Regular Review

Prostaglandins in human reproduction

M P EMBREY

Prostaglandins undoubtedly play a major part in reproduction, including the control of parturition, and are now believed also to be concerned in many other vital processes, but their precise functions are not fully understood. Nevertheless, much is known; and the prostaglandins are now widely used. Current clinical applications include prelabour cervical priming as well as induction of labour, termination of first and second trimester pregnancy, and management of abnormal pregnancy.

The prostaglandins are hormone-like compounds. They differ from classical hormones in being synthesised and released locally on demand from precursor fatty acids and are rapidly inactivated and metabolised in the blood stream. Within cells they are thought to exert their effects by changes in cyclic AMP; release of calcium ions may be important in some target tissues, including the myometrium.

The naturally occurring prostaglandins are a group of at least 14 related compounds, each a 20-carbon hydroxyfatty acid possessing a five-carbon ring and two side chains. Prostaglandin chemistry and nomenclature are complex, but of the naturally occurring prostaglandins only two, prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), are clinically important in reproduction. Biosynthetic and metabolic pathways need not be considered here except to observe that some of the endoperoxide precursors are physiologically active and that two recently discovered related compounds, prostacyclin (PGI_2) and thromboxane A_2, are powerful regulators of blood clotting. The activity of prostaglandins may be modified by substitution of artificial groups in the molecule (for example 15-methyl- or 16:16-dimethyl-groups), resulting in analogues resistant to degradation or more specific in action; some already show promise in clinical use.

The therapeutic uses of the prostaglandins in labour and abortion depend on three properties. Firstly, they are strikingly uterotonic, stimulating or augmenting uterine contractions. Despite contradictions in very early work, both PGE_2 and $PGF_{2\alpha}$ stimulate contractions, PGE_2 being some five times more potent than $PGF_{2\alpha}$. Secondly, the prostaglandins are responsible for the structural alterations in its connective tissue which soften and "ripen" the uterine cervix. A third possible role as a luteolytic agent, inhibiting the corpus luteum and preventing production of progesterone, has been substantiated in animals but remains unproved in man.

The prostaglandins are also concerned in other reproductive functions including ovulation and the control of menstruation, so that their clinical uses seem likely to be extended. In other instances (for example, dysmenorrhoea, thought to be due to accumulation of endometrial prostaglandins) there is a place for non-steroidal, anti-inflammatory drugs which are "prostaglandin synthesis inhibitors." The use of prostaglandin inhibitors in premature labour is more controversial; there is a potential risk that the fetus could be compromised since patency of the ductus arteriosus is believed to be maintained by endogenous prostaglandins.

The prostaglandins were first used clinically by intravenous infusion to induce labour in 1968[1 2] and to induce abortion in 1970.[3 4] As it became apparent that intravenous administration, especially in the high concentration needed for abortion, caused unpleasant side effects (notably vomiting and diarrhoea), this route has since been largely superseded, with varying degrees of success, by alternatives including oral, intramuscular, intrauterine (extra-amniotic or intra-amniotic), and vaginal administration.

Induction of labour and cervical ripening

The early studies of induction of labour using intravenous prostaglandins showed the effectiveness of the method and established dose ranges. Initial comparisons with orthodox oxytocin infusion produced conflicting views,[5] but continuing experience showed that generally prostaglandins were no more effective than oxytocin—except in patients in whom the cervix was unripe[6] (see later). Early fears that prostaglandins would produce hypertonus and fetal distress more often than oxytocin have not been clearly substantiated.[7] The chief disadvantage of the method is the frequency of gastrointestinal side effects, and as a result oral, vaginal, and intrauterine (extra-amniotic) routes of administration have been explored in recent research studies.

The convenience of oral treatment makes it attractive, but it is generally less effective than other routes of administration. The necessary systemic absorption produces troublesome side effects, which with $PGF_{2\alpha}$ are severe. Oral tablets of PGE_2 are available and are usually prescribed at a dose of 0·5 mg hourly (increasing step-wise to 2 mg) and combined with amniotomy. Gastrointestinal side effects occur in about one-fifth of patients, and vomiting reduces the likelihood of successful induction (especially in primigravidae, who require higher doses). The usefulness of the method is chiefly in multiparae with favourable induction prospects.[8]

The most recently identified obstetric use of the prostaglandins is that of "priming" or "ripening" (that is, softening and effacing) the cervix—in practical terms an important development. Though the ripening effect was commented on in some early clinical studies,[2] many assumed that it was the indirect result of induced uterine contractions. Now there is increasing evidence that prostaglandins, especially PGE_2, bring about the structural alterations in the connective tissue of the cervix accompanying ripening which are a necessary prelude to progressive labour and delivery.[9 10]

The prognosis in induced labour is governed primarily by the degree of ripeness of the cervix, best expressed in a Bishop score or "inducibility" score.[11] When the cervix is unripe (long, tightly shut, and rigid) labour is difficult to establish and it may "fail to progress" or be prolonged, often resulting in a high caesarean section rate and a poor outcome for mother and fetus.[12]

Prospects can be much improved by ripening of the cervix with prostaglandins before induction. Latent-phase cervical effacement and dilatation are achieved with little or no distress to the patient, with intact fetal membranes, and without jeopardy to the fetus. Local administration is best; the technique first used (in 1976) was extra-amniotic administration through a transcervical catheter of PGE_2 in a methyl cellulose gel the night before planned induction.[12] Assessment of this method in 121 primigravidae with unripe cervices (inducibility score 0-3) showed that one-fifth laboured without further intervention, while in the remainder labour was shorter, the caesarean section rate was halved, and fetal well-being improved compared with a control group.

Soon, however, essentially similar benefits were being obtained by the simpler non-invasive technique of vaginal administration of PGE_2 gel.[13] In a group of 168 primigravidae the instillation of PGE_2 gel resulted within half to 2 hours in backache and uterine contractions of mild intensity (recurring at one to three minute intervals and not exceeding 40 mm Hg pressure), persisting for four to five hours and then waning or else progressing to established labour. With PGE_2 5 mg the cervical score improved in 88% while 49% began labour before planned induction. There were no maternal or fetal side effects.[13]

As the method was extended to primigravidae and multigravidae with Bishop's scores in all ranges the results showed that as the pretreatment cervical score increased so did the proportion of patients labouring during priming, while the average duration of labour decreased, the frequency of spontaneous vaginal delivery increased, analgesic requirements diminished, and caesarean section was less often required. These benefits were greatest when labour followed priming without the need for formal induction—which occurred in about 40% of primigravidae with an unripe cervix rising to 90% in multigravidae with a favourable cervix.[14]

The value of preinduction ripening of the cervix with vaginal PGE_2 has since been confirmed in a much wider experience; an alternative to the gel is the use of glyceride-based or other simple pessaries prepared in hospital pharmacies.[15 16]

Differences in patient selection, treatment protocols, and criteria for success make comparisons of induction studies difficult. Nevertheless, in one representative study using 3 mg pessaries of PGE_2 43% of the 110 primigravidae with Bishop scores of 0-4 laboured after a single priming pessary without formal induction while the remainder received a second pessary. There were six failed inductions. In multigravidae when the cervix was ripe (Bishop score ≥ 4) 90% laboured without additional measures.[16] In another trial, when inducibility scores were favourable, pretreatment with PGE_2 pessaries (5 mg in primigravidae, 2·5 mg in multigravidae) was followed by amniotomy in three hours. Successful labour and delivery ensued in about 80% of multigravidae and 60% of primigravidae without the need for oxytocin infusion; further, there was a reduced requirement of epidural analgesia and the incidence of postpartum haemorrhage was lowered.[16]

While there have been no control studies, the cervical ripening method has been used successfully in many patients previously delivered by caesarean section and in those with breech presentation, in whom the promotion of the effacement and dilatation of the latent phase of labour with intact membranes may have merit.[15] Most authors have not considered it necessary to monitor "low risk" and uncomplicated cases, but continuous monitoring (at least for the first four to five hours) would seem prudent for patients in whom insufficiency is suspected.[14 15]

The evidence from all these published data points to the relative safety of the method and its freedom from adverse effects. Because priming doses are low, gastrointestinal symptoms are very uncommon (less than 1%), as is any thermogenic effect. Uterine hypertonus is likewise rare, while if it occurs fetal distress is not always evident.

Nevertheless, while the value of vaginal prostaglandins in ripening the unfavourable cervix when labour needs to be induced may be considered well established, their use for routine induction of labour is perhaps more controversial. The method is gaining in popularity, for it offers important benefits in patient acceptability and ease of management for medical personnel. Labour tends to be more natural than after formal induction, analgesic requirements are reduced, and both women in labour and nursing staff appreciate the likely avoidance of intravenous oxytocin infusion and the immobility it entails, while permitting patients to walk about during early labour may actually hasten delivery.

The prostaglandin cervical priming method would be still more widely used were a conveniently packaged product available. Unfortunately, in the current simple formulations PGE_2 does not possess adequate long-term stability and this has prevented development of a commercial product. This lack has prompted the use in some units of oral tablets of PGE_2 by the intravaginal route.[17] An additional practical problem is that dissolution and absorption of the available products are rapid (within two to four hours), with the possible risk in some multiparae of unduly rapid labour. A recent report of induction of labour using a novel polymer vaginal device suggests that these drawbacks can be resolved to provide a stable delivery vehicle giving controlled sustained release of PGE_2.[18] Such a development would be welcome, for on grounds of efficacy, safety, and acceptability vaginal PGE_2 seems likely to be used increasingly for cervical ripening as a prelude to formal induction or as an alternative procedure which may make induction unnecessary.

Other obstetric uses

The management of fetal death in utero has been much simplified by the prostaglandins, which now provide safe and effective means of emptying the uterus in missed abortion or intrauterine death near term and also in cases of hydatidiform mole and anencephaly. Intravenous infusion or extra-amniotic injection may be used, but equally good results follow simple vaginal administration of PGE_2 in gels or pessaries.[19] High dosage, as in one series,[20] provokes gastrointestinal irritation, but if dosage is related to gestation and the size of the uterus, side effects are not troublesome.

Termination of pregnancy

Despite their potential as fertility-regulating agents, the prostaglandins have not yet fulfilled all their promise. Experience has so far fallen well short of expectations in relation to termination of early pregnancy. Prostaglandins have,

however, established a place in the termination of second trimester pregnancy, and in many units they are used to the exclusion of alternative methods.

Second trimester terminations—The shortcomings of the natural prostaglandins (PGE_2 and $PGF_{2\alpha}$) as abortifacients are related to their rapid inactivation and the degree of gastrointestinal irritation caused by systemic absorption. Early studies showed that intravenous treatment for abortion requires high dosage (five times that required for induction of labour) and causes unacceptably severe vomiting and diarrhoea, while oral treatment is ineffective. Vaginal administration also results in prominent side effects and is not consistently successful.

Fortunately, however, the prostaglandins act locally and are effective when given by the intrauterine route. This was first achieved by the simple technique of extra-amniotic instillation using a catheter introduced just through the cervix, and later by intra-amniotic injection through the abdominal wall. The latter was promoted as a "one shot" method, but a large experience of treatment with intra-amniotic $PGF_{2\alpha}$ has shown that, for an acceptable level of efficacy (90% or more abortions within 48 hours; mean abortion time less than 24 hours), an injection of 25 mg frequently needs to be repeated, while if the initial dose is increased to 40-50 mg gastrointestinal side effects are severe.[5 21] Because of its limited availability intra-amniotic PGE_2 has been used less widely, but several studies have shown its effectiveness, the administration of 20 mg, or 10 mg repeated in six hours, giving a high success rate with relatively few side effects.[5 21]

The extra-amniotic method is comparable in efficacy with the intra-amniotic route. Two hourly instillations of PGE_2 200 μg (or $PGF_{2\alpha}$ 750 μg) or equivalent amounts by continuous infusion results in abortion within 48 hours in some 90% of patients.[22 23] In 1975 it was shown that the extra-amniotic administration of PGE_2 1·5-3 mg in a viscous methyl cellulose gel provides a more prolonged effect, limiting or eliminating the need for frequent or continuous injection and gives equivalent results.[24] Nowadays this is the method commonly used. Because the dosage is low the incidence of gastrointestinal effects is lower with extra-amniotic than with other routes of administration, while the theoretical risk of infection has in practice not proved a hazard.

To shorten abortion times prostaglandins may be used in conjunction with other methods such as the intra-amniotic injection of hyperosmolar saline or urea solutions,[25] or laminaria tents (advocated particularly in the United States). Alternatively, abortion can be accelerated by using the enhancement effect of intravenous oxytocin (100 mU/min).[26] Intra-amniotic hypertonic solutions carry a risk of serious adverse effects—for example, hypernatraemia or consumptive coagulopathy—and are probably best reserved for ensuring lack of fetal viability in gestations of 20 weeks or over.

Though prostaglandin analogues are not available in Britain except for investigations, several have been evaluated clinically and the $PGF_{2\alpha}$ analogue 15-methyl $PGF_{2\alpha}$ has been widely tested in other countries. Longer acting than the parent compound (because the 15-methyl-group inactivates the dehydrogenase enzyme responsible for the first and most rapid step in prostaglandin metabolism), it has the merit that a single intra-amniotic injection of 2·5 mg[27 28] or a single extra-amniotic administration of 1 mg[28 29] usually suffices, but side effects are unfortunately troublesome. While repeated intramuscular injection is effective, the accompanying severe gastrointestinal side effects are generally unacceptable.[30] The analogue has also been administered per vaginam (1-1·5 mg three hourly) in glyceride-based pessaries.[31] Its high efficacy (resulting in about 90% abortions in 30 hours) is again marred by the high level of gastrointestinal symptoms. Moreover, these success rates were not substantiated when a single "longer acting" Witepsol pessary was used,[32] while incorporation of the agent in a silastic vaginal device did not provide the expected controlled, sustained release and gave disappointing results.[33 34] Equally or more effective, yet causing many fewer side effects, the 16:16-dimethyl-PGE_2 analogue and its semicarbazone ester would have great potential were it not for their lack of stability.[35] Improved products may be forthcoming. Meantime, the vaginal route remains an attractive goal because of its non-invasive nature, though in mid-pregnancy a considerable proportion of incomplete abortions occur (40-70%) requiring evacuation.

First-trimester termination—Most first trimester abortions are dealt with surgically by vacuum aspiration and generally complications are few, but potential risks from injury and haemorrhage are associated with rapid mechanical dilatation of the cervix. With the aim of reducing these problems and—possibly—the risk of premature delivery from cervical incompetence in a subsequent pregnancy, prostaglandins may be administered not to induce abortion but for their cervical "priming" effect before surgery. Endocervical administration of PGE_2 gel and intravaginal PGE_2 in a pessary[36] have both been used, but the most promising results have come from one of the newer PGE analogues either in a vaginal suppository[37] or intramuscularly.[38] Such methods are likely to be used more frequently as these newer preparations become available.

Early investigators prophesied an important place in fertility regulation for the prostaglandins when used to induce menstruation or prevent or interrupt early pregnancy through luteolysis or interference with implantation by effects on uterotubal contractility. At this early stage of pregnancy abortion may be almost indistinguishable from normal menstruation, and, provided bleeding is not unduly prolonged and pain and side effects are kept to a minimum, the method has great potential.

To date, however, the luteolytic effect in women has not been substantiated and the attainment of the expected objectives has proved elusive. Yet the prospect of a simple, safe, non-invasive, chemical method for early abortion remains a major goal, and recent research has concentrated on the development of vaginal pessaries containing newer prostaglandin analogues.

Though the natural prostaglandins are effective by transcervical intrauterine injection the results have been disappointing when they are given vaginally. Nevertheless, vaginal treatment became practicable with the synthesis of prostaglandin analogues which, by resisting metabolic degradation, have enhanced potency and longer action or show greater specificity of action, so causing fewer side effects. The new compounds have been administered in cellulose derived gels or simple lipid-based pessaries (usually three to four hourly) with a degree of success, though clinical trials have shown that not all the problems have been resolved. For example, while the uterotonic potency of the $PGF_{2\alpha}$ analogue 15-methyl-$PGF_{2\alpha}$ (the most widely tested analogue) is high, the severity of gastrointestinal side effects limits its clinical applicability.[39 40]

More selective in action, the 16-16-di-methyl-PGE_2 analogue and its semicarbazone ester are, at least, equally effective and cause fewer adverse effects when given in repeated vaginal pessaries[35 40] and would have considerable clinical impact were it not that problems of chemical instability have hampered commercial development. The same lack

of stability affects other recent PGE derivatives which have shown clinical promise. One of these, 16-phenoxy-ω-tetranor-PGE_2, has given encouraging results by the intramuscular route,[41] the other 16:16-di-methyl-trans-Δ_2-PGE_1 when administered vaginally.[42]

Current research is seeking to overcome the disadvantages of the products available. The instability of PGE_2 and PGE analogues may be resolved by the employment of improved gels[43] or by new sustained-release vaginal delivery systems.[18] The development of such devices would undoubtedly promote the use of vaginal PGE_2 in the induction of labour on a much wider scale and might be expected to result in better prostaglandin products for use in the termination of early pregnancy and menstrual induction. A prostaglandin analogue with an appreciable luteolytic effect in women remains an actively pursued research goal, while other derivatives exhibiting greater specificity of action and therefore fewer side effects are being sought in pharmaceutical laboratories. These and other related research developments may be expected to extend to the range of the clinical uses of these remarkable compounds in obstetrics and gynaecology.

M P EMBREY

Clinical Reader in Obstetrics and Gynaecology,
University of Oxford
and Honorary Consultant, Nuffield Department of Obstetrics

[1] Karim SMM, Trussell RR, Patel RC, Hillier K. Response of pregnant human uterus to prostaglandin-Fs_α—induction of labour. *Br Med J* 1968;iv.621-3.
[2] Embrey MP. The effect of prostaglandins on the human pregnant uterus. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1969; **76**:783-9.
[3] Karim SMM, Filshie GM. Therapeutic abortion using prostaglandin $F_{2\alpha}$. *Lancet* 1970;i:157-9.
[4] Embrey MP. Induction of abortion by prostaglandins E_1 and E_2. *Br Med J* 1970;ii:258-60.
[5] Embrey MP, Hillier K. Prostaglandins in reproduction. In Stallworthy J, Bourne G, eds. *Recent advances in obstetrics and gynaecology*. Edinburgh: Churchill-Livingstone, 1977:75-104.
[6] Calder AA, Embrey MP. Comparison of intravenous oxytocin and prostaglandin E_2 for induction of labour using automatic and non-automatic infusion techniques. *Br J Obstet Gynaecol* 1975;**82**:728-33.
[7] Friedman EA, Sachtleben MR. Effect of oxytocin and oral prostaglandin E_2 on uterine contractility and fetal heart rate patterns. *Am J Obstet Gynecol* 1978;**130**:403-7.
[8] Gordon-Wright AP, Dutt TP, Elder MG. The routine use of oral prostaglandin E_2 tablets for induction or augmentation of labour. *Acta Obstet Gynecol Scand* 1979;**58**:23-6.
[9] Hillier K, Wallis RM. Prostaglandins, steroids and the human cervix. In: Ellwood DA, Anderson ABM, eds. *The cervix in pregnancy and labour*. Edinburgh: Churchill Livingstone, 1981:144-62.
[10] Ellwood DA, Mitchell MD, Anderson ABM, Turnbull AC. A significant increase in the in-vitro production of prostaglandin E by ovine cervical tissue at delivery. *J Endocrinol* 1979;**81**:133P-4P.
[11] Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol* 1964;**24**: 266-8.
[12] Calder AA, Embrey MP, Tait T. Ripening of the cervix with extra-amniotic prostaglandin E_2 in viscous gel before induction of labour. *Br J Obstet Gynaecol* 1977;**84**:264-8.
[13] MacKenzie IZ, Embrey MP. Cervical ripening with intravaginal prostaglandin E_2 gel. *Br Med J* 1977;ii:1381-4.
[14] MacKenzie IZ, Embrey MP. The influence of pre-induction vaginal prostaglandin E_2 gel upon subsequent labour. *Br J Obstet Gynaecol* 1978;**85**:657-61.
[15] Shepherd J, Pearce JMF, Sims CD. Induction of labour using prostaglandin E_2 pessaries. *Br Med J* 1979;ii:108-10.
[16] MacKenzie IZ, Embrey MP. A simpler approach to labor induction using a lipid-based prostaglandin E_2 vaginal suppository. *Am J Obstet Gynecol* 1981 (in press).
[17] Gordon-Wright AP, Elder MG. Prostaglandin E_2 tablets used intravaginally for the induction of labour. *Br J Obstet Gynaecol* 1979;**86**: 32-6.
[18] Embrey MP, Graham NB, McNeill ME. Induction of labour with a sustained-release prostaglandin E_2 vaginal pessary. *Br Med J* 1980; **281**:901-2.
[19] MacKenzie IZ, Davies AJ, Embrey MP. Fetal death in utero managed with vaginal prostaglandin E_2 gel. *Br Med J* 1979;i:1764-5.
[20] Southern EM, Gutknecht GD, Mohberg NR, Edelman DA. Vaginal prostaglandin E_2 in the management of fetal intrauterine death. *Br J Obstet Gynaecol* 1978;**85**:437-41.
[21] Karim SMM, Amy JJ. Interruption of pregnancy with prostaglandins. In: Karim SMM, ed. *Prostaglandins and reproduction*. Lancaster: M T P Press Ltd, 1975:77-148.
[22] Embrey MP, Hillier K, Mahendran P. Induction of abortion by extra-amniotic administration of prostaglandins E_2 and $F_{2\alpha}$. *Br Med J* 1972; iii:146-9.
[23] Miller AWF, Calder AA, Macnaughton MC. Termination of pregnancy by continuous intrauterine infusion of prostaglandins. *Lancet* 1972;ii: 5-7.
[24] MacKenzie IZ, Embrey MP. Single extra-amniotic injection of prostaglandins in viscous gel to induce abortion. *Br J Obstet Gynaecol* 1976; **83**:505-7.
[25] Craft I. Intra-amniotic urea and prostaglandin E_2 for abortion. A clinical study to determine the efficacy of using a variable prostaglandin dosage. *Prostaglandins* 1973;**4**:755-63.
[26] Embrey MP, Hillier K, Mahendran P. Termination of pregnancy by extra-amniotic prostaglandins and the synergistic action of oxytocin. In: Bergstroem S, ed. *International workshop on prostaglandins, Vienna 1972. Advances in the biosciences*. Vol 90. London: Pergamon Press, 1973;507-13.
[27] World Health Organisation Task Force on the use of prostaglandins for the regulation of fertility. Prostaglandins and abortion III. Comparison of single intra-amniotic injections of 15-methyl prostaglandin $F_{2\alpha}$ and prostaglandin $F_{2\alpha}$ for termination of second-trimester pregnancy: an international multicentre study. *Am J Obstet Gynecol* 1977;**129**:601-6.
[28] Tejuja S, Choudhury SD, Manchanda PK. Use of intra- and extra-amniotic prostaglandins for the termination of pregnancies: report of multicentric trials in India. *Contraception* 1978;**18**:641-52.
[29] World Health Organisation Task Force on the use of prostaglandins for the regulation of fertility. Prostaglandins and abortion II. Single extra-amniotic administration of 0·92 mg of 15-methyl prostaglandin $F_{2\alpha}$ in Hyskon for termination of pregnancies in weeks 10 to 20 of gestation: an international multicentre study. *Am J Obstet Gynecol* 1977;**129**:597-600.
[30] World Health Organisation Task Force on the use of prostaglandins for the regulation of fertility. Prostaglandins and abortion I. Intramuscular administration of 15-methyl prostaglandin $F_{2\alpha}$ for induction of abortion in weeks 10 to 20 of pregnancy. *Am J Obstet Gynecol* 1977;**129**:593-6.
[31] World Health Organization Task Force on the use of prostaglandins for the regulation of fertility. Repeated vaginal administration of 15-methyl-$PGF_{2\alpha}$ methyl ester for termination of pregnancy in the 13th-20th week of gestation. *Contraception* 1977;**16**:175-81.
[32] Tejuja S, Choudhury SD, Manchanda PK, Malhotra U. Indian experience with a single long-acting vaginal suppository for the termination of pregnancies. *Contraception* 1979;**19**:191-6.
[33] Hendricks CH, Dingfelder JR, Gruber WS. Clinical observations with a prostaglandin-containing silastic vaginal device for pregnancy termination. *Prostaglandins* 1976;**12**, suppl:99-122.
[34] Lauersen NH, Wilson KH. The abortifacient effectiveness and plasma prostaglandin concentrations with 15(S)-15-methyl prostaglandin $F_{2\alpha}$ methyl ester-containing vaginal silastic devices. *Fertil Steril* 1976;**27**: 1366-73.
[35] Karim SMM, Ratnam SS. Termination of pregnancy with vaginal administration of 16, 16 dimethyl prostaglandin E_2 p-benzaldehyde semicarbazone ester. *Br J Obstet Gynaecol* 1977;**84**:135-7.
[36] MacKenzie IZ, Fry A. Prostaglandin E_2 pessaries to facilitate first trimester aspiration termination. *Br J Obstet Gynaecol* 1981 (in press).
[37] Karim SMM, Choo HT, Cheng P. Cervical dilatation with prostaglandin analogues prior to vaginal termination of first trimester pregnancy in nulliparous patients. *Prostaglandins* 1975;**9**:631-8.
[38] Ulbrich I, Bartels H. Clinical results with sulprostone. In: *International sulprostone symposium, Vienna*. Berlin: Schering AG, 1978:61-6.
[39] Bygdeman M, Martin JN Jr, Leader A, *et al*. Early pregnancy interruption by 15(S) 15 methyl prostaglandin $F_{2\alpha}$ methyl ester. *Obstet Gynecol* 1976; **48**:221-4.
[40] MacKenzie IZ, Embrey MP, Davies AJ, Guillebaud J. Very early abortion by prostaglandins. *Lancet* 1978;i:1223-6.
[41] Schmidt-Gollwitzer M, Schussler B, Schmidt-Gollwitzer K, Nevinny-Stikel J. Recommendations for the treatment of induction of abortion with sulprostone. In: *International sulprostone symposium, Vienna*. Berlin: Schering AG, 1978:119-26.
[42] Karim SMM, Ratnam SS, Ilancheran A. Menstrual induction with vaginal administration of 16, 16 dimethyl trans-Δ^2-PGE methyl ester (ONO 802). *Prostaglandins* 1977;**14**:615-6.
[43] Ulmsten U, Kirstein-Pedersen A, Stenberg P, Wingerup L. A new gel for intracervical application of prostaglandin E_2. *Acta Obstet Gynecol Scand* 1979;suppl 84:19-21.