1984; 5: 36-8
125. Paull JD, Ratten GJ. Ergometrine and third stage blood loss. Med J Aust 1977; 1: 178-9

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