Special Article

The Role of Prostaglandins in Labour Induction

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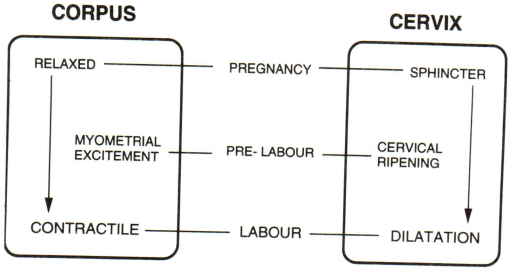
The search for safe and reliable methods of labour induction has led to the exploration of many different techniques and the application of a variety of pharmacological agents. Many of these have had little in common with normal physiology but those proving to be the most successful and most acceptable to patients have been those with a sound basis in normal physiology. The reason the prostaglandins have made such an impact on labour induction is that they represent the method which has hitherto most closely replicated the physiological control of spontaneous labour.

The factors which are responsible for the initiation of human labour, although steadily becoming clearer, are not yet fully understood[1].

The transition from pregnancy to labour entails fundamental physiological changes in the two principal components of the uterus namely the uterine corpus and the uterine cervix. The smooth muscle of the corpus (myometrium) must escape from the inhibitory influences which have maintained it in a state of quiescence while the fetus has grown and developed to the point of maturity required for its birth. Similarly the cervix must abandon its duties as the sentry at the gate of the uterus. It has required to remain rigidly closed to keep the developing fetus within the cavity of the quiescent uterus. Thus both components of the uterus require to undergo a *volte-face*. In the case of the cervix the change is from one of rigid resistance to compliance and dilatation. These changes, however, do not occur suddenly but rather as a gradual phenomenon evolving during the phase of pregnancy which is best described as *prelabour*. The normal onset of labour requires that these two changes occur in synchrony (Fig. 1).



While the precise controlling mechanisms governing these changes have not yet been fully elucidated, the

prostaglandins, especially PGE_2 and $PGF_{2\alpha}$ are indisputably and intimately concerned in the processes of myometrial excitement and cervical ripening[2,3]. The surge of prostaglandin release which accompanies the progression of normal labour is seen most dramatically in amniotic fluid, but changes in the activity of these substances within uterine tissues such as amnion, decidua, myometrium and cervix, together with the well recognised clinical effects of prostaglandins on the myometrium and cervix, point quite clearly to an essential biological role for these agents in the process of parturition. Furthermore, inhibitors of prostaglandin synthesis such as indomethacin represent the most potent tocolytic agents so far described[4]. It is therefore no exaggeration to say that in the absence of prostaglandins labour is not possible and when they are present in abundance, labour is irresistable.

Clinical use of Prostaglandins

When it comes to labour induction, prostaglandin $F_{2\alpha}$ is the poor relation of prostaglandin E_2. It is inferior in terms of potency, specificity and toxicity and its use in clinical practice can only be justified in countries where PGE_2 is available. While it does represent a potent stimulator of myometrial contractility, it appears to have little or no role in the process of cervical ripening and therefore might be considered to be very similar in its actions to oxytocin. Since it causes many more side effects than does oxytocin, it has no clinical advantages as a labour inducing agent over the time honoured use of oxytocin and it will not be further considered here. Prostaglandin E_2 is superior in every regard and will be the main subject of the remainder of this discourse.

It has become abundantly clear in recent years that local routes of prostaglandins hold the key to success. The obstetrician's ability to access the genital tract for the local delivery of prostaglandins has greatly enhanced their value. The local routes which are applicable for cervical ripening and induction of labour are vaginal, endocervical and extraamniotic. The last of these is the most effective and since it requires only a very small dose (0.5 mg PGE_2 in gel), side effects can be minimised. On the other hand it is the most invasive and perhaps the most potentially hazardous. In theory, infection may be introduced although in practice this has not proved to be a serious problem. In addition, haemorrhage may be provoked within the choriodecidual space and if so, the prostaglandins may be absorbed too rapidly with the potential for provoking uterine spasm. The possibility of inadvertent rupture of the membranes during the insertion of an extraamniotic catheter must also be borne in mind although this is also extremely rare in practice.

The vaginal route has the major attraction of simplicity although a significantly larger dose of prostaglandin may be required in order to ach-

ieve cervical ripening (usually 5 to 10 times as much). It may also be necessary to repeat vaginal applications to achieve this purpose and if so, an interval of no less than 6 hours should be allowed between doses and the dose in a gel formulation should not exceed 2 mg PGE_2. A half-way house between these two routes is represented by endocervical administration which may be an appropriate compromise. It is clearly less invasive and less hazardous than extraamniotic therapy and it may allow a more precise delivery of the prostaglandins to the target tissue. The appropriate dose is similar to the extraamniotic dose (around 0.5mg) provided such a dose can be made to stay in the endocervical canal. This technique suffers from disadvantages which arise from the anatomy of the cervix. If the cervix is already effaced and partially dilated it is difficult to identify an endocervical canal in which to place the therapy. On the other hand where the cervix is very unripe the canal may be quite narrow and the space available in which to deposit the prostaglandin gel may be quite small. Prostaglandins administered by this route may quite commonly either pass into the extraamniotic space or run back into the vagina thereby being less effective.

Much interest has concerned the search for appropriate vehicles for delivering prostaglandins and a variety of pessaries and gels have been developed for their differing release and absorption properties. The objectives should be to maximise efficiency and safety margins while minimising the dose rate and side effects. Local administration of prostaglandin E_2 can accomplish this while bringing the additional benefit of representing a form of intervention which has proved popular with mothers. They find it an agreeable approach resembling as it does more closely than any other method, the spontaneous onset of labour.

The intriguing aspect of the mechanism whereby vaginal PGE_2 induces labour lies in the observation that the onset of contractility is delayed for several hours after PGE_2 has been absorbed from the vagina and metabolised[5]. The establishment of uterine contractions is accompanied by a rise in circulating metabolite of $PGF_{2\alpha}$ suggesting that labour is the result of endogenous $PGF_{2\alpha}$ activated by exogenous PGE_2. This would go some way to explaining why the labour we see resembles spontaneous labour so closely.

A Rational Approach to Labour Induction

Three principal weapons are available for induction of labour in modern obstetric practice. These are :

1. Local administration of prostaglandin E_2
2. Amniotomy
3. Intravenous administration of oxytocin.

These three weapons should be applied either separately or in combi-

nation and the success of labour induction will depend on tailoring these techniques to the particular circumstances of the individual clinical case. The essence of success lies in an accurate assessment of the degree to which the events of prelabour have occurred. Two expectant mothers, both at their expected date of confinement, might represent two very different propositions and indeed be the opposite ends of a spectrum. The first may be on the threshold of spontaneous labour (i.e. at the end of prelabour) while the second may still be a long way from beginning labour and indeed prelabour may hardly have begun. In outward appearance, they may be indistinguishable, but the best way of distinguishing between them will be to carry out a pelvic assessment and calculate the Bishop score[6]. This particularly applies to primigravidae. A high Bishop score presages the imminent onset of spontaneous labour, while a low score suggests that this remains a distant prospect. More importantly, the response to labour induction is influenced very profoundly by the state of the cervix and again this is particularly in primigravidae. The mother whose labour is a distant prospect will almost certainly have a very low Bishop score, and if her labour is induced by inappropriate techniques such as amniotomy and intravenous oxytocin titration, the response will be disappointing with a high probability of prolonged labour, fetal distress, caesarean section and birth asphyxia[7]. In contrast, the mother on the threshold of spontaneous labour may require nothing more than amniotomy to achieve a successful and satisfactory outcome.

A simple way of viewing this is to focus on the most appropriate timing of amniotomy. Figure 2 shows a developing arc of the processes which make up the components of human parturition, namely prelabour, latent labour, active labour and delivery. This has been deliberately drawn to resemble the speedometer on a motor car. Rather than kilometres per hour, the units of measurement would in this instance be strength and frequency of uterine contractions.

Amniotomy should never be performed before the cervix is ripe. To do so is to increase dramatically the risk of fetal and maternal complications[8]. The optimal time for amniotomy is when uterine contractions are established and the cervix has attained full effacement and is already 3 or 4cm dilated. In spontaneous labour, adherence to this principle maximises the efficiency of labour and the ability of the attendants to supervise the welfare of the fetus. In addition, the amount of analgesia required may be

minimised[9].

If labour induction is required and the above conditions do not prevail, local administration of prostaglandin E_2 should be employed to bring them about. Where the cervix is already ripe, it is still appropriate to initiate the labour with a single applicantion of vaginal PGE_2 and then to add the influence of amniotomy once contractions are established. Such a policy was shown to be highly effective by Kennedy et al[10]. Their study compared the obstetric outcome of two groups, each of 50 mothers with a ripe cervix, requiring induction of labour. They were randomly allocated to a group receiving a single vaginal tablet of PGE_2, 3mg whose membranes were then ruptured 3-6 hours later, or to a group in whom amniotomy was performed at the outset and followed by immediate intravenous infusion of oxytocin. The two groups showed very similar obstetric results in the sense of lengths of labour and mode of delivery, but the prostaglandin approach was found to be markedly superior in respect of a lower incidence of postpartum haemorrhage and of neonatal jaundice. Moreover, the mothers who participated in this study showed a very clear preference for the prostaglandin technique rather than amniotomy and oxytocin (Table 1).

The overwhelming matermal preference for the prostaglandin technique is one of the most compelling arguments in favour of this approach.

Oxytocin remains a very potent pharmacological weapon but its used should now perhaps be restricted to mothers whose labours are not progressing effectively after the membranes have been ruptured.

Conclusions

Prostaglandin E_2 is currently the most effective agent available for the purpose of cervical ripening. If the cervix is already ripe, a small dose of PGE_2 may be all that is required to initiate a labour which very closely resembles spontaneous labour.

Amniotomy is the central event in the labour induction process. Al-

Table 1 Mother's response

Mother's response	Amniotomy +oxytocin	Vaginal PGE_2 tablet
Favourable	8	43
Non-committal	16	7
Unfavourable	26	0
TOTAL	50	50

though labour may progress to delivery with the membranes remaining intact, they would generally rupture at an earlier stage and such rupture is usually associated with a heightened activity of endogenous prostaglandins. The timing of amniotomy is crucial. Peformed too early before the cervix is ripe, it will lead to an increased rate of complications. If delayed beyond the optimal point for its introduction (a fully effaced cervix 3-4cm dilated) we may lose the advantage of its uterine sensitising influence.

Oxytocin remains a powerful myometrial stimulant if the uterus is already primed to respond to it by prostaglandins, either endogenous or exogenous. It must be given intravenously and many mothers find this disagreeable. In most instances of labour induction, a proper combination of prostaglandin therapy followed by amniotomy, may allow the use of oxytocin to be avoided but it remains an important therapy of final resort to carry labour through to its completion.

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