Prostaglandins in the induction of labour – do we have the optimal substance, dose, and route of administration? Literature review

Prostaglandyny w indukcji porodu – czy mamy odpowiednią substancję, dawkę i drogę podawania? Przegląd piśmiennictwa

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Abstract
Induction of labour (IOL) is a procedure that reduces mortality and morbidity of the mother and the newborn in particular clinical settings. Currently the number of indications for this procedure is increasing; at the same time, intensive work is underway to optimize IOL in terms of duration, obstetric results, and costs. There are no universal standards regarding the optimal way to pre-induce patients in the case of unfavourable cervix, but prostaglandin analogues play an important role in this process. In this paper we discuss the physiological role of prostaglandins and review the current evidence-based literature on this topic, trying to find optimal substance, dose, and route of administration in pre-induction of labour in terms of effectiveness, obstetrical outcomes, and intrapartum complications.

Streszczenie
Indukcja porodu (IOL) to procedura zmniejszająca śmiertelność i zachorowalność matki oraz noworodka w wybranych sytuacjach klinicznych. Aktualnie obserwujemy wzrost liczby wskazań do tej procedury, jednocześnie prowadzone są intensywnie badania nad optymalizacją IOL pod względem czasu trwania, wyników położniczych i kosztów. Obecnie nie ma uniwersalnych standardów dotyczących optymalnego sposobu przygotowania szyjki u pacjentek w przypadku jej niedojrzałości, ale analogi prostaglandyn odgrywają niezwykle ważną rolę w tym procesie. W niniejszym artykule omawiamy fizjologiczną rolę prostaglandyn i dokonujemy przeglądu aktualnego piśmiennictwa opartego na dowodach naukowych w celu znalezienia optymalnej substancji, dawki i drogi podania w preindukcji porodu pod względem skuteczności, wyników położniczych i powikłań śródporodowych.

Introduction
Induction of labour (IOL) is one of the most common medical procedures used in obstetrics. It is estimated that currently in developed countries the induction of labour affects every 4th pregnant woman [1]. In developing countries, the prevalence of IOL differs significantly from centre to centre. Recently, new data on the safety of this procedure as well as on the benefits of using it even in low-risk pregnancies at the end of 39 weeks of pregnancy are emerging [2]. This is likely to result in further expansion of the indications for IOL [3]. In addition, the worldwide availability of methods for monitoring foetal and maternal well-being and epidemiological data on the possibility of reducing maternal and foetal mortality and morbidity in certain pregnancy complications (i.e. intrauterine growth restriction, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, pre-eclampsia, prelabour rapture of membranes) is likely to result in an increased percentage of IOL in the future. This paper aims to provide the reader with information on the physiological role of prostaglandins in the parturition process and the availability of their synthetic analogues on the market, and to present the
current knowledge on the differences between them. This is a narrative review.

We based this paper on articles published in the Medline database in the last 10 years and information provided by drug manufacturers in summaries of product characteristics. The papers were subjectively chosen based on their substantive value (mainly systematic reviews, meta-analyses, and controlled randomized trials). No specific search strategy was used.

**Outcome measures of labour induction**

Before starting an IOL, one should always consider the chances of success. Different measures of effectiveness are considered in the literature [4, 5]. The basic and most important measures are vaginal delivery (VD), caesarean section (CS), and instrumental delivery (ID) rates – these are the most common endpoints in scientific studies, which are also the most clinically relevant endpoints. IOL is a long process, and therefore the time in the form of a combined outcome measurement like “percentage of vaginal deliveries not achieved within 24 hours” is also taken into account in the studies. Other indicators that are considered are the percentage of maternal and neonatal complications (such as the newborn’s clinical condition, acid-base balance parameters, and frequency of hospitalization in the neonatal intensive care unit (NICU)). These parameters as outcome measures are more complex and difficult to interpret due to the multitude of pregnancy complications that are an indication for IOL (a priori high risk of poor condition of the newborn in some cases). Other indicators taken into account mainly for pharmacoeconomic reasons are induction to delivery time (I-D time, time from the beginning of the IOL procedure to the delivery of the newborn by VD), the need to use oxytocin in induction or augmentation of the labour, the chance to reach cervical ripening on the Bishop pelvic score ≥ 7, the costs of the pre-induction agents, adverse reactions, ease of use, and patient acceptance and satisfaction. ID time is the most important pharmacoeconomic indicator because the greatest part of the costs in the hospitalization process is educated staff remuneration, and the ID time directly translates into the number of personnel shifts. Knowing these parameters, it is possible to create predictive models that allow us to adjust the time of the commencement of IOL so that the medical personnel are the least burdened with additional work [6].

**Predictive factors of the effectiveness of labour induction**

One of the best predictive factors for completing IOL with vaginal delivery is favourability of the cervix. Classically, this parameter is evaluated on the basis of the Bishop pelvic score developed in 1964 [7]. The score consists of 5 elements available for internal gynaecological examination (4 of them characterize cervical properties – position, consistency, effacement, and dilatation; the fifth parameter assesses advancement of the foetus’s head in relation to the interspinal line). The maximum cervix that can be rated is 13 points [8]. It is generally accepted in the literature that a value of < 7 means that the cervix is not prepared for IOL (unfavourable cervix).

The Bishop score has passed the test of time, and even today systematic reviews of multi-parameter regression models that estimate the chance of IOL success indicate the usefulness of its overall and individual elements [9]. Inducing uterine contractions in patients with a low Bishop score generates high pressure inside the uterine cavity, causing severe pain to the patient and potential foetal distress [10]. Considering the above, the use of oxytocin in the case of unfavourable cervix is now being abandoned, and cervical ripening by mechanical (Foley’s catheter, Cook’s double balloon catheter) or biochemical (prostaglandins) methods should be employed earlier. Despite the use of these methods, the low favourability of the cervix at the time of the IOL decision seems to translate into a higher percentage of caesarean sections compared to favourable cervix, without affecting the neonatal outcome [11]. Other factors that affect the chances of success of IOL are as follows: gestational age, parity, maternal height, body mass index, maternal age, and foetal size. Some studies indicate that the obstetrician’s caesarean section rate as well as the woman’s attitude towards caesarean delivery are independent predictors of IOL success [9].

**Physiological role of prostaglandins in parturition**

Prostaglandins (PGs) in the human organism are formed in the so-called arachidonic acid cascade. Arachidonic acid released from the cell membrane can be metabolized into intermediate products (PGG2 and PGH2) by means of constitutional cyclooxygenase 1 (COX-1) or cyclooxygenase 2 (COX-2), the activity of which is regulated by growth factors and cytokines. Intermediate products are used to produce prostacyclins, thromboxanes, and prostaglandins, of which the most important ones involved in parturition physiology are PGE1, PGE2, and PGE2α [9]. Prostaglandins are produced in all compartments of the maternal reproductive system (decidua, muscles of uterus, and cervix) as well as in the foetal membranes. Each of these compartments has its own specific concentration profile. The concentration of prostaglandins increases in urine, amniotic fluid, and maternal plasma before the onset of uterine contraction, which proves that the increase is not the result of the onset of labour but one of its causes [12]. Prostaglandins can induce myometrial contractility, proteolysis of the extracellular matrix of
the cervix (cervical ripening), and promote rapture of membranes [12]. Cyclooxygenase inhibitors are also used as tocolytic drugs (indomethacin). The administration of prostaglandins induces an abortion in the case of termination of pregnancy or missed abortion and promotes cervical ripening and the onset of delivery [12]. Three analogues of prostaglandins: PGE1 (misoprostol), PGE2 (dinoprostone), and PGF2 (dinoprost), are used in obstetric practice, of which misoprostol and dinoprostone are most commonly used in the pre-induction of labour.

**Synthetic prostaglandins in the pre-induction of labour**

Contraindications for the use of prostaglandins in the perinatal period include all contraindications for IOL. Special care should be taken in patients with asthma and glaucoma or elevated intraocular pressure. A special group of patients we have to consider are women after previous CS. In this group the use of PGs is limited [13]. Mechanical pre-induction of labour is currently the method of choice. It is commonly believed that PGs are contraindicated due to increased chances of intrapartum uterine rupture. Retrospective observational studies indicate an increased risk of this complication in this group of patients [14]. However, this study does not specify the proportion of patients depending on the prostaglandin used (PGE2 or PG1E1). A prospective randomized trial of misoprostol in patients after previous CS was discontinued because of safety concerns [15]. Misoprostol now appears to be well-established in the literature as a substance that increases this risk, as supported by the American College of Obstetricians and Gynaecologists (ACOG) recommendations, while this scientific society does not indicate that dinoprostone is contraindicated in this group of patients [16]. However, the British National Institute for Health and Care Excellence allows the use of dinoprostone in this group of patients [17], which is supported by some observational studies that indicate that it does not carry additional risk for this group [18, 19]. A randomized trial is currently underway to evaluate the efficacy and safety of dinoprostone compared to the Foley catheter in women after previous CS [20]. The Polish Society of Gynaecology and Obstetrics in its recommendations for labour induction currently takes the position that all prostaglandins are contraindicated in patients after previous CS [21].

**Dinoprostone in the pre-induction of labour**

Dinoprostone is a synthetic prostaglandin PGE2. The estimated half-life is 2.5–5 min [22]. A hormone that is not degraded locally is broken down in the pulmonary circulation. Currently, it is believed that the main pathway of action is induction of the ripening of the cervix and stimulation of prostaglandin PGF2 production, which increases the sensitivity of myometrium to oxytocin [23]. In addition to its action on the genital organ, prostaglandin PGE2 also reduces platelet aggregation, causes vasodilation resulting in hypotension, participates in the immune response and inflammation, intensifies gastrointestinal muscle contractions, and increases gastric mucus secretion. It also affects the smooth muscles of the bronchial tree and iris sphincter muscle [23].

For the pre-induction process, dinoprostone can be used in the form of a vaginal or intracervical gel as well as a constant release vaginal insert. The doses used are in the range of 0.5 mg to 10 mg. Doses up to 3 mg are considered as “low dosage”.

The authors of the available 2014 meta-analysis analysed 39 studies comparing dinoprostone with placebo for induction of labour [5]. In most studies included in the meta-analysis, vaginal use of dinoprostone reduces the risk of not achieving vaginal delivery within 24 h compared to placebo or expectant management. However, due to the high coefficient of heterogeneity among the studies (I² = 97.7%) resulting from the different inclusion criteria, endpoints, and doses of dinoprostone used, the authors were unable to aggregate the results to a common numerical value [5]. The meta-analysis also indicated an increased risk of uterine hyperstimulation with foetal heart rate (FHR) changes in comparison with placebo (RR = 3.16, 95% CI: 1.67–5.98, 15 trials, 1359 women). Patients treated with dinoprostone demonstrated a reduction in the rate of caesarean section; however, the difference was borderline statistically significant (13.5% vs. 14.8%, RR = 0.91, 95% CI: 0.81–1.02, 36 trials, 6599 women). The use of PGE2 also promotes the chance of increasing the Bishop score within 12 and 24 h and reduces the need for oxytocin labour augmentation [5].

Two forms of dinoprostone are currently available in Poland. The first is in the form of a gel (ICDG – intracervical dinoprostone gel) 0.5 mg dinoprostone/3 g gel (Prepidil®, Pfizer Europe). The gel should be administered below the inner cervical os. It reaches its maximum concentration in plasma after 30–40 min. The acting time after application is 6–12 h. The dose can be repeated 3 times within 6–12 h [24]. ICDG should not be used together with oxytocin infusion, and the administration of oxytocin can be started 6 h after the last dose of the preparation. Compared to placebo, the use of the above-mentioned form of dinoprostone was characterized by a higher incidence of such complications as gastrointestinal disorders (5.7% vs. 2.6%), back pain (3.1% vs. 0%), and foetal heart rate abnormality (17% vs. 14.5%). Foetal cardiac decelerations were reported in 2.8% (vs. 2.1% for placebo) [24].

The second form available in Poland is dinoprostone vaginal insert 10 mg (DVI 10 mg, Cervidil®, Ferring Pharmaceuticals Poland). The insert is applied to
the posterior vaginal fornix. DVI is released at about 0.3 mg/h over 24 h. The insert can be used after 37 weeks of gestation [17]. The system has a tape for easy removal from the vagina. The indication for removal is the commencement of regular uterine contractions every 3 min or rapture of the foetal membranes. The system should be removed after a maximum of 24 h. If oxytocin infusion is indicated, the infusion should not start earlier than 30 min after DVI removal. Compared to placebo, the risk of complications is relatively small. The risk of uterine hyperstimulation with foetal distress and without foetal distress is 2.9% and 2%, respectively (vs. 0% for placebo) [25]. Drug-related diarrhoea, fever, nausea, vomiting, and abdominal pain were seen in less than 1% of cases [25].

A meta-analysis of randomized trials indicates that there are no differences between the forms of dinoprostone in terms of effectiveness, or the differences are so small that studies currently available in the literature are insufficiently powered to detect a difference [4]. There is also currently no evidence of a difference in the effectiveness of low (< 3 mg) and high doses of dinoprostone [4]. The primary advantage of DVI is its ease of removal in the case of adverse effects. This increases the safety of use (especially with the short half-life of dinoprostone). In the case of a cervical gel usage, it is necessary to rinse the vagina when drug-related complications occur. The second advantage is greater flexibility in the management of the IOL; when it becomes necessary to administer oxytocin, it can be done after 30 min after DVI removal (6 h after ICDG application). Currently, experience with DVI in patients with rupture of membranes is limited, mainly due to the unknown release profile, and nowadays it is not recommended in Poland [21, 26].

Misoprostol in pre-induction of labour

Misoprostol is a synthetic prostaglandin PGE1, with a plasma half-life of approximately 40 min [27]. PGE1 receptors are found in most tissues and organs of the human body. PGE1 regulates many physiological functions. Acting in the circulatory system, it causes vasodilation, lowers blood pressure generating transient tachycardia and increases cardiac output, protects the gastric mucosa by increasing mucous secretion, takes part in inducing an erection by increasing the flow in penile cavernous bodies, and maintains the patency of the ductus arteriosus during foetal life [23]. Misoprostol, a synthetic analogue of PGE1, is widely used in gynaecology and obstetrics. It promotes the effacement of the cervix and the generation of uterine contractile activity. In gynaecology, it can be used for the biochemical dilatation of the cervical canal before intra-uterine procedures. In obstetrics it is used to treat postpartum haemorrhage (PPH), for medical treatment of missed abortions and intrauterine foetal demise, therapeutic abortions, mole pregnancies, and finally to induce labour for medical indications [23]. It can be used orally, sublingually, buccally, vaginally, and rectally. Oral administration results in the fastest onset of action, the drug is absorbed slower from the vagina [23]. A slow-release form is also available in Poland: misoprostol vaginal insert (MVI), containing 200 μg of misoprostol releasing 7 μg of the substance per hour (Misodel®, Ferring Pharmaceuticals, Poland) [27].

Meta-analyses show that misoprostol is the most effective prostaglandin in labour induction when the measured outcome is VD within 24 h. The probability of not achieving VD within 24 h after vaginal misoprostol administration at a dose of ≥ 50 μg is the lowest among prostaglandins and amounts to 48% (95% credible interval (95% CrI) – 34–61%). For sustained-release misoprostol vaginal pessary, titrated (low) oral misoprostol solution (25 μg every 2 h up to 24 h), vaginal misoprostol < 50 μg, and buccal/sublingual misoprostol the probability is approximately 50% [4].

Misoprostol or dinoprostone?

Considering the VD not achieved within 24 h as an endpoint, dinoprostone is a slower acting prostaglandin. In the case of vaginal delivery, depending on the pharmaceutical form of dinoprostone, from 52% to 62% of patients do not achieve VD within 24 h. Cervical PGE2 is the least effective in this respect, with a failure rate of 65% (for the mechanical methods popular in Poland – the Foley catheter and Cook’s double balloon catheter, the failure rate is approx. 63–65%) [4]. Misoprostol seems to have the fastest and the strongest effect on the uterine muscle. However, this has an impact on its safety profile. The use of sustained-release misoprostol vaginal pessary and vaginal doses of misoprostol ≥ 50 μg is characterized by an estimated absolute risk of hyperstimulation at the level of 11% and 9%, respectively; in the case of dinoprostone it is lower and estimated (depending on the form and dose) at 3–6% [4]. A 2014 meta-analysis indicated that the use of low-dose oral misoprostol (< 50 μg) is characterized by lower caesarean section rates compared to placebo (OR = 0.62, 95% CrI: 0.47–0.80) [4]. It is worth noting, however, that in Poland the oral misoprostol preparation (200 μg) (Cytocept®, Pfizer Europe) is registered only for the prevention of gastric and duodenal ulcers during the use of non-steroidal anti-inflammatory drugs (NSAIDs), and its use in gynaecology and obstetrics is an out-of-label application [28]. An additional question about the oral form of misoprostol was raised in a 2021 meta-analysis comparing intracervical Foley catheter with oral misoprostol (≤ 50 μg) in IOL. Despite increasing the chance of a vaginal delivery the authors found a trend toward increasing adverse perinatal outcome in the misoprostol group. The study showed no difference in adverse maternal outcome [29]. The only form of misoprostol
registered for induction of labour is MVI 200 μg. The advantage of this preparation is that it can be used in the case of preterm repute of the membranes from 36 weeks [21, 26, 27]. When comparing the 2 types of inserts available on the Polish market (MVI200 μg and DVI 10 mg), it is worth noting the fundamental differences between the preparations. The EXPADITE study [30] directly comparing the use of MVI 200 μg vs. DVI 10 mg indicated a shorter median time to VD both in the nulliparous women (respectively, 29.2 ± 43.1 h, p < 0.001) and parous women (13.4 ± 20.1, p < 0.001), shorter time to achieve the active phase of labour (12.1 vs. 18.6 h, p < 0.001), and a lower percentage of patients requiring labour augmentation with oxytocin (48.1% vs. 74.1%) in the MVI group. There were no differences between groups in the percentage of CS. When analysing the available data from the study, it can be seen that DVI 10 mg had a better safety profile. Uterine tachysystole was more common in the MVI group (RR = 3.34, 95% CI: 2.2–5.07), as well as uterine tachysystole with foetal heart rate involvement (like late decelerations, bradycardia, or prolonged decelerations) (RR = 3.9, 95% CI: 2.35–6.48) and the need for intra-partum tocolysis use (RR = 2.97, 95% CI: 1.96–4.5) [30]. Also, in a cohort of Polish patients the use of MVI in labour pre-induction was associated with an increased risk of CS (OR = 2.14, 95% CI: 1.42–3.23) and vacuum extraction (OR = 3.29, 95% CI: 1.08–10.00) compared to intracervical Foley catheter [31].

In daily practice, such adverse events generate the need for close monitoring of the foetus and labour progression, and increase the workload for staff. The need for close monitoring of the foetus and labour pre-induction was associated with an increased risk of CS (OR = 2.14, 95% CI: 1.42–3.23) and vacuum extraction (OR = 3.29, 95% CI: 1.08–10.00) compared to intracervical Foley catheter [31].

In another randomized controlled trial Debo rah A, Wing [32] compared the efficacy of DVI 10 mg with MVI, but with a 100 μg dose. There were no differences in median time to VD (both nulliparous and parous women) and percentage of CS between patient groups induced with 100 μg MVI and 10 mg DVI. The groups also did not differ in terms of side effects such as uterine tachysystole, non-reassuring foetal heart rate pattern, need for tocolytic administration, meconium in amniotic fluid, and neonatological outcomes. Therefore, studies indicate that DVI 10 mg is a drug with a similar potency and adverse effect profile as MVI 100 μg (dose not available in Poland).

The adverse effect profile of DVI 10 mg made it extremely popular in Western Europe; in France is DVI used in 92.6% of maternity units during IOL (only 48.9% of the units used a balloon catheter) [33]. We found no studies in the literature on the most common practices currently employed in Polish maternity wards. However, it seems that the Foley catheter is the most popular pre-induction method.

Summary

The synthetic prostaglandins PGE1 and PGE2 are effective and widely used preparations for labour pre-induction. Taking into account the safety profile, strength of action, form of supply, as well as limitations resulting from registration indications, DVI 10 mg seems to be the optimal choice for labour pre-induction nowadays among prostaglandin preparations.

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Conflict of interest

The authors declare no conflict of interest.

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