THE UNRIPE CERVIX

a thesis presented in two volumes by

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VOLUME I

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"O that this too too solid flesh would melt,

thaw and resolve itself into a dew."

HAMLET: Act 1, Scene 2.

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ABBREVIATIONS

cm	.....	centimetre (s)
d.p.m.	..	degradations per minute
G	.....	gramme (s)
^{3}H	.....	tritium
mg	.....	milligram (s)
min	.....	minute
ml	.....	millilitre (s)
mm	.....	millimetre (s)
mu	.....	milliunit (s)
ng	.....	nanogram (s)
n.s.	...	not significant
pH	.....	hydrogen ion concentration
PG	.....	prostaglandin
pg	.....	picogram (s)
r.p.m.	.	revolutions per minute
µg	.....	microgram (s)
µl	.....	microlitre (s)
µu	.....	microunit (s)
%	.....	per cent
^{o}C	.....	degrees centigrade

S U M M A R Y

SUMMARY

The thesis describes clinical and laboratory research conducted between October 1972 and August 1975 during the candidate's tenure of a Research Fellowship in the Nuffield Department of Obstetrics and Gynaecology, the University of Oxford. All the clinical studies were performed in the Maternity Department of the John Radcliffe Hospital, Oxford.

The central theme of the thesis is the phenomenon of cervical ripening which usually takes place during the last few weeks of pregnancy. Cervical ripening is recognised clinically by the changes which occur in the cervix, and these include softening of the tissues, progressive effacement and finally dilatation of the cervix. As these changes take place, the cervix becomes more anteriorly situated in the pelvis and the presenting part may descend. Based on these clinical criteria, a scoring system was developed which enabled an objective assessment of three central questions:

1. What mechanisms control cervical ripening?
2. What are the clinical implications of failure of cervical ripening?

and 3. How may the clinical outcome for such patients be improved?

The significance of an unripe cervix lies in its association with prolongation of pregnancy beyond term and with increased maternal and fetal morbidity especially if labour is induced

induced/

by conventional methods. These problems are commoner and more serious among primigravidae and so the research was concentrated on such patients. A major objective of the work described in this thesis was to examine how prostaglandins influenced cervical ripening and how they could be used therapeutically to improve the clinical outcome.

The thesis begins with a historical review which is presented in two parts: a critical review of induction of labour, and an account of the discovery, development and experience with prostaglandins up to the time the research was commenced. Increased knowledge and availability of prostaglandins had progressed to the stage where these agents were being investigated in a few centres for induction of abortion and labour.

The historical review is followed by a discussion of the current understanding of the physiological control of cervical ripening. This appears to be a complex interaction of central changes in the physical properties of cervical tissue, in particular collagen fibres, and the gradual evolution over several weeks of uterine contractility which will culminate in the onset of labour. Both appear to be mainly the result of hormonal changes..

The clinical studies are then presented. By means of two studies, one retrospective and one prospective, amniotomy

amniotomy/

and intravenous oxytocin infusion is shown to be a satisfactory method of labour induction for primiparae who have ripe cervices before the onset of labour; in sharp contrast the two studies show that a poor response to this method of induction may be expected if the cervix is unripe at the time of amniotomy.

Such patients show high rates of morbidity in the form of prolonged labour, maternal pyrexia, caesarean section and birth asphyxia.

A randomised, double blind study is then described in which 100 primiparae had labour induced by amniotomy followed by either intravenous prostaglandin E_2 or intravenous oxytocin. While those patients who received prostaglandins showed a better response in terms of progress in labour and fewer adverse fetal effects, these benefits were offset by frequent and distressing maternal side effects such as vomiting and a painful erythema at the site of infusion.

Attention then turned to local (intra-uterine) administration of prostaglandins, following the success of this approach for therapeutic abortion. To demonstrate its safety and effectiveness in more advanced pregnancies, the extra-amniotic technique of prostaglandin E_2 infusion was first applied to cases of anencephaly and fetal death in utero. As well as affording reassurance that the technique might usefully and safely be applied in viable pregnancies, these studies also established its value in management of these problematic non-viable

non-viable/

pregnancies. After a pilot study of unselected cases of labour induction, the method was applied with good effect in a large series of primiparae with very unripe cervices. This achieved low rates of caesarean section and birth asphyxia with almost total elimination of the maternal side effects of prostaglandins.

The final clinical study in the thesis describes a technique which was developed to achieve ripening of the unripe cervix before labour induction is undertaken. Prostaglandin E_2 was suspended in a highly viscous gel ("Tylose") and given as a single extra-amniotic bolus dose to patients with an unripe cervix on the day before induction of labour. In a series of 121 primiparae this was shown to be a highly effective technique for ripening the cervix and bringing about a shortening of labour and a similar reduction of maternal and fetal morbidity as that seen with extra-amniotic infusion of prostaglandin E_2. The value of these techniques in cases of breech presentation, trial of labour and previous caesarean section is also discussed .

Laboratory studies carried on in parallel with the clinical studies investigated the role of endogenous prostaglandins in parturition and cervical ripening. Prostaglandins of the E and F series were shown to increase sharply in the amniotic fluid between mid-pregnancy and term. Higher levels were found in early spontaneous labour than in

than in/

oxytocin induced labour at a time of greater uterine activity, and in both types of case the levels rose steeply during the active or acceleratory phase of labour. The levels of both E and F prostaglandins in amniotic fluid obtained at the time of amniotomy and oxytocin induction were found to be closely related to the degree of cervical ripeness, the uterine sensitivity to oxytocin and the length of induced labour.

The conclusions of the thesis are as follows:-

1) The phenomenon of cervical ripening in late pregnancy is an essential part of the normal transition from pregnancy to spontaneous labour.

2) Failure of such ripening is an indication of an abnormality in the endocrine millieu of the pregnancy associated with impaired endogenous prostaglandin production.

3) Induction of labour by conventional means without regard to the condition of the cervix is likely to result in greater morbidity for those in whom it remains unripe.

4) The use of extra-amniotic prostaglandin therapy in such patients, either for induction of labour or for pre-induction cervical ripening, will go some way towards restoring their prospects of a satisfactory labour and delivery.

Future research should be directed to further understanding of the mechanisms responsible for the spontaneous onset of labour.

labour./

In this way, it is hoped that new techniques will be developed which will enable more precise control of uterine activity and cervical changes so as to ensure greater safety for both mother and child.

C H A P T E R I

INTRODUCTION

CIRCUMSTANCES OF THE RESEARCH WORK.

OUTLINE OF THE THESIS.

PRECISE ROLE OF THE CANDIDATE IN THE RESEARCH.

ACKNOWLEDGEMENTS.

C H A P T E R I

INTRODUCTION

This thesis describes work carried out between October 1972 and August 1975 while the candidate held a Clinical Research Fellowship in the Nuffield Department of Obstetrics and Gynaecology of the University of Oxford. Before taking up this appointment I was Registrar in Obstetrics and Gynaecology at Glasgow Royal Maternity Hospital and Glasgow Royal Infirmary. While there I had acquired an interest in prostaglandins encouraged by Professor M.C. Macnaughton and Dr. A.W.F. Miller, who had allowed me to participate in the first clinical trials in Scotland of prostaglandins for therapeutic abortion (Miller, Calder and Macnaughton, 1972).

In Oxford I was fortunate to join a newly formed prostaglandin research group led by Mr. Mostyn Embrey, Clinical Reader in the Nuffield Department. The John Radcliffe Hospital had been opened earlier in 1972 to rehouse the maternity departments from the Radcliffe Infirmary (Nuffield Department) and the Churchill Hospital (Area Department). The new hospital occupied a site adjacent to the Nuffield Institute for Medical Research where the main emphasis was on reproductive biology.

Mr. Embrey had a distinguished reputation as a research worker, particularly in the field of the physiology and pharmacology of the uterus. As First Assistant to the late Professor J. Chassar Moir, his studies of the clinical effects

effects/

of ergometrine, oxytocin, vasopressin and "Syntometrine" had helped to shape the use of such agents in clinical practice. More recently he had been at the forefront of the emerging research field of prostaglandins and was the first British investigator to study their actions on the uterus.

The Research Group

Having attracted research funds from the Worcester Foundation for Experimental Biology, the Upjohn Company and the World Health Organisation, Mr. Embrey was able to form a prostaglandin research group consisting of two clinicians, two research nurses, a pharmacologist, two laboratory technicians and a secretary. The pharmacologist was Dr. Keith Hillier who had just completed three years at Makerere University in Kampala, Uganda, working with Professor S.M.M. Karim in an extensive programme of prostaglandin research. Dr. Hillier had employed biological assay procedures to study physiological roles of prostaglandins in human reproduction. On his arrival in Oxford he set about developing more specific radio-immunological methods which soon proved reliable for estimating F prostaglandins in body fluids (Hillier and Dilley, 1974). I was privileged to work under his supervision in the laboratory using these methods and to be involved subsequently in the development and application of a similar assay procedure for E prostaglandins. Our collaborative studies to measure prostaglandins in body fluids during pregnancy and labour form an important part of this thesis (Chapter 8).

While maintaining a keen interest throughout, Mr. Embrey delegated the responsibility for the clinical studies to the two research clinicians, one of whom was mainly concerned with abortion (Mr. I.Z. MacKenzie) and the other with labour (myself). We were each greatly assisted by a research midwifery sister who attended to the nursing care of the patients and assisted in data recording.

Other Associates

When Professor A.C. Turnbull came from the Welsh National School of Medicine in October 1973 to be Nuffield Professor of Obstetrics and Gynaecology, he took a keen interest in the research and gave valuable advice and encouragement. He was already a leading authority on the control of myometrial contractility and parturition. He was accompanied by a small group of research workers actively interested in the field. The research laboratories received a fresh impetus under the day to day supervision of Dr. A.B.M. Anderson and the facilities were developed for measuring a wide variety of hormones important in human reproduction. Dr. A.P.F. Flint and Dr. M.J.N.C. Keirse, both of whom had a special interest in prostaglandins, also joined the department. While this group concentrated mainly on studies in the sheep, we pursued our studies in human subjects and close contacts between the groups were maintained.

Professor Turnbull had been mainly responsible for the development of the fully automatic Cardiff Infusion System and he encouraged me to use this apparatus in my studies.

studies./

This was to prove most valuable, and a description of the system is given in Appendix A.

Another group with whom valuable collaboration was possible was that led by Dr. M.K. Ounsted. This was basically a group of paediatricians concerned with neonatal development, and a number of joint studies were carried out, some of which are discussed in Chapter 7.

In addition to those mentioned, a wide variety of individuals both in the hospital and in the Nuffield Institute were kind enough to interest themselves in the research and to offer helpful advice. The holding of regular seminars to discuss work in progress in both establishments proved an invaluable stimulus to sustaining and developing the research.

OUTLINE OF THE THESIS

The thesis is presented in two volumes. Volume I contains the main narrative in nine chapters. Volume II contains two appendices describing clinical and laboratory methods, followed by the tables, the figures and the list of references.

The subject of the thesis is the problem of the unripe cervix in primiparous women. By late pregnancy the uterine cervix is usually soft, short and partially dilated in contrast to the long, firm, closed cervix of early and mid pregnancy. This

This/

change is called ripening. A small number of patients depart from this pattern and the cervix remains unripe. The thesis is concerned with the reasons for failure of ripening, the clinical problems which result, and the development of methods to improve the clinical outcome.

The present Chapter describes the circumstances in which the research work was conducted and gives an outline of the thesis. The precise role of the candidate in the research is defined and acknowledgements are made to those who assisted.

Chapter 2 presents a historical review of the literature relating to induction of labour and examines in detail the emerging interest in the actions of prostaglandins which was gaining great momentum at the time the research was started. The normal pattern of cervical ripening is described in detail in Chapter 3 and a critical appraisal is made of the postulated mechanisms controlling this important physiological process.

The starting point for the present thesis was the clinical impression that the conventional method of induction of labour, namely amniotomy followed by intravenous oxytocin infusion, was unsatisfactory in an important minority of patients. Chapter 4 describes the two initial studies, one retrospective and one prospective, which were undertaken by the author to quantify this impression. The retrospective analysis was made of all primiparous confinements occurring in the John Radcliffe Hospital during a six months period; this strongly suggested

suggested/
that much of the morbidity, both fetal and maternal, was concentrated among women whose labours had been induced in the face of an unripe cervix. In the prospective study the degree of cervical ripeness was measured precisely at the time of amniotomy and this was related to the clinical outcome. This study confirmed the association between amniotomy in the presence of an unripe cervix and high complication rates during labour for both mother and fetus.

The following Chapters (5, 6 and 7) describe work carried out by the author which had the central objective of developing methods to overcome the clinical problems presented by the unripe cervix. The first method which was used was intravenous prostaglandin therapy and in Chapter 5 a randomised, double blind trial is described in which patients were allocated to treatment with amniotomy and intravenous oxytocin or amniotomy and intravenous prostaglandin E_2. This study showed that those patients who received PGE_2 had a lower incidence of fetal distress, birth asphyxia and caesarean section, but these benefits were offset by an unacceptably high incidence of unpleasant maternal side effects.

Attention was therefore turned to local routes of prostaglandin administration in the hope of maintaining the clinical benefit while minimising the unpleasant side effects. The technique chosen was the extra-amniotic administration of prostaglandins which had hitherto been limited to use for therapeutic abortion. The development and the application of

application of/

this technique for induction of labour is described in Chapter 6. Two distinct techniques were developed: firstly continuous extra-amniotic infusion of a PGE_2 solution to induce labour, and subsequently the use of PGE_2 in a viscous gel to bring about cervical ripening prior to induction of labour. Using these methods in patients presenting with an unripe cervix the results were much superior to those obtained with amniotomy and intravenous oxytocin infusion and these results are presented in Chapter 7. This chapter concludes with a review of the experience of other workers using prostaglandins administered by local routes to induce labour or to ripen the cervix, and with a discussion of the safety of these techniques with particular reference to the fetus.

In parallel with the clinical studies, laboratory investigations were conducted in an attempt to throw further light on the mechanisms responsible for the phenomenon of the unripe cervix and these are described in Chapter 8. Evidence is presented which suggests that the primary prostaglandins play a central role in the processes of cervical ripening and the initiation of parturition. This supports the hypothesis which is advanced throughout the thesis that these two processes of cervical ripening and the onset of parturition are intimately and essentially related. This is further discussed in Chapter 9 which concludes the thesis and, as well as interrelating the clinical and laboratory data, considers the implications of the research and the possible direction for subsequent investigations.

investigations./

Chapters 4 to 8 inclusive contain the original data included in the thesis. This consists of nine separate but closely related studies of which five have been published in scientific journals. Reprints of these are included in Volume I at the relevant points in the development of the thesis. These five papers are as follows:-

In Chapter 5

"Comparison of intravenous oxytocin and prostaglandin E_2 for induction of labour using automatic and non-automatic infusion techniques".

by A.A. CALDER and M.P. EMBREY.

Reprinted from the British Journal of Obstetrics and Gynaecology. Volume 82, No. 9, September 1975.

In Chapter 6

"Intrauterine (extra-amniotic) prostaglandins in the management of unsuccessful pregnancy".

by A.A. CALDER, I.Z. MACKENZIE and M.P. EMBREY.

Reprinted from the Journal of Reproductive Medicine. Volume 16, No. 5, May 1976.

"Extra-amniotic prostaglandin E_2 for the induction of labour at term".

by A.A. CALDER, M.P. EMBREY and K. HILLIER.

Reprinted from the Journal of Obstetrics and Gynaecology of the British Commonwealth. Volume 81, No. 1, January 1974.

In Chapter 7

"Ripening of the cervix with extra-amniotic prostaglandin E_2 in viscous gel before induction of labour".

by A.A. CALDER, M.P. EMBREY and T. TAIT.

In Chapter 7 /

Reprinted from the British Journal of Obstetrics and Gynaecology. Volume 84, No. 4, April 1977.

In Chapter 8

"Concentrations of prostaglandin $F_{2\alpha}$ in amniotic fluid and plasma in spontaneous and induced labours".

by K. HILLIER, A.A. CALDER and M.P. EMBREY.

Reprinted from the Journal of Obstetrics and Gynaecology of the British Commonwealth. Volume 81, No. 4, April 1974.

PRECISE ROLE OF THE CANDIDATE IN THE RESEARCH

As has already been stressed, the research was conducted while I was a member of a research group consisting of nine individuals and all the work described in the thesis was therefore to some degree collaborative. Under the overall direction of Mr. Embrey, the research proceeded in three main areas, namely, abortion, labour and laboratory and these were under the immediate supervision of Mr. MacKenzie, myself, and Dr. Hillier, respectively. The work was discussed at all stages among the group as a whole, but I had complete freedom to initiate and direct the clinical labour studies and, in consultation with Dr. Hillier, such laboratory studies as had a bearing on labour.

Clinical Studies

Clinical Studies

The clinical studies described in Chapters 4, 5, 6 and 7 were all conceived, organised and executed by myself under the guidance of Mr. Embrey. I was responsible for the selection of all patients and personally conducted all assessments of cervical score and clinical procedures for induction of labour and pre-labour cervical ripening. The only exceptions to this were the last 42 of the 121 cases of cervical ripening with PGE_2 in viscous gel described in Chapter 7. These cases were managed by Mr. T. Tait who succeeded me as Clinical Research Fellow when I left Oxford.

After induction of labour the clinical management of all patients was in the hands of the duty obstetric staff but the nursing care of the patients remained the responsibility of Sister S.E. Johnston, the research midwife who also assisted me with data collection and documentation.

The assessment, including the statistical analysis, of all the clinical data was made by myself and I was principal author and responsible for writing all the clinical papers included in the thesis.

Laboratory Studies

The laboratory studies described in Chapter 8 were conceived and designed in collaboration with Dr. Hillier. I was responsible for selecting the patients to be studied and for the collection and storage of all the biological samples analysed. I personally carried out laboratory

laboratory/

assays for prostaglandins on a significant proportion of the samples but the majority of these were carried out by Dr. Hillier or his technician, Mrs. Susan Dilley. The measurements of progesterone, oestradiol 17_{β} and cortisol made in parallel with some of the prostaglandin estimations were kindly performed by Dr. Anne Anderson and her laboratory staff.

The paper included in Chapter 8 on the subject of prostaglandins in spontaneous and induced labours was written jointly by Dr. Hillier and myself. As overall director and grant holder, Mr. Embrey's name appears on all the papers and he often made helpful suggestions of amendments to the original texts.

In compiling the thesis I have personally carried out all the literature research and the composition of the text, but I wish to acknowledge the invaluable assistance of a large number of individuals.

ACKNOWLEDGEMENTS

Mr. Mostyn Embrey made the project possible. He raised the finance for the research and throughout proved an ideal supervisor, striking a fine balance between allowing me freedom to develop the research and maintaining a keen and

keen and/
informed interest.

The successful marriage of clinical and laboratory research was wholly due to the personality and expertise of Dr. Keith Hillier. The rapport he developed with Mr. MacKenzie and myself is the abiding memory of my research attachment in Oxford. The laboratory studies were also enhanced by Mrs. Susan Dilley who, as well as displaying particular skills in radio-immuno assay of prostaglandins, remained cheerful and uncomplaining in spite of the many frustrations inherent in the procedure and in helping a clinician to learn it.

Sister Susan Johnston gave expert and sympathetic nursing care to the patients and was most diligent in recording clinical data on the mother, fetus and neonate. She developed a valuable expertise in handling the complicated infusion and monitoring apparatus used throughout the studies.

Miss M.J. Bremner-Milne was a most attentive and helpful secretary to the group.

Professor A.C. Turnbull took an active and practical interest in the research and fostered an atmosphere of collaboration with his own group, of whom Dr. Anne Anderson was especially helpful.

None of the research would have happened without the

the/

willing co-operation of the patients together with that of the obstetricians, midwives, anaesthetists and paediatricians of the John Radcliffe Hospital.

The main funding agencies for my part of the research were the Worcester Foundation for Experimental Biology and the Upjohn Company.

I wish to thank Miss Sylvia Barker in Oxford and Mr. William McNally in Glasgow for expert art and photographic assistance.

The thesis has been typed throughout by Miss Thelmar Morrison who has worked tirelessly and has shown remarkable patience.

I have been encouraged throughout, to undertake the fellowship, to pursue the research and to write the thesis by Professor M.C. Macnaughton and Dr. P.W. Howie. These gentlemen have given unsparingly of their time to offer invaluable advice and criticism.

C H A P T E R 2

HISTORICAL BACKGROUND TO THE THESIS

A CRITICAL REVIEW OF INDUCTION OF LABOUR.

THE PROSTAGLANDINS.

A CRITICAL REVIEW OF INDUCTION OF LABOUR

Over the centuries there have been times when man has attempted to interfere with the natural course of pregnancy and bring about its interruption. His motives have been, and continue to be, either medical or social but the interference has often aroused passionate disagreement in medical, theological, legal and lay circles.

The past century has witnessed dramatic changes in all aspects of life and not least in obstetric practice. The horrendous mortality rates, both fetal and maternal associated with child-bearing in the late nineteenth and early twentieth centuries have been steadily whittled down so that they are now approaching irreducibly low levels. Each generation has seen increased safety in childbirth, and women can now embark on pregnancy free from the very real fears which beset their grandmothers and great-grandmothers.

The same period has seen induction of labour increase from an occasional weapon used in desperate straits usually where the mother's life was threatened, to a widespread practice employed in some hospitals in almost half the total confinements (Annual Reports for 1973 for the Simpson Memorial Maternity Pavilion, Edinburgh and the John Radcliffe Hospital, Oxford). The steepest increase in its use has occurred in the past dozen years, but as long ago as 1920 Reed in the first issue of the Americal Journal of Obstetrics and Gynecology, (Reed 1920) advocated routine induction of labour

labour/

at term on the grounds that "the end of profitable intra-uterine life had been accomplished and continuance thereof is only ..... an invocation to all those dangers, morbidities and mortalities which are so familiar to us all". The passing years have seen a wider acceptance of Reed's viewpoint, so very extreme in his day, and there are those who consider that, in many respects, induced labour may be preferable to spontaneous labour. They point to the increased safety when the whole process is conducted from start to finish in a well supervised maternity hospital. On the other hand, the sharp increase in the use of induction of labour has had its stern critics (Dunn 1977). It has been condemned as an unnatural interference contributing to a variety of perinatal problems.

The obstetrician must, therefore, assess the balance between the risks of continuing the pregnancy with those of its interruption (figure 2.1). An important factor in this assessment are those risks associated with the method chosen to interrupt the pregnancy, be it induction of labour or elective caesarean section. The history of induction of labour has been dictated by the constantly changing weight of the different risk and benefit factors which a fuller understanding of the pathology of pregnancy and the physiology of labour has progressively brought about.

Indications for Induction of Labour

Induction of labour is indicated whenever the risks of continued intra-uterine life are greater than those of induced labour and delivery (Howie 1977). The risks to the undelivered fetus are very great in severe pre-eclampsia, essential hypertension, renal disease, rhesus iso-immunisation, diabetes and fetal growth retardation. In these conditions the need for induction of labour, usually before term, is not in dispute. The frequency of these indications will vary depending on the nature of the obstetric population but together they may account for an induction rate of about 10 per cent (Tennant and Black 1954).

The sharp increase in the use of induction of labour, in recent years, owes much to the pioneer work on perinatal mortality by Baird, Walker and Thomson (1954). They established that prolonged pregnancy represented an increasing risk to the fetus. For example, Walker, in his Blair-Bell Memorial Lecture of 1954 (Walker 1954) showed that 21% of primigravidae delivered after 41 weeks. In this group, however, there were 51% of all unexplained stillbirths, 83% of all anoxic stillbirths in labour, and 40% of all traumatic deaths associated with difficult labour. These risks were increased in association with increased maternal age, mild pre-eclampsia, and impaired maternal weight gain. A number of other reports (Clayton 1941; Racker, Burgess and Manly 1953; Butler and Bonham 1963) have confirmed

confirmed/

these conclusions.

As a result of their epidemiological studies, the Aberdeen workers used induction of labour and caesarean section more frequently and noted a sharp improvement in perinatal mortality, particularly in the groups most at risk (Baird 1977). Other studies tended to confirm the value of induction of labour in reducing the risks associated with prolonged pregnancy (Racker, Burgess and Manly 1953; Theobald 1963; Turnbull and Anderson 1968a). More recently, McNay et al (1977) in Glasgow examined the impact of an aggressive induction policy upon perinatal mortality and found that an increase in the induction rate from 15% to 35% was associated with a fall in the number of perinatal deaths due to placental failure in late pregnancy.

Chalmers and his colleagues in Cardiff have challenged the value of induction of labour in a series of papers (Chalmers, Lawson and Turnbull 1976a, b; Chalmers et al 1976c). They found that a high number of deaths due to anoxia and birth trauma did not respond to an increase in the induction rate from 9% to 26%. The reasons for the differences between the Glasgow and Cardiff reports are not clear. It may be that differing obstetric populations or differing criteria of selection for induction may explain the apparent contradictions. Although the precise indications for induction of labour have not yet been finally determined, it is certainly

certainly/
clear that, for the forseeable future, the ability to control the timing of delivery will remain an importnat weapon in the obstetrician's armamentarium.

Methods of Labour Induction

Through the ages a host of widely differing methods have been used to try to induce labour or procure abortion. The Ancient Greeks are said to have sometimes bound the mother to a couch which was then upended and bounced against a bunch of faggots. Other bizarre methods from Canada and Indo-China are illustrated in Figure 2.2 (a and b). The success rates are not on record.

Munro Kerr, Johnstone and Phillips (1954), and Donald (1972) have reviewed mediaeval practices for induction. A certain Reverend Maister Alexis of Piemont in 1595 described a comprehensive list of medicaments which he claimed could stimulate the uterus. This included junniper berries, cinnamon, and castor oil (the last has still not gone out of vogue in some institutions) and to these were added a century later by Nicolas Culpepper in 1684 red pepper, Pennyroyal and mugwort not to mention a concoction of swallow's nests and rain water, strained and taken warm. Even more exotic was a method recommended by Dr. Henry Bracken in 1735 whereby "the oil of sweet almonds be applied, warm, with a bunch of feathers to the privites and vagina".

Probably the most important milestone was the introduction of amniotomy by Denman in 1756. This remains a fundamental part of labour induction to this day.

Theobald (1961) has described intact forewaters as "the greatest single hindrance to progress in labour" and yet only recently has it been possible to perform amniotomy with impunity as a method of labour induction. Although successful induction of labour may be anticipated in 80-90% of patients following amniotomy alone (Tennant and Black 1954; Manly 1956) in the absence of a suitable additional method of stimulating myometrical contractions, the remaining 10-20% of patients remained an important deterrant to the use of amniotomy without a compelling indication. The sword of Damocles was intra-uterine sepsis which inevitably follows amniotomy if delivery is long delayed (McCallum and Govan 1963) and demanded delivery by caesarean section in these case of failed induction (MacVicar 1971).

The search continued therefore for methods which would induce labour without the need to perform amniotomy. Kraus introduced uterine bougies in 1850, and six years later Scanzoni advocated hot carbolic acid douches. In 1861 Barnes adapted a traditional method which used pigs bladders employing water filled bags made of rubber. None of those methods was reliable, and all carried risks.

In 1909 another milestone was passed when William Blair-Bell published his account of the parturigenic properties of extracts

extracts/

of the posterior pituitary, (Blair-Bell 1909) thereby initiating the chain of events which culminated with the identification and therapeutic availability of oxytocin. But progress remained slow. "A Glasgow Manual of Obstetrics" (1924) edited by S.J. Cameron described only two methods of labour induction, one the use of intra-uterine bougies, the other a medical method combining the use of quinine (to sensitise the uterus) and "pituitrin extract" to stimulate it (Cameron 1924). In 1931 Drew-Smyth described hindwater rupture of the membranes by means of a specially designed metal catheter (Figure 2.3) the advantages of which were claimed to be a reduction in the incidence of intra-uterine infection and "forewater preservation" (Donald 1966).

Even when oxytocin did become available in pure form, several years elapsed before obstetricians learned to use it rationally. As has so often happened in obstetrics, especially with methods of labour induction, judgement was outstripped by enthusiasm on the part of a few clinicians and catastrophes occurred. It took only a few cases of injudicious management to bring oxytocin into disrepute. Many older clinicians even today fear oxytocin following bitter memories from those days, and impose arbitrary limits on its use. At a famous meeting in the United States Joseph Bolivar de Lee held up a ruptured uterus in one hand and a dead fetus in the other, quoting from the scriptures (Proverbs 23, 32) in his condemnation of oxytocin: "It biteth like a serpent, and stingeth like an adder" (Mr. E.A. Williams, personal communication).

A school of thought of whom Theobald was the main proponent maintained that oxytocin should be used only at "physiological" dose rates (Theobald et al 1948) the maximum allowed being 10 milliunits/minute. It is now clear that this was based on mistaken beliefs regarding the physiological control of labour and on wrong assumptions regarding the role of oxytocin.

While such attitudes undoubtedly served to prevent tragedies from oxytocin overdosage, this over-cautious approach resulted in a higher failure rate for induction of labour.

MacVicar (1971) reviewed all 3,359 cases of amniotomy for labour induction in the Queen Mother's Hospital from 1965-1969. Three hundred and seventy-one of these patients (11%) were subsequently delivered by caesarean section, and in almost exactly half of these the sole indication or main contributory indication for this was a failure of the uterus to contract effectively.

When the author began his obstetrical career in the Queen Mother's Hospital, Glasgow, in 1969, a variety of methods were employed in the 25.4% of patients in whom labour was induced (Table 2.1). The criterion of successful induction was delivery within 24 hours, and in barely two-thirds (68%) of patients was this achieved (Queen Mother's Hospital Report 1968-1969).

Four different methods of labour induction were employed reflecting a wish to avoid amniotomy and oxytocin therapy if

therapy if/

possible. These are as shown in Table 2.2. Without amplification the figures are misleading. Firstly method (2) (amniotomy alone) appears the most successful in achieving delivery within 24 hours (91%) but it was precisely because of a successful response that patients remained in this group. If the response to amniotomy alone was poor then oxytocic stimulation was usually added after 12 or 24 hours, but rarely immediately after amniotomy, and the patient was then managed under method (3) or (4). What seems remarkable, a mere ten years later, is that almost 4 per cent of patients managed by amniotomy alone were later delivered by caesarean section for failed induction without resort to oxytocic stimulation ever being made. There may have been additional contributory factors such as a uterine scar in some cases but these figures serve to underline the caution of the day.

The poorest results were associated with amniotomy and intravenous oxytocin infusion, the method which subsequently became the standard method of labour induction. The reason for this paradox is that this method was reserved for patients in whom undue difficulty was anticipated or other methods had already failed. Such patients probably included the hard core of labour induction candidates with which this thesis is mainly concerned.

The following three or four years witnessed a continuing rise in induction rates nationally (D.H.S.S. 1974).

This resulted from a number of developments in the methods applied. The main ones are listed here:-

listed here:-

1) The appreciation that in most cases nothing is gained by delaying oxytocin infusion (Bradford and Gordon 1968; Patterson 1971).

2) The recognition that a large variation exists from patient to patient in the uterine sensitivity to oxytocin (Embrey 1962; Wood 1972).

3) The application of fundamental pharmacological principles leading to the concept of oxytocin "titration" in which the dose rate is titrated by logarithmic increments against the uterine response (Turnbull and Anderson 1968; Scott 1972).

4) The development of sophisticated machines to control the rate of oxytocin infusion (MacVicar and Howie 1967; Frances, Turnbull and Thomas 1970; Hamlett 1972).

The attractions of these policies were quickly appreciated. The uncertainty was largely removed from labour induction and delayed labour disappeared. No longer did patients languish after induction with the sun setting twice or more before they were delivered. The incidence of failed induction of labour and intra-uterine infection fell sharply.

The Hazards of Induction of Labour

Mention has already been made of some potential hazards of labour induction and these will now be considered in greater depth. Just as the main aim of obstetric care is to secure a healthy baby and a healthy mother, so the object of induction of labour should be to achieve vaginal delivery of an infant in optimal condition after a labour which has been both safe and satisfying to the mother. It should at once be pointed out that spontaneous labour is not always successful in these respects. Many of the criticisms of induced labour in the past have pointed to problems which were less the result of induction than of the obstetric pathology which necessitated it. Where studies have been conducted on populations matched for these factors (D'Esopo, Moore and Lenzi 1964; Booth and Kurdyak 1970; Cole et al 1975) induction has not been found to cause increased morbidity or mortality.

A number of potential hazards must be considered, however. The most important are listed in Table 2.3.

Prematurity

Because induction results in artificial interruption of pregnancy, the risk of delivering an immature infant is an ever present one. Niswander and Paterson (1963) reported a perinatal mortality of seven per thousand from prematurity and respiratory failure in association with elective induction of labour, but

but/

this has not been general experience, (Husbands 1950; Erving and Kenwick 1952) and clearly the value of this therapeutic weapon depends heavily on the care with which it is applied. One essential pre-requisite to induction is an accurate knowledge of the fetal maturity, and where this is in doubt, as for instance when the menstrual history is unreliable, additional steps must be taken to pinpoint it. Ultrasonic measurements of the fetus, especially of the crown-rump length in early pregnancy (Robinson 1973), and assessment of fetal pulmonary surfactant by examining the amniotic fluid in late pregnancy (Gluck et al 1971) are often helpful in such cases. In practice, if rigorous attention is paid to establishing the fetal maturity before labour is induced it should be possible to avoid delivery of an unexpectedly premature infant.

Neonatal Jaundice

Several reports have linked an increased incidence of neonatal hyperbilirubinaemia with induction of labour or the drugs by which it is achieved (Ghosh and Hudson 1972; Davies et al 1973; Calder et al 1974; Roberts and Weaver 1974). The jaundice has been mild and transient however, and probably of little clinical importance. These studies only detected the association by routine measurements of bilirubin, and it is notable that studies of infants with clinically recognisable (and therefore perhaps significant) jaundice (Friedman and Sachtleben 1974) have failed to demonstrate any link with induction.

Fetal Hypoxia and Birth Asphyxia

It is difficult to assess the contribution of induced labour to the development of fetal hypoxia and birth asphyxia. Patients undergoing induction are very often those at greatest risk of these problems during labour, regardless of whether it is spontaneous or induced.

The critical question is: all other things being equal, is induced labour more likely to cause fetal hypoxia than spontaneous labour? All the studies which have tried to answer this question have suffered from the same failing; all other things were not equal. In the study of Liston and Campbell (1974) the babies from the induced group had a higher incidence of depressed Apgar scores and special care unit admission, but the mothers in the induced group were usually obstetrically abnormal while the control group was essentially normal. The studies of Turnbull and Anderson (1968) and Cole et al (1975) which showed less fetal hypoxia (as indicated by meconium staining) in labour among those patients in whom labour was induced, suffer from a different type of bias, namely the difference in the timing of delivery.

The best way to answer the question would be to carry out a randomised controlled study of matched populations in which one group had labour induced while in the other it was arranged that "spontaneous" labour began at the same time. For obvious reasons such a study is impossible. Nevertheless, it should be our aim to pursue the study of the mechanisms controlling parturition

parturition/

so that ultimately we can carry out induction of labour that will be identical in all respects to spontaneous labour.

For the meantime there are several theoretical reasons why existing methods of induction of labour might increase the risks of fetal hypoxia. Donald (1966) has suggested that since amniotic fluid is released by amniotomy this reduces the volume of the uterine contents and must result in some shrinkage of the uterus as a whole. This, he suggests, must inevitably cause some retraction in the upper uterine segment with reduction in the area of the placental site and blood flow therein. The data of Caldeyro-Carcia et al (1974) support this theoretical contention. He has demonstrated that early amniotomy in spontaneous labour causes more perinatal problems (type I fetal heart decelerations, fetal skull moulding, depressed Apgar scores) than if the membranes are maintained intact.

Mention must also be made of the additional risk of acute asphyxia due to cord prolapse at the time of amniotomy. This is of little importance however since intelligent awareness of the type of case at risk should minimise this possibility; and since this complication is probably as likely to happen at the time of spontaneous membrane rupture, how much better that it should occur when there is an examining finger present in the vagina to detect it.

Infection

Mention has already been made of this risk in association with delay following amniotomy (McCallum and Govan 1963). Although Donald (1966) has stated that "there is no such thing as an aseptic amniotomy" it is clearly important to adhere to a strict aseptic technique both for amniotomy and vaginal examinations in labour if the problems of infection both to the fetus and the mother are to be minimised. The rational use of oxytocin has greatly reduced this problem, but the potential hazard of introducing infection remains one important drawback to amniotomy.

Haemorrhage

Fetal haemorrhage may occur as a result of direct injury to the fetus or placenta during amniotomy. Fortunately this is rare, particularly since the Drew Smythe catheter (Figure 2.3) is deservedly on its way to the obstetric museum. The rare possibility of a vasa praevia remains and should encourage analysis for the presence of fetal cells of any blood noted at amniotomy (Mitchell, Anderson and Russell 1957).

Maternal bleeding, usually from the cervix, is much commoner but is rarely a serious problem.

Caesarean Section

It has been claimed (Bonnar 1976) that increased use of induction

induction/

of labour could lead to a higher rate of caesarean section. National figures do not bear this out (D.H.S.S. 1974). Between 1965 and 1972 the rate of labour induction in hospitals in England and Wales rose from 15 per cent to 33 per cent : during the same period the caesarean section rate only rose from 5.0 per cent to 5.3 per cent. Clearly a multitude of factors are involved in determining the caesarean section rate especially when national figures are examined, but Cole, Howie and Macnaughton (1975) found no increase in resort to caesarean section when in a randomised controlled study, elective induction of labour at term was compared with a more conservative management. Other retrospective comparative studies have supported the view that the induction rate is not the primary factor in determining the caesarean section rate (Chalmers et al 1976c).

Nevertheless, the aim of induction of labour is to deliver babies in better health than would happen without induction, and should anticipate problems which might lead to fetal distress in labour. If this were successful one would expect a reduction in the caesarean section rate but this has not materialised. One reason for this may be the false assumption that the stresses and strains of induced labour are identical to those of spontaneous labour. That this is patently not true, especially if the cervix is unripe, is of central importance to this thesis.

Uterine Rupture

Awais and Lebherz (1970) have drawn attention to this potential hazard in oxytocin inductions especially in patients of high parity. When such an accident happens after the active intervention of induced labour there is usually a tendency to blame the induction. But Howie (1977) has pointed out that such accidents may also happen in spontaneous labours. Clearly the careless use of oxytocin must increase the risk of uterine rupture but there is no evidence that, properly controlled, it constitutes any additional hazard.

Amniotic Fluid Embolism

In common with uterine rupture, when this rare but usually fatal catastrophe strikes during or after induced labour, recriminations follow and doubts are raised about the contribution induction made to the event. Courtney (1974) has reviewed the literature on this subject, and been able to find depressingly few pointers to the etiology. There is certainly no direct association with induction of labour; indeed it might be argued that by rupturing the membranes and allowing some of the liquor to drain away, the dangers of this complication are slightly reduced.

Maternal Dissatisfaction

While perhaps not strictly a "hazard" of induction of labour,

labour,/

there can be no doubt that maternal dissatisfaction with the procedure has become increasingly apparent in recent years (Robinson 1975; Riley 1977). It has been claimed that induction depersonalises the experience of childbirth so that the mother feels that things are being done to her rather than she doing them herself (Tweedie 1975). Much of this dissatisfaction may derive from a failure to explain properly to patients the reasons for induction, but there is no doubt that they also derive in part from the defects of the methods used and in part from the fact of the interference itself.

Cartwright (1977) has investigated mothers experiences of induction of labour. While she found no differences in the degree of pain reported by mothers following induction than following spontaneous labours, only 17 per cent indicated a preference for induced labour. This contrasts with much higher rates for epidural analgesia (63%) and hospital confinement (83%), and would seem to reflect a deep rooted desire among women for "natural" spontaneous labour. In a similar study Stewart (1977) found that many experienced pain during amniotomy, especially if the cervix was unripe.

THE PROSTAGLANDINS

In 1930 two New York gynaecologists reported an observation and thereby set in motion a chain of events which led to the discovery of a hitherto unknown group of biologically active substances - the prostaglandins. Raphael Kurzrok and Charles C. Lieb noted that when attempting to carry out artificial insemination in a human subject, 0.5 ml. of semen injected into the uterine cavity was promptly expelled back through the cervix. This did not occur if Ringers solution was substituted for semen. They subsequently studied the in vitro response to semen of human myometrial strips and showed that this could vary in different conditions between stimulation and relaxation (Kurzrok and Lieb 1930).

During the preceding 25 years a number of workers had reported biological activity in extracts made from the prostate and seminal vesicles. Jappelli and Scafa (1906) described effects on the central nervous and cardiovascular systems of dogs and rabbits following intravenous injection of extracts of the dog prostate. Five years later Dubois and Boulet (1911) found a similar extract could influence the mobility of the gut in dogs, cats, rabbits and sheep. These and other reports by Thaon (1907), Camus and Gley (1907), Götzl (1910), and Battez and Boulet (1913) all indicated the existence of extractable substances with biological activity but no studies were made of uterine responses, and interest declined until re-awakened by the Kurzrok and Lieb report.

In 1933 M.W. Goldblatt of St. Thomas' Hospital, London, read a paper to the Biochemical Society describing powerful contractions of the isolated guinea-pig uterus when alcohol or acetone extracts of human seminal fluid were applied to it (Goldblatt 1933). Working independently at the Karolinska Institutet in Stockholm, Von Euler made almost simultaneous and identical observations not only with seminal extracts, but also those of the accessory genital glands (Von Euler 1934). He assumed the active principle found in semen to be a secretion of the prostate gland and coined the name "prostaglandin"; he also considered the extract of seminal vesicles to be a different substance which he called "vesiglandin" (Von Euler 1936). When it later became clear that a variety of different prostaglandin substances existed and it seemed likely that the different effects he had noted with the two extracts were due to differences in the variety and concentrations of different prostaglandins, the latter name was abandoned.

Goldblatt had suggested that the effect he had observed was due to histamine (Goldblatt 1935) but Von Euler (1936) disproved this by making an extract with ether, and proceeded to demonstrate that his "prostaglandin" was capable of stimulating human myometrial strips in vitro.

The foundation was thus laid for the momentous work that followed. In 1947 Von Euler, a physiologist, persuaded his colleague at the Karolinska Institutet, Sune Bergström,

Sune Bergström,/
a chemistry professor, to try to purify the active substance from a concentrate of seminal vesicle material from Icelandic sheep. The material was limited and little progress was made until 1956 when it was possible to organise collection of vast numbers of frozen sheep glands. Hence in the late 1950's "prostaglandin" was shown to be not a single substance but a mixture of several closely related unsaturated hydroxy fatty acids. This may explain the variable results seen previously.

The isolation in pure crystalline form from sheep prostate glands of the first two prostaglandins was described in 1960 (Bergström and Sjövall 1960a, 1960b), and their chemical structure in 1962 (Bergström, Ryhage, Samuelsson and Sjövall 1962). Identification and characterisation of more prostaglandins followed from sources other than the genital tract so that ultimately as many as 17 natural compounds were identified originating from practically every type of mammalian tissue.

Following work by van Dorp et al (1964) in Holland and groups at the University of Harvard and at the Upjohn Company in Kalamazoo, biosynthesis and ultimately total chemical synthesis of the primary prostaglandins became possible in the early 1970's (Corey 1971; Axen Pike and Schneider 1972). The scene was now set for widespread clinical trials.

By 1972, when the work described in this thesis began, a large number of reports had appeared of the use of prostaglandins for therapeutic abortion and induction of labour. Many of the

of the/

early studies were made by Professor Karim in Kampala (Karim et al 1969; Karim 1971a, b and c) and these, together with those in this country in London (Beazley, Dewhurst and Gillespie 1970; Craft 1972), Glasgow (Miller, Calder and Macnaughton 1972; Barr and Naismith 1972) and Oxford (Embrey 1970a and b, 1971) and others in Sweden (Wiqvist et al 1968) and the United States (Anderson et al 1972) had investigated a variety of routes of administration. By 1972 it had been established that PGE_2 was more potent than $PGF_{2\alpha}$ and caused fewer side effects.

During this time many biological observations were being reported which are now known to be attributable to prostaglandins. It was generally assumed that the presence in seminal fluid of such potent substances could not be without purpose and that they might facilitate sperm transport. Doubt was cast on this by Karlson (1959) who suggested that uterine stimulation was more likely to hinder than to help sperm transport but Eliasson (1959) by <u>in vitro</u> experiments and Eliasson and Posse (1960) by others <u>in vivo</u> demonstrated that the usual effect of seminal fluid was to inhibit rather than to stimulate uterine contractions. This together with the later report by Sandberg, Ingleman-Sundberg and Ryden (1964) that its effect on the fallopian tubes was to stimulate their medial portions while relaxing their outer portions led to the postulation that seminal prostaglandins influence conditions in the female genital tract to halt the ovum in the uterine tube at the optimal point for fertilisation.

Meanwhile in Cardiff, Pickles had been pursuing a different line of research. He had been intrigued by suggestions of the existence of a "menstrual toxin". Dr. Schick of Vienna in 1919 notice that sometimes gifts of flowers handled by his maid-servant quickly withered, and he learned that this only happened when she was menstruating. He concluded that the cause was a"menstrual toxin" secreted in the palmar sweat at the time of menstruation. Other anecdotal accounts of this kind reinforced this belief, and Macht and Davis (1934) were able to show that crude menstrual toxin obtained from menses could potentiate contractility of the rat vas deferens.

Pickles repeated this experiment with extracts of menstrual fluid, endometrium and blood obtained during menstruation, and extended the study to other smooth muscle systems including the myometrium. He was able to postulate that menstrual fluid contained a smooth muscle stimulant which was probably responsible for the expulsive uterine contractions during menstruation. He called this "menstrual stimulant" (Pickles 1957). Later by chromatography two fractions were distinguished, one containing "menstrual toxin" and the other "menstrual stimulant", the latter being lipid in nature (Clitheroe and Pickles 1961). Further chromatographic studies (Eglinton et al 1963) showed that the menstrual stimulant fraction contained a number of substances with molecular structures similar to the prostaglandins which Bergström had characterised.

In other tissues a variety of smooth muscle stimulants came to light and were given names associated with their sites

sites/

of discovery. Thus "irin" (Ambache 1957) from the iris of the rabbit, "medullin" (Lee et al 1965) from the renal medulla of the rabbit, and "darmstoff" (Vogt 1949) from the frog intestine were substances with properties which have since been shown to be due to their prostaglandin content.

The sources of prostaglandins are now known to embrace a bewildering variety of mammalian tissues and fluids. In the human alone their sites of occurrence and biological actions are legion (see Tables 2.4 and 2.5; Figure 2.4) and the richest source found so far is the unlikely Carribean coral Gorgonian plexaura homomalla (Schneider 1975).

Chemistry

Most of the credit for the chemical characterisation of prostaglandins must go to Bergström and his colleagues at the Karolinska Institutet in Stockholm. Indeed it was this group who first recognised that the new phenomenon was not a single substance but a variety of closely related lipid soluble unsaturated hydroxy fatty acids. In 1957 Bergström and Sjövall isolated two pure cystalline prostaglandins from sheep seminal vesicles. One, more soluble in ether, they called prostaglandin E; the other, more soluble in phosphate buffer (spelt in Swedish with an F) they called prostaglandin F. The ensuing years saw identification of several more variants, so that 17 different naturally occurring prostaglandins are now recognised. All prostaglandins are long chain hydroxy

hydroxy/

fatty acids with 20 carbon atoms arranged with a cyclopentane ring and two side chains. They are thus all derived from the same basic structure represented by the hypothetical substance prostanoic acid (Figure 2.5).

There are four groups designated by the letters E, F, A and B, according to the composition of the cyclopentane ring (Figure 2.6). Naturally occurring prostaglandins of the E and F series are referred to as primary prostaglandins since all others are derived from these. The primary prostaglandins are those of particular relevance to this thesis and are illustrated in Figure 2.7.

They all contain a hydroxyl group in position 15 and a 13, 14 trans double bond. Each group is further divided according to the degree of unsaturation of the side chains and a numerical suffix is added depending on the number of double bonds they contain (see Figure 2.7). Compounds of the F series may be either α or β isomers depending on the stereochemical arrangements of the hydroxyl groups in positions 9 and 11, although only the α isomer occurs naturally.

Biosynthesis

Prostaglandins are synthesised naturally from fatty acid precursors, under the control of a microsomal enzyme system - prostaglandin synthetase. The initial precursor is linoleic

linoleic/

acid obtained from the diet and the main pathways are illustrated in Figure 2.8. This synthetic capacity has now been demonstrated in a wide variety of tissues.

Once the biosynthetic pathways had been elucidated, (van Dorp, Beerthius, Nugteren and Vonkeman 1964; Bergström, Danielsson and Samuelsson 1964) it was possible to exploit this knowledge to manufacture primary prostaglandins in amounts sufficient for the early clinical trials, but their availability was limited by supplies of enzymes. Only since total chemical synthesis has been possible have prostaglandins become widely available and this has been achieved mainly by the efforts of Corey and his associates at Harvard (Corey 1971), and those of scientists in the laboratories of the Upjohn Company at Kalamazoo (Axen, Pike and Schneider 1972). An important bonus of this ability to synthesise prostaglandins chemically is the seemingly limitless variety of analogues of prostaglandins which can be produced. It is already clear that some such analogues may have distinct therapeutic advantages over natural compounds especially in possessing greater specificity of actions, and greater resistance to metabolic degradation. This gives rise to hopes of overcoming two important limitations on the use of primary prostaglandins, namely troublesome side effects and short duration of action.

Metabolism

It should be emphasised that, although often loosely

loosely/

described as hormones, the primary prostaglandins do not behave as hormones in the accepted sense of substances released into the circulation from a specific organ in order to influence the activity of remote organs or tissues. They are synthesised and released either at or adjacent to their site of action (Karim and Hillier 1975).

Once in the general circulation they are rapidly metabolised. Animal experiments suggest that as much as 90 per cent of primary prostaglandins are inactivated during a single passage through the lungs with a further proportion being removed by other organs such as the liver. Samuelsson et al (1971) produced evidence of a similar situation in the human when they showed that only 3 per cent of intravenously injected ^{3}H labelled prostaglandin E_2 remained unaltered in the plasma after 90 seconds, and more than half the total radioactivity can be recovered from the urine within five hours.

There appear to be four main stages in the metabolic degradation of primary prostaglandins. First the hydroxyl group at position 15 is oxidised by 15 - OH prostaglandin dehydrogenase to form the 15-keto metabolite. This is in turn rapidly converted to the 15-keto, 13, 14-dihydro compound when the 13, 14 double bond is reduced under the influence of Δ -13-prostaglandin reductase. The remaining stages, β-oxidation of the carboxylic side chain and ω-oxidation of the alkyl side chain, then occur more slowly.

It would seem likely from Samuelsson's observations (Samuelsson et al 1971) and those of Vane (1969) that metabolic degradation of intravenously administered primary prostaglandins is so rapid that little or no pharmacological effects should be expected except with very large doses. Clinical experience does not bear this out, however, and this may be explained at least in part by the discovery (Bygdeman et al 1974) that the metabolites (especially the 13, 14-dihydro compound) possess some biological activity as smooth muscle stimulants.

CLINICAL APPLICATIONS OF PROSTAGLANDINS IN OBSTETRICS AND GYNAECOLOGY

The speed with which new clinical applications of prostaglandins appear is such that I propose to consider here the situation which had been reached by late 1972, the time the work described in this thesis was begun. Subsequent developments will be discussed where applicable in the ensuing chapters.

At that time the early clinical trials in the United Kingdom had been completed, and the results were under scrutiny by the Committee of Safety of Medicines. As a result of the trials the Committee granted the Upjohn Company permission in 1973 to release prostaglandins E_2 and $F_{2\alpha}$ commercially for use in hospitals for induction of labour and termination of pregnancy.

The areas of clinical application of these compounds which had then been investigated can be considered under three main headings:-

1) Therapeutic Abortion
2) Abnormal Pregnancies (fetal death and abnormality)
3) Induction of Labour.

In reviewing the results of these studies I propose to make only broad observations. Too much effort has been wasted in the past in trying to compare the results of different studies and express these in simple terms (like percentage success,

success,/
incidence of side effects, etc.) when owing to fundamental differences in protocol — parity and gestational age of the patient, dose schedule of the drug, criteria of success — the studies are simply not comparable.

1) Therapeutic Abortion

With the passage of new legislation in 1967 the demand for therapeutic abortion in the United Kingdom increased sharply. If performed before the 12th week of pregnancy, the procedure was fairly straight forward since the uterus could be evacuated simply and with reasonable safety by the surgical method of suction curettage (Stallworthy 1972). But difficulties arose in more advanced pregnancies. The therapeutic options in such cases fell into two categories:

a) Surgical Methods
b) Methods of Inducing Abortion

a) Surgical Methods:

It is generally agreed that the risks inherent in emptying the uterus by surgically dilating the cervix, rise very steeply after 12 weeks gestation. In particular haemorrhage and sepsis are common (Tietze and Lewit 1972). In most departments therefore the surgical method of choice in such cases is hysterotomy, either abdominal or vaginal. This has a number of serious drawbacks. The primary operative mortality

mortality/

is high and the resulting uterine scar may rupture in a subsequent pregnancy, and may call for elective caesarean section to avoid this risk in labour. The use of hysterotomy is now generally restricted to cases in which tubal ligation is also requested. The operation also carries a remarkably frequent incidence of the delayed complication of implantation endometriosis in the abdominal or vaginal scar (Stallworthy 1972).

b) Methods of Inducing Abortion

Because of the drawbacks of surgical methods of second trimester pregnancy termination, techniques of inducing abortion were sought. A variety of myometrial stimulants were tried including oxytocin and ergometrine but because the myometrium in normal second trimester pregnancies is relatively insensitive to these agents, the results were unsatisfactory, even when "sensitising" agents such as quinine or oestrogens were added. Other techniques such as the use of Utuh's paste painted on the cervix, or laminaria tents placed in the endocervical canal were more effective but carried a high morbidity rate, especially of haemorrhage and sepsis.

Resort was made to intra-amniotic therapy, and good results were reported using hypertonic solutions of saline (Wagatsuma 1965) and glucose (Lewis, Smith

(Lewis, Smith/

and Speller 1969). It now seems clear that these techniques worked at least in part by causing local release of prostaglandins from disrupted decidual cells (Gustavii and Green 1972). But while highly effective, these methods could also be dangerous and deaths were reported due to overwhelming infection in association with glucose therapy and due to hypernatraemia with saline (Stallworthy 1972). More recently hypertonic urea has been employed and seems free of such risks (Craft and Musa 1971). A major drawback of intra-amniotic therapy, however, is the need for amniocentesis which cannot be reliably performed before 14 or 15 weeks of pregnancy. Thus in a patients who wished to preserve her childbearing capacity, termination of pregnancy could only be carried out before 12 or after 14 weeks with any reasonable degree of safety, and even so the methods left much to be desired.

Such was the state of affairs before the availability of prostaglandins and this largely explains their immediate impact as agents for therapeutic abortion. The obvious benefit was their ability to produce effective myometrial contractions at any stage of pregnancy, something of which no hitherto available agent had been capable.

The property of the prostaglandins to stimulate myometrial contractions had been clearly demonstrated by early studies

studies/

(Embrey 1966; Karim et al 1968; Embrey and Morrison 1968). Two questions remained to be resolved:

i) Which compound was best suited as an abortifacient?
ii) How could this capacity be most effectively utilised?

The answer to both these questions centred on the matter of side effects.

As to which compound was best suited, the field was quickly narrowed down to PGE_2 and $PGF_{2\alpha}$. Although $PGF_{2\alpha}$ is widely used in other countries, PGE_2 gained wider popularity in Europe because of greater potency and fewer side effects (Embrey and Morrison 1968; Bygdeman et al 1968; Embrey 1969). The preference for $PGF_{2\alpha}$ in other parts of the world resulted from problems of stability of PGE_2 in hotter climates.

In order to find the best method of employing these agents, several routes of administration were explored. It was quickly apparant that oral therapy was unsatisfactory since very large doses were required, and even intravenous therapy was often unsatisfactory because of an intolerable level of side effects (Embrey 1972). Despite favourable early claims for the value of vaginal pessaries (Karim and Sharma 1971c) most other workers reported a high level of side effects suggesting that systemic absorption is required (Wiqvist et al 1972; Brenner et al 1972).

The explanation of these troublesome side effects lies in two important observations alluded to earlier, namely the lack

lack/

of specificity of these compounds and the speed with which they are metabolised in the circulation. Fortunately, however, these substances are locally acting and it was this that led to the development of intra-uterine routes as the most effective means of administering prostaglandins for second trimester abortion.

Two different techniques were developed : intra-amniotic and extra-amniotic. The intra-amniotic route will not be considered further since it has no relevance to this thesis. The extra-amniotic route had previously been employed for administration of dye substances such as rivanol for induction of abortion (Nabriski et al 1971). The administration of prostaglandins by this route was first reported by the Swedes (Wiqvist and Bygdeman 1970) and by Embrey and Hillier (1971). Intermittent injections of PG solution were given (200 µg PGE_2 or 750 µg $PGF_{2\alpha}$) at two hourly intervals and this was found to be highly effective with a minimum of side effects. Embrey (1972) reported 61 per cent aborting within 24 hours if $PGF_{2\alpha}$ was employed and 79 per cent if PGE_2 was employed.

The dosage required was only about a tenth of that required by intravenous infusion and side effects were virtually eliminated.

Miller, Calder and Macnaughton (1972) modified the method by giving a continuous extra-amniotic infusion with the aid of a mechanical pump. This achieved a shortening of the mean time taken to abort (from 22.2 hours to 15.75 hours) and simplified the practical management of the patients. After six years the

years the/

technique remains the method of choice for terminating 2nd trimester pregnancies in Glasgow Royal Infirmary.

2) Clinical Uses in Abnormal Pregnancies

The use of prostaglandins in the management of cases complicated by fetal death in utero and hydatidiform mole was reviewed by Miller in 1972. All the published work to that time (Karim 1970; Beazley and Gillespie 1971; Filshie 1971; Karim and Trussell 1971) described intravenous therapy, and the total number of cases described in the five reports (including Miller's own experience) amounted to only 87. However, although the side effects commonly seen with intravenous prostaglandin therapy had at times been troublesome, the use of these agents appeared to represent a substantial improvement over previous methods of dealing with patients in these difficult clinical situations.

3) Induction of Labour

By 1972 a number of reports had appeared describing the use of prostaglandins for induction of labour at term. The previous few years had seen a widespread move towards a uniform approach to labour induction by amniotomy and immediate oxytocin titration (Turnbull and Anderson 1968; Bradford and Gordon 1968), and the appearance of new substances with oxytocic properties led to the inevitable question of which agent was superior for labour induction, oxytocin or prostaglandins? One of the

One of the/

conclusions of this thesis is that such a question was as futile then as it is now, and that the choice of method of labour induction should depend on the particular clinical circumstances.

Nevertheless, it was already clear that the prostaglandins would make a considerable impact as agents for labour induction. Although successful induction had been reported by Karim and Sharma (1971) using vaginal pessaries or rectal suppositories the only routes extensively investigated had been oral and intravenous. In general these agents had been used in conjunction with amniotomy and a large number of reports had been published (Embrey 1969; Karim et al 1969; Embrey 1970; Karim et al 1970; Beazley, Dewhurst and Gillespie 1970; Beazley and Gillespie 1971; Karim and Sharma 1971; Barr and Naismith 1972; Craft 1972).

The place of these agents was reviewed in a Lancet leading article in 1973. This emphasised that intravenous prostaglandins had not established any wide popularity in routine obstetric practice and seemed to have few advantages over oxytocin except in situations where the antidiuretic properties of oxytocin (Roberts et al 1970) might be considered a drawback, such as cardiac disease and severe pre-eclampsia. It was suggested that amniotomy and oral prostaglandins had proved a convenient and acceptable method of labour induction in patients with favourable induction features where a good response and a short labour could be anticipated.

C H A P T E R 3

CURRENT CONCEPTS OF CERVICAL RIPENING

CURRENT CONCEPTS OF CERVICAL RIPENING

It has been convenitonal to regard the different dynamic roles played by the corpus uteri and the cervix uteri during parturition as active and passive respectively, and to consider that this represents a reversal of the state of affairs which has hitherto obtained during pregnancy. As a broad generalisation this is true enough. On the face of things the onset of labour witnesses a dramatic change in the behaviour of both parts of the uterus: the apparently dormant corpus wakens into life while the cervix can at last relax its weary sentinel of keeping the door of the womb closed and its contents safe within.

The need for a dormant corpus and a sentinel cervix is not in dispute and failure on either part may lead to abortion or premature labour. Nevertheless, it is wrong to suppose that the corpus uteri remains completely dormant throughout pregnancy or that the cervix shows no signs of relaxing its vigil before the clinically recognisable onset of labour.

From the patient's point of view, pregnancy and labour are distinct, and the transition from the one to the other is a fairly sudden event associated with the recognition of rhythmic contractions which cause discomfort. There may be additional sudden events such as the passage per vaginam of a "show" of blood and mucus, or spontaneous rupture of the fetal membranes. Wood (1972) has pointed to a distinction, however, between the clinical and the physiological onset of labour, and of

and of/

fundamental importance to this thesis is the acceptance that in physiological terms the onset of labour is not so sudden as it appears, rather that it involves a transitional phase occupying several weeks which Demelin (1927) has called "pre-labour". This time witnesses a steady increase in the contractile activity of the upper uterine segment (Caldeyro-Barcia 1958) of which the mother is usually hardly aware, and a progression of changes in the shape, chemistry and physical characteristics of the cervix of which she is entirely unaware. It is this progressive change in the cervix which is called ripening.

NORMAL PATTERN OF CERVICAL CHANGES IN PREGNANCY

a) Shape Changes

It is first necessary to describe briefly the non-pregnant cervix. It is a barrel shaped structure measuring about 2.5 - 3.5 cms. in length, and the same in diameter (Jeffcoate 1967). These measurements are almost certainly under-estimates for the reproductive phase of life because they are probably based in part on autopsy material largely from post-menopausal women. The larger values are probably more accurate for the childbearing years (see Table 3.1). The upper part of the cervix has some smooth muscle fibres which connect with those of the corpus and there is a thin layer of muscle peripherally which connects with the muscle of the vagina. The remainder

remainder/
of the cervix is almost entirely composed of fibrous tissue (mainly collagen). The endocervical canal is spindle shaped.

Within a very few weeks of conception clinically obvious changes appear in the cervix. Indeed these are important clinical signs of pregnancy and are of diagnostic value. In common with the vagina the cervix takes on a characteristic blúe colour and it becomes noticeably softer to the touch. Arterial pulsation may also be detected indicating an increased blood supply. The size and shape, however, show little change. Calder and McManus (1977, unpublished observations) have measured the length of the cervix in vivo in the non-pregnant and early pregnant subject by passing a Foley catheter into the uterus and distending the balloon with 1 ml. of water; the catheter was then retracted to bring the balloon against the internal cervical os, and the catheter marked where it emerged from the external os. The catheter was then removed, and the distance between the balloon and the mark recorded. As can be seen from the results (Table 3.1) there is little change in the observed cervical length during the first half of pregnancy. In particular there is no evidence of an increase in the length to suggest hypertrophy or reinforcement of the cervix during this time.

Johnstone et al (1974) have measured the diameter of the endocervical canal at the level of the isthmus in non-pregnant and early pregnant subjects using a specially designed instrument. They found a steady but very slight increase in these measurements

measurements/
during the first trimester (Table 3.2) but after 12 weeks gestation the mean diameter was less than 25 per cent above non-pregnant values.

Anderson and Turnbull (1969) have studied the changes that occur in the cervix in later pregnancy. In a series of 77 healthy primigravidae with well documented pregnancies, they performed serial vaginal examinations at 24, 28, 32, 34 and 36 weeks gestation, and weekly thereafter until the onset of labour. They recorded the times at which the external and internal os could first admit an examining finger, and at which the cervix appeared to become fully effaced. Their findings are illustrated in Figure 3.1 and point to the progressive nature of the process as well as considerable inter-patient variability.

They also showed a clear relationship between the development of these changes and the time of onset of spontaneous labour. Thus the internal cervical os could admit an examining finger at 32 weeks gesation in all those primigravidae who subsequently laboured before 38 weeks gestation, in 55 per cent of those who laboured between 38 weeks and term, and in less than 20 per cent of those whose pregnancies continued beyond term (Table 3.3).

Bishop (1964) devised a sophisticated scoring system to assess the degree to which changes in the cervix have progressed (Figure 3.2). This approach which will be discussed in greater detail in Chapter 4 is now widely accepted as the most satisfactory

satisfactory/
method of assessing cervical ripeness. Using this system he performed 500 vaginal examinations in late pregnancy, on patients (parity unstated) who were then allowed to await the onset of labour. He found (Figure 3.3) that a very ripe cervix indicated by a cervical score of 9 or more was associated with the onset of labour after an average of two or three days, and always within ten days, whereas if the cervix was very unripe (score 3 or less) the average delay before labour was two - three weeks and in some cases as much as five weeks.

Hendricks, Brenner and Kraus (1970) made serial vaginal examinations throughout pregnancy in 303 patients, and recorded changes in cervical effacement, and dilatation, and the station of the fetal head. In primigravid patients they estimated that the mean cervical dilatation at the internal os increased from 0.5 cms. four weeks before the start of labour to 1.8 cms. during the final three days (Figure 3.4). They also recorded a progressive increase in effacement of the cervix during the same interval from 20 to 60 per cent (Figure 3.5) and progressive descent of the fetal head. The same pattern was seen in multigravidae although the absolute values for dilatation and effacement were slightly greater throughout.

These studies establish a clear temporal link between the process of cervical ripening and the spontaneous onset of labour. Furthermore, three of the central elements of cervical ripening, namely effacement and dilatation of the cervix and descent of the fetal presenting part, are the essential requirements of

requirements of/

normal progressive labour, although the rate of change is obviously very different. It seems highly probable then that similar mechanisms are responsible for the cervical changes during late pregnancy and during parturition, with a sudden increase in rate at the start of recognisable labour ("clinical labour", Wood 1972).

Beazley (1975) in describing this change as one from non-progressive to progressive uterine activity appears to be expressing a similar view.

Before proceeding to examine in greater depth the mechanisms which may control cervical ripening it may be worth considering a further question: if we accept that in most subjects the cervix has progressed to a high degree of ripeness before the recognisable onset of labour, is it possible for normal spontaneous labour to begin while the cervix remains unripe? Routine clinical experience suggests that this is rarely if ever seen, and the data from Bishop's study (1964) supports this (Figure 3.3). Fewer than one in a hundred of his patients with cervical scores below 3 were in labour within three days. Although these patients may perhaps have laboured with the cervix still unripe or have demonstrated unusually rapid cervical ripening before labour, the other (perhaps likelier) explanation is that of observer error in the cervical assessment. Nevertheless, it should be pointed out that in very rare instances (Jeffcoate 1952) complete annular detatchment of the cervix during labour has

labour has/
been seen suggesting lack of synchronisation between the contractility of the upper uterine segment and the changes in the lower segment and cervix.

b) Physical Changes in the Cervical Tissue

To examine the factors controlling cervical ripening, it is first necessary to consider in greater detail the structure of the cervix.

Structure of the Cervix

The cervix is composed of two distinct fractions, namely formed elements and ground substance. The main formed element is collagen which is organised in densely packed fibrous bundles. Muscle fibres are sparse, and represent no more than 10 per cent of the mass (Schwalm and Dubrauszky 1966). Furthermore, there is no increase in the muscle content of the cervix such as occurs in the upper part of the uterus during pregnancy. In contrast the collagen component predominates, and is in proportion ten times more abundant in the cervix than in the uterine fundus.

The muscle content of the cervix has been studied in detail by Danforth and his colleagues (1947, 1954, 1960, 1964 and 1973). Such muscle as is present is embedded in the collagenous matrix. It is very sparse and consists of isolated attenuated strands of smooth muscle except in the most peripheral areas of the portio supravaginalis of the cervix where they tend to be

to be/

concentrated. But the muscle of the cervix is much less abundant than that of the corpus uteri, and shows no increase in amount during pregnancy such as occurs in the corpus.

The ground substance (the term derives from a mistranslation of the word "grundsubstanz" (fundamental substance) used by early German histologists) of the cervix is the extracellular, extrafibrillar amorphous matrix of connective tissue (Hafez 1973). It has components derived from fibroblasts such as acid mucopolysaccharide, acid mucoprotein, water ions, cell metabolites and plasma proteins.

Alterations in Physical Characteristics of Cervix

The extent to which tissue is able to yield to a mechanical force has been called tissue compliance, and where the cervix is concerned this largely depends on the behaviour of the collagen elements. Bryant, Greenwell and Weeks (1968) studied changes in tissue compliance in the cervix of the rat during gestation and parturition. They found no significant change in total collagen content, but a marked increase in hexosamine and water coinciding with the time of maximum tissue compliance, i.e., at term. They suggested that the degree of compliance is an inverse function of the ratio of collagen to mucopoly-saccaride content. The rise in hexosamine and water pre-partum produces an imbalance in the cohesive and dispersive forces inter-acting between the collagen fibres allowing longitudinal cleavage of the bundles. Thus instead of being tightly bound together the fibres are able to glide freely upon one another, and the tensile strength of the tissue is reduced.

Danforth et al (1974) have studied the structural changes in the human cervix between the non-pregnant and post-partum states. It must be stressed that because of the obviously disruptive mechanical forces applied to the cervix during labour, the post-partum cervix cannot be equated to that immediately pre-partum. Nevertheless, restrictions on the availability of suitable tissue pre-partum preclude direct study of the structure of the human cervix in late pregnancy, and the post-partum condition may shed some light on the pre-partum situation. Danforth found that in the post-partum cervix the collagen framework had dissolved. The water content had increased slightly and there was a marked decline in the content of collagen and glycoprotein. As well as an absolute loss of collagen, the bundles were widely separated and appeared able to slide on one another. In the ground substance glycosaminoglycans were more abundant and qualitatively changed; there appeared to be a ten-fold increase in keratin sulphate over the non-pregnant level, and a large amount of an unidentified material, probably a glycosaminoglycan, which was almost absent from the non-pregnant cervix.

Because the changes in the cervix during labour appear to be a logical progression of those during ripening (indeed since labour resembles an extension of pre-labour) we may reasonably consider the possibility that the structural condition of the post-partum cervix may be an extension of that of the ripe pre-partum cervix.

Further, Turnbull and Anderson have drawn attention to other body sites of connective tissue which undergo similar changes during pregnancy - striae gravidarum appear as a result of a reduction in the tensile strength of the skin, the pelvic joints relax and the mobility of the nipples and the teeth increase. All these changes may be due to changes in the ground substance of connective tissue, and may be side effects of a physiological mechanism whose primary purpose is to ripen the cervix.

FACTORS CONTROLLING CERVICAL RIPENING

Having established that cervical ripening has two components, viz., a shape change and a change in the physical properties of the cervix, we must now consider what factors bring these changes about.

1) Mechanical Forces

The degree to which the shape of the cervix alters in late pregnancy must depend in part on how compliant it has become and in part on the degree to which such compliance has been exploited by mechanical forces. The forces to which the cervix may be subject are of three main types:

a) Uterine Contractility
b) Cervical Contractility
c) Direct Pressure

a) Uterine Contractility

The notion that the uterine muscle remains dormant throughout pregnancy until the start of labour has long since been dispelled. Caldeyro-Barcia (1958) has demonstrated an evolutionary pattern of uterine contractility throughout pregnancy and labour. By recording amniotic fluid pressure at intervals throughout pregnancy he was able to quantify uterine contractility: he devised a system of expressing this quantity as a product of the amplitude and frequency of contractions, and expressed the results as millimetres of mercury per 10 minute period, units which became known as Montivideo Units.

Thus he showed that during the first 30 weeks of gestation the amount of uterine contractility remains small (less than 20 Montivideo Units) contractions (usually called Braxton-Hicks contractions) being infrequent and of low intensity. After 30 weeks there is a very gradual increase in the intensity and frequency of these contractions until the state of prelabour commences, usually at around 36 weeks. From then until the onset of labour there is a sharper increase with contractions every 5 - 15 minutes with an amplitude of 15 - 30 mm. Hg., i.e., uterine contractility in the range 25 - 100 Montivideo Units. The range during labour is normally 100 - 250 Montivideo Units.

Braxton-Hicks contractions used to be thought purposeless but they probably play an important role in cervical ripening. Since the progressive changes seen in the cervix during labour are the direct result of uterine contractility it seems highly unlikely that the contractions of prelabour do not also have a direct bearing on the state of the cervix.

Turnbull and Anderson (1968) studied spontaneous contractility using a similar quantitative method and confirmed the gradual increase during the last 8 - 10 weeks of pregnancy. In addition they showed that the rate of increase was related to the time of onset of labour: they noted a sharp rise between 32 and 36 weeks, followed by a plateau in patients who laboured before term, but a much lower rise among patients in whom labour was delayed beyond term. The time course of these observations corresponds with their previously mentioned findings (page 67 , Figure 3.1, Table 3.3) of cervical changes (Anderson and Turnbull 1969) and support a close relationship between uterine contractility and cervical ripening.

b) Cervical Contractility

The relative sparseness of muscle tissue in the cervix may or may not reflect its functional importance, and this has been the subject of some controversy. Disagreement has been voiced among anatomists and physiologists and the debate remains unresolved.

It appears that the amount of muscle tissue is very variable not only between subjects but also in different parts of the cervix. Danforth (1954) contends that the absolute amount is usually 10 - 15 per cent of the mass but occasionally may be as much as 45 per cent, but he describes a fibromuscular junction corresponding approximately with the histological internal cervical os of Aschoff, below which the tissue is predominantly fibrous.

Hughesdon (1952) claims that the outer or circumferential fourth is muscular while the inner three-fourths are collagenous. These differing views probably arise from different methods of obtaining material and from differences in the pregnant and non-pregnant state. Danforth takes the view that such muscle as there is in the cervix consists of isolated attenuate strands of smooth muscle embedded in a heavy collagen matrix: they are more abundant in the region of uterine vessels than elsewhere, and bear a much closer resemblance to the muscle of the upper vagina than to that of the uterine corpus. He suggests that their functional importance lies in affording protection for vessels during pregnancy and labour and perhaps also in returning the cervix to its normal contours after delivery.

Many observers have suggested that the cervix might be capable of independent contractility. Nixon (1951) Coutinho (1976) and MacKenzie (1977) have produced

produced/

convincing traces of cervical contractility obtained using intra-cervical balloons *in vivo*. Majak, Hillier and Karim (1970) have shown similar effects *in vitro* in response to prostaglandins but such pressure changes as have been seen in the cervix *in vivo* may have been due in part to transmitted stresses from the uterine corpus or elsewhere and in part to a primary response of cervical muscle.

c) Direct Pressure

The resting pressure of the amniotic fluid - the tonus - alters very little as pregnancy progressed (Caldeyro-Barcia 1958). The mean level of about 5 - 7 mm Hg in mid-pregnancy rises to around 10 mm Hg in pre-labour and first stage labour, and it seems unlikely that so small an increase could have an important part to play in cervical ripening. In cases complicated by tense polyhydramnios it is not uncommon to find a tightly closed uneffaced cervix.

Local pressure influences are probably of greater importance. Just as normal progressive labour appears to require a well fitting presenting part over which the cervix and lower uterine segment may be stretched by the traction of the upper segment fibres, the normal process of cervical ripening may require similar conditions. Thus malposition or malpresentation of the fetus may contribute to a failure of cervical ripening.

A well fitting presenting part may act not merely

merely/

as a cast over which the cervix can be moulded into ripeness by the Braxton-Hicks contractions. Embrey and Mollison (1967) have shown that gradual ripening of the cervix may be artificially induced by the introduction of a Foley catheter so that its balloon lies just beyond the internal cervical os. This effect appears to be due to a direct pressure stimulus to the tissues, although it is probably mediated by local endocrine changes (see later). Lindgren (1955) has demonstrated pressure differentials in different areas of the uterus even when the fetal membranes are intact, and that after engagement of the fetal head in the pelvis the pressure on the lower uterine segment and cervix may be as much as three or fourfold higher than the corresponding pressure on the upper segment. This influence, especially when accentuated by gravity with the mother ambulant, may contribute to the ripening process.

2) Neural Influences

The uterus and cervix are innervated by both sympathetic and parasympathetic fibres of the pelvic antonomic system (Johnston and Whillis 1954). It is unlikely that the nervous connections of the uterus play more than a minor role in controlling uterine contractility, except perhaps at spinal reflex level. Uterine action in labour and delivery may be entirely normal in patients with complete transection of the spinal cord or division of the presacral plexus (Turnbull and

Turnbull and/
Anderson 1972).

Nevertheless, neural influences in the form of emotional upsets such as anxiety or fear could theoretically interfere with normal cervical ripening. Coupland (1969) has demonstrated the presence of a network of cholinergic fibres in the cervix, but the functional importance of these are not clear. Where the uterus is concerned Garrett (1954) first showed the ability of noradrenaline to stimulate uterine contractility in late pregnancy and that of adrenaline to inhibit it. Owman, Rosengren and Sjöberg (1967) have used histochemical fluorescent techniques to identify α and β- adrenergic receptors in the myometrium, and found noradrenaline to be mainly α -adrenergic (stimulating contractions) and adrenaline mainly β- adrenergic (inhibiting them), confirming the earlier observations of Garrett.

Some of the synthetic betamémetic amines such as "Ritodrine" and "Salbutamol" can be effective inhibitors of premature labour (Landesman et al 1971; Liggins and Vaughan 1973) but there is no evidence that endogenous catecholamines normally inhibit uterine contractions (Liggins et al 1977). Furthermore, Zuspan (1970) found little change in the urinary excretion of either adrenaline or noradrenaline through the course of human pregnancy with the levels at term almost identical to non-pregnant levels.

While the possibility cannot be discounted, it seems

seems/

improbable that emotional factors could interfere to a significant extent with the normal pattern of uterine contractility in late pregnancy. Even more difficult to imagine are any direct influences on the cervix effecting either the muscular activity or the physical properties of the tissue.

3) Hormonal Effects

Hormones probably exert the most important influence in the control of cervical ripening. They may be involved in all the aspects already discussed which bring about the shape change of ripening, i.e., changes in the physical properties of the tissue, control of uterine and cervical contractility, and mediation of pressure andneural effects.

A large number of endocrine substances may be involved at different stages and these will now be considered individually.

a) Oestrogens

Oestrogens have been shown to induce myometrial hypertrophy, actomyosin formation, storage of high energy phosphates, and the development of myometrial cell membrane potentials and myometrial excitability (Reynolds 1949; Csapo 1962) in short, to prepare and sensitise the uterus for the needs of labour. Jarvinen et al

(1965), Pinto et al (1967) and Larsen et al (1973) found increased uterine contractility in women at term in response to large systemic doses of oestrogens but this did not result in induction of labour.

The very low levels of oestrogens found in pregnancies complicated by placental sulphatase deficiency are associated with prolongation of pregnancy, and failure to respond to induction of labour especially in primigravidae (France, Seddon and Liggins 1973). Of even greater interest is the tendency in these pregnancies for the cervix to fail to ripen. There is good theoretical support for the contention that oestrogens may play a direct role in modifying cervical collagen. Firstly oestradiol 17-β is known to modify collagen in other body sites, such as skin (Henneman 1973). Leppi and Kinnison (1971) using histochemical and electron microscopic techniques have demonstrated loosening and scattering of the collagen fibrils in the cervix of mice treated with oestradiol.

The evidence in women is more tenuous. In addition to the observations in sulphatase deficiency already mentioned, Pinto et al (1964) have claimed to have produced clinical evidence of cervical softening in the human cervix in late pregnancy by intravenous infusion of oestradiol 17_{β} in large doses. They have suggested that this hormone is responsible for the changes in the cervical

cervical/

ground substance (see page 71) which modify the tensile strength of collagen.

In support of these claims is the finding that the levels of oestradiol 17-β measured in the peripheral circulation rise steadily during the last six weeks of pregnancy (Turnbull et al 1974), that is the time of rapidest cervical ripening (Figure 3.6). These two events could be closely related if indeed increasing production of oestradiol results in an increase in Braxton-Hicks contractility, and also a direct reduction in cervical resistance.

b) Progesterone

By its very name this hormone has traditionally been considered to be essential for maintenance of pregnancy. Certainly surgical removal of the corpus luteum in the early weeks of pregnancy before the placenta has taken over responsibility for progesterone production, will result in abortion (Csapo, Pulkkinen and Weist 1973) which may be prevented by exogenous replacement of progesterone. Less certain is an essential role in later pregnancy.

Csapo has long expounded his theory of the progesterone "block" on the onset of labour (Csapo 1959) but, as Bengtsson (1973) has pointed out, groups other than Csapo's (Csapo et al 1971) have consistently failed to demonstrate any drop in peripheral progesterone levels

levels/

before labour starts (Woolever and Goldfien 1965; Runnebaum and Zander 1971; Turnbull et al 1974). Turnbull et al (1974) showed a steady decline from mean levels of around 160 mg./ml., five weeks before labour, to 115 mg./ml. one week before hand, but found no further fall during labour. Further doubt is cast on the "block" theory by the consistent failure of experiments to inhibit uterine activity with large doses of progesterone or medroxyprogesterone whether given intramuscularly, intravenously, intra-amniotically or even intra-myometrially (Hendricks et al 1961; Wood et al 1963). One possible explanation for this (Liggins et al 1977) is that progesterone receptors in the late pregnancy uterus may be fully saturated at normal plasma progesterone concentrations and that a waning influence of progesterone requires either its displacement by another substance or reduction in the absolute number of binding sites. Neither of these changes has yet been described.

A possible influence of progesterone in normal or abnormal cervical ripening due to the presence or absence of Braxton-Hicks contractions as determined by the foregoing considerations cannot be ruled out. Another, more direct influence on the cervix must also be considered. Jeffrey, Coffey and Eisen (1971) have demonstrated in tissue culture that progesterone may inhibit collagenase activity in the uterus and more recently Hillier (1977) has made similar observations on a culture of cervical tissue. These studies raise the possibility that

that/

progesterone might inhibit cervical ripening until the peripheral levels begin to decline in the last few weeks of pregnancy(Turnbull et al 1974).

c) Catecholamines

The possible roles of catecholamines have already been discussed under the heading "Neural Influences" (page 78) and will not be considered further here.

d) Relaxin

The role of relaxin in human pregnancy is, to say the least, obscure. It has long been thought to be responsible for increasing the mobility in pregnancy of such joints as the pubic symphysis and the sacro-iliac joints (Donald 1966). A possible link between this (presumably) connective tissue change and those occurring in the cervix has already been suggested (page 73). Leppi and Kinnison (1971) have demonstrated such an effect of relaxin on the cervix of the mouse. The collagen fibrils were loosened and scattered but this effect remains to be confirmed in the human.

Several years ago its possible role as a uterine inhibitor was mooted (Kroc, Steinetz and Beach 1959), but while interesting results were obtained in several animal species, clinical trials involving women in labour proved inconclusive. For a number of reasons these studies cannot be taken to demonstrate that relaxin is of no importance in human parturition. Firstly, human

human/

relaxin has not yet been made available for clinical trials and the porcine relaxin used may be inactive in the human (Bryant 1972). Secondly the doses used may have been too low (Slate and Mengert 1960) and thirdly most studies looked at the effects of relaxin on artificially induced uterine contractility, and this may not reflect its role in physiological situations (Porter 1972). Bryant (1972) has developed a specific radioimmunoassay for human relaxin and the roles of relaxin in human pregnancy may soon become clearer.

e) Oxytocin

Oxytocin is another hormone whose traditional role in the control of uterine contractions now seems in considerable doubt. The notion that it is the physiological activator of the uterus in labour was based mainly on two facts: that the uterus at term is very sensitive to oxytocin, and that oxytocin induced labour closely resembles spontaneous labour. This notion has been widely held since the days of Blair-Bell (1909) and, as Chard (1977) has pointed out, remains to this day the standard teaching in many textbooks of obstetrics. But, although oxytocin may be found in a proportion of blood samples taken during first stage labour and a higher proportion during the second stage (Figure 3.7) there is no evidence of increased maternal secretion of oxytocin before the onset of labour (Chard 1973). It should be pointed out, however, that Chard has suggested that oxytocin

oxytocin/

is released by the posterior pituitary in intermittent spurts; while this explains why the hormone is only detected in a proportion of blood samples in labour, it could also explain why it has not so far been found before labour. Chard et al (1971) have also shown consistently high levels of oxytocin in fetal plasma at delivery and in demonstrating an arterio-venous gradient in the umbilical vessels have suggested uptake of oxytocin at the placenta. Of further interest was their finding of levels around 5 μu per ml., again with an arterio-venous gradient, in cases delivered by elective caesarean section who had not been in labour. While the haemochorial placenta of the human mother presents conceptual difficulties in suggesting a direct action on the myometrium of fetal oxytocin without its first passing through the maternal circulation, this observation may have some minor significance in the process of cervical ripening.

Finally, the little that is known of the factors causing release of oxytocin may be relevant (apart from mammary stimulation which is unlikely to be). Ferguson (1941) was able to demonstrate that local stimulation to the vagina and cervix during labour was often followed by heightened uterine activity and acceleration in its progress. This became known as Ferguson's reflex and in 1961 Debackere, Peeters and Tuyttens used an elegant cross circulation experiment in sheep to show that the effect was mediated by an oxytocic hormone which was later

later/

confirmed by Roberts and Share (1968) to be oxytocin. This may go some way towards explaining the mechanism whereby local mechanical stimuli modify the condition of the cervix (see page 77).

f) Prostaglandins

The ability of prostaglandins to stimulate uterine contractions at any stage of pregnancy (see page 58) makes them likely candidates for a role in the contribution made by Braxton-Hicks contractions to cervical ripening. Kloeck and Jung (1973) have shown that PGE_2 is released when myometrial strips are stretched in a water bath. Stretching has long been thought to play a role in the evolution of myometrial contractility and this finding may point to an important mechanism in the production of Braxton-Hicks contractions. The possibility of a similar mechanism causing local release of PGE_2 from stretching the cervix, could have an important direct bearing on physical changes in the cervix. Conrad and Euland (1976) studied the stretch modulus of human cervical tissue in vitro and showed that this was reduced by addition of PGE_2 to the bathing solution. They also found lower stretch moduli in cervical tissue taken post-partum from patients whose labours had been induced with PGE_2 than if they had been spontaneous or oxytocin induced. The tissue studied was described as the fibrous inner portion of the cervix and at no stage was contractility, either spontaneous or induced, observed. This suggests that the effect of the

effect of the/

PGE_2 was on the connective tissue elements rather than on muscle. Others, (Najak, Hillier and Karim 1970; Karim and Ratnam 1974) have purported to show contractility of the cervix in response to prostaglandins but the anatomical structure of the cervix makes these of doubtful importance in the process of ripening. More recently Fitzpatrick (1976) has infused PGF_2 into the arterial supply of the cervix in pregnant sheep, and reported softening and dilatation of the cervix.

Lastly, continuing the theme of Ferguson's reflex begun in the last section (page 86), Flint et al (1974) have recently shown a rise in utero-ovarian venous prostaglandin F levels in sheep following vaginal or cervical stimulation, and later (Flint et al 1975) that this appeared to result from the reflex release of oxytocin. A possible role of exogenous prostaglandins derived from seminal fluid must also be considered but Anderson and Turnbull (1969) could detect no association between the ripeness of the cervix and the frequency of coitus during pregnancy

SUMMARY

The most important factors likely to play a part in the normal process of cervical ripening are illustrated in Figure 3.8. Ripening consists of two main changes, namely a change in the physical properties of the tissue of the cervix (especially collagen) and a shape change.

In the first of these, chemical changes in the ground substance alter the cohesive and dispersive forces acting between the collagen fibres so that they glide more readily upon one another and this reduces the tensile strength of the collagen bundles. This change may be principly controlled by oestradiol although prostaglandins and relaxin may also be important. In addition there may be an absolute reduction in the mass of collagen due to the action of collagenase, perhaps after withdrawal of inhibition of this enzyme by progesterone.

The second, the shape change, is the early or preliminary manifestation of the changes which proceed much more rapidly during labour, namely effacement and dilatation. There seems little doubt that the same set of circumstances produce these changes in late pregnancy as do so in labour, i.e., the combined effect of uterine contractions and local pressure from the presenting part of the fetus.

For a high degree of cervical ripening to be produced it seems likely that well developed tissue changes must be exploited by efficient Braxton-Hicks contractions. Failure in either respect will lead to failure of cervical ripening and the clinical problems which this brings.

C H A P T E R 4

A REVIEW OF EXISTING METHODS OF MANAGEMENT: AMNIOTOMY AND INTRAVENOUS OXYTOCIN INFUSION IN PRIMIGRAVIDAE

AMNIOTOMY AND INTRAVENOUS OXYTOCIN INFUSION IN PRIMIGRAVIDAE

Existing Methods of Management

This chapter attempts to define the clinical problems associated with failure of cervical ripening in primiparous women, and the deficiencies of the methods of management available in the early 1970's. Although several workers (Garrett 1960; Embrey and Anselmo 1962) had emphasised the poor results from induction of labour if the cervix was unripe, others (Tennant and Black 1954; Manly 1956) had stated that no regard should be taken of the cervical state before performing amniotomy. Indeed Manly (1956) saw "no cause for alarm if labour has not ensued within three days". Many highly respected teachers of obstetrics held that if there were indications for induction of labour, the step should be taken decisively and that if the method failed and caesarean section was required, this had to be accepted as the justifiable cost of the particular indication for induction. When oxytocin began to be used more rationally (Turnbull and Anderson 1968) results improved generally, with 90 per cent of patients delivered within 12 hours of induction, and a fall in the caesarean section rate. This might have suggested that the unripe cervix had ceased to be a problem, but the Medical and Clinical Report for 1973 of the Simpson Memorial Maternity Pavilion, Edinburgh, posed the following question: "Is it not possible that we are still failing to pay sufficient attention to the unripe cervix and by failing to do so are laying on

laying on/

unnecessary trouble for our patients and ourselves?" The same criticism could probably have been made with some justification in most of the maternity hospitals in the land. Little or no attention was generally paid to the cervix when a decision was made to carry out induction of labour.

To assess the importance of the state of the cervix, two studies were made in the John Radcliffe Hospital, one retrospective and one prospective.

RETROSPECTIVE STUDY

A retrospective analysis was made of the confinements conducted in the specialist unit of the hospital during the six months period, March to August inclusive, 1974. During this time 2,173 patients were delivered of whom 1,250 were multiparas (57%) and 923 primiparas (43%).

The pattern of delivery among the primiparas was examined in detail. Twenty-six (2.8%) were delivered by elective caesarean section. Labour began spontaneously in 360 (39%) and was induced in 537 (58%). This period coincided with the peak incidence of induction of labour in the hospital, which has since seen a steady decline (Turnbull 1977). With the exception of a small number whose labours were induced by amniotomy and intravenous prostaglandin E_2 infusion (see Chapter 5), the method of induction was amniotomy and intravenous oxytocin

oxytocin/

titration. Eighty-six of the patients whose labours began spontaneously were given intravenous oxytocin to augment labour (including 37 patients admitted near term following spontaneous rupture of the membranes in whom uterine contractions had not begun). Thus a total of 643 (70%) from the total 923 primiparous population received some form of oxytocic stimulation. The outcome in those 897 patients who were allowed to labour is summarised in Table 4.1.

There was no instance of intrapartum stillbirth and the overall results examined in this way appear satisfactory. Eighty-two per cent of the patients had labours lasting less than 12 hours and the mean duration was 9.1 hours, with even better results following induced labour.

One must expect higher rates of caesarean section and birth asphyxia in the induced group since this will inevitably contain almost all cases with impaired placental function (pre-eclampsia, fetal growth retardation, etc.). Nevertheless, close examination of the 76 cases of non-elective caesarean section showed that all but three could be attributed to one of three primary indications for the operation, namely fetal distress, cephalopelvic disproportion or failure to progress in labour. The three other causes were severe pre-eclampsia in one case, maternal distress in one and cord prolapse in one. The breakdown of these cases by indication for caesarean section and mode of onset of labour is shown in Table 4.2. Further analysis of the duration of labour and the degree of cervical

cervical/
dilatation reached before caesarean section, and the condition of the neonates related to the main indication for caesarean section is set out in Table 4.3.

The most striking observation in this analysis is that "failure to progress in labour" was only found as the main indication for caesarean section among patients in whom labour had been induced, and this occurred in 4.1% of such patients. Their labours were prolonged and were characterised by inco-ordinate uterine action and poor cervical dilatation. The fetal outcome in these patients appeared worse than in those sectioned for disproportion, suggesting a greater degree of stress to the fetus from such labours.

It might be argued that cephalo-pelvic disproportion cannot be ruled out in some cases delivered by caesarean section for "fetal distress" or "failure to progress in labour". While this may be so it is unlikely to apply in many cases in this analysis since the incidence of disproportion among the well nourished Oxford primigravidae is unlikely to be much higher than the 3% sectioned (four electively and 25 during labour) for this stated reason.

While "failed induction" (in the old sense of failure of the uterus to contract following amniotomy) was not seen, some might regard the cases of "failure to progress" as "failed inductions" and failure to produce uterine action capable of leading to vaginal delivery can properly be regarded as failure

failure/

of the method. They may indeed represent the same clinical problem.

A number of different obstetricians had carried out the inductions, but because the case notes included a format for recording cervical findings at induction, it was possible to divide according to their cervical state those 63 primigravidae who had caesarean sections after induced labour into three broad groups namely ripe, intermediate and unripe (Table 4.4). It was immediately clear that caesarean section was much commoner in those with an unripe cervix at the time of induction.

Whereas the cases who had caesarean sections on account of disproportion and "other" indications had an even scatter of cervical ripeness at induction, those sectioned for fetal distress more commonly had an unripe cervix at the time of induction and this was even more striking in those who demonstrated failure to progress in labour.

It was also possible to calculate for each case an approximate cervical score (see Appendix A) at the time of amniotomy. The mean score so obtained in each group is shown in Table 4.4.

For comparison the case-sheets of a further 63 patients were selected at random from the total group of 537 primigravidae who had labour induced. These were examined in the same way and the cervix found to have been ripe in 18, intermediate in 31 and unripe in 14. The mean approximate cervical score

cervical score/
was 5.9 and this was significantly greater than for those who came to caesarean section (4.0).

The conclusion from this retrospective study was that caesarean section was more commonly required in patients who had come to induction of labour with an unripe cervix, and this was particularly apparent among those requiring the operation on account of fetal distress or failure to progress in labour. Having in mind, however, the defects of such a retrospective study (particularly in respect of inter-observer error) a detailed prospective study was carried out to further examine the question.

PROSPECTIVE STUDY

During a six weeks period from 27th October, until 12th December, 1974, the candidate personally carried out all labour inductions in primigravidas referred for the purpose, who fullfilled the criteria: 152 cms. or more in height, singleton pregnancy, vertex presentation, 38 weeks gestation or more, no prior evidence of spontaneous labour. This produced a series of 125 primigravid inductions.

The indications for induction were as shown in Table 4.5.

Forewater amniotomy was performed in every case and a

and a/

cervical score recording (Bishop (1964) system modified, see Figure 3.2 and Appendix A : Clinical Methods). The scores in the patients studied ranged from 1 to 11 and the mean was 5.4 (Figure 4.1). An electrode was attached at this time to the fetal scalp and a fluid filled catheter passed into the amniotic cavity; these were attached to a Hewlett-Packard 8021 A cardiotocograph to give a continuous record of the fetal heart rate and the intra-uterine pressure (see Appendix A). The intra-uterine pressure signal was also used in conjunction with the fully automatic Cardiff Infusion apparatus to control the dose rate of the intravenous oxytocin infusion which was commenced within 15 minutes of amniotomy. The use of this apparatus (Figure 4.2; for a description see Appendix A) allowed uniformity of dosage since this was determined by the response of the uterus and thus free of any possible bias on the part of the attendants. The obstetric management of the patient was thereafter entirely in the hands of the duty obstetric staff. Epidural analgesia was employed in 95 (76%) of the total 125 cases.

Labour and Delivery

In Figure 4.3 the time from amniotomy to delivery is plotted against the cervical score at induction. There is a strong inverse correlation between these two factors ($r = -0.68$; $P \ll 0.001$). Seventy-eight per cent of all patients were delivered within 12 hours of induction: every patient with a score greater than six was delivered within this time, but fewer than 40 per cent of those with a score below four.

The breakdown of length of labour and mode of delivery by cervical state was as shown in Table 4.6.

Spontaneous delivery was commoner the riper the cervix at induction, but this was partly related to the length of labour. Those with longer labours more commonly requested epidural analgesia and hence required forceps deliveries because of failure of the secondary powers (Hoult, McLennan and Carrie 1976). By contrast all 13 cases requiring caesarean section had scores of five or less. Indeed as the cervical score fell so the caesarean section rate rose, and all five patients with a score of one were eventually delivered in this way (Figure 4.4).

The indications for caesarean section were disproportion in two cases, fetal distress in four and failure to progress in seven (Table 4.7). Those cases in whom failure to progress in labour was the primary indication for caesarean section appeared to have a satisfactory pattern of uterine contractility, but they were the longest in labour and achieved the slowest and least cervical dilatation. Delivery usually became necessary when after 18 hours or more of slow progress the fetal condition began to deteriorate.

Fetal and maternal complications were also found to be related to the cervical state at induction (Table 4.8). The individual Apgar scores at one minute are plotted against the cervical score in Figure 4.5. All the babies who required to be resuscitated by endotracheal intubation and intermittent positive pressure ventilation were born to mothers whose cervical

cervical/

scores were five or less.

This study served to reinforce the findings of the retrospective study, and in particular to identify the common and unsatisfactory pattern of labour which may follow amniotomy and oxytocin infusion in the primigravida if the cervix is unripe. Whereas the overall results for the group as a whole (mean length of labour 10.2 hours, caesarean section rate 10 per cent, maternal pyrexia rate 10 per cent, birth asphyxia rate 9 per cent) might appear acceptable in the context of induced labour for recognisable obstetric abnormalities, they conceal within them a small hard core whose results are clearly unacceptable, namely those with an unripe cervix. The results in these patients (mean length of labour 14.9 hours, caesarean section rate 32%, maternal pyrexia rate 32%, birth asphyxia rate 23%) are unsatisfactory, especially when one considers that the induction rate in all primigravidae was approaching 60 per cent, and this must have included many patients with trivial obstetric abnormalities.

Examination of the results from the opposite view point, that is those 94 primigravidae who did not have an unripe cervix (scores 4 - 12), shows that the mean length of labour was 8.2 hours, the caesarean section rate 3%, the maternal pyrexia rate 2% and the birth asphyxia rate 4%. This suggests that the indifferent results after induction of labour were much more related to the state of the cervix than to the obstetric complications which called for induction.

If failure of cervical ripening were never encountered the results from induction of labour would be greatly improved. The studies described, while identifying and quantifying the clinical problem of the unripe cervix, offer nothing in the way of a solution. They show that amniotomy and oxytocin titration is an inappropriate management if the cervix is unripe, but what alternatives would be better? To try to answer this question we must first examine the possible reasons for the poor results and then consider the therapeutic options.

The two most likely reasons for poor results are:-

1) If the cervix is unripe, the uterus may be less responsive to the method of induction.

and

2) The mechanical work required to overcome the unripe cervix is too great and may put too much stress on the feto-placental unit.

There is some theoretical support for the first in that uterine sensitivity to oxytocin normally develops only in late pregnancy (Csapo and Sauvage 1968) during the time when the cervix is normally ripening. Indeed these two events may be associated in that the cervix may ripen because of the increase in contractility of the uterus as its sensitivity increases (see page 65). That being so, better results might be expected if prostaglandins were used, since the uterus is highly sensitive to these agents at any stage of pregnancy (Embrey 1975).

It is self-evident that if the main factor responsible for

responsible for/

producing effacement and dilatation of the cervix in labour is uterine contractility, the more unripe the cervix is at the outset, the more uterine work will be required. Caldeyro-Barcia and Poseiro (1959) have stated that the induction of labour requires 200 - 300 contractions of 40 mm. Hg. intensity or greater if the cervix is unripe, but less than 100 if it is ripe; and Cibils (1972) has quantified the mechanical work required from the uterus to ripen the cervix. The distinct clinical impression was gained in the course of the studies described in this Chapter that of the five elements of the cervical score, the least valuable prognostic index was the degree of dilatation of the cervix. Analysis of the points awarded for each element according to whether labour was longer or shorter than the median confirmed this impression (see Table 4.9). The most valuable index was the level of the presenting part, followed by the degree of effacement and the consistency of the cervix. It seems that the time consuming part of the latent phase of labour is that part concerned with effacing the cervix and allowing descent of the head. Once the cervix is fully effaced, dilatation can readily proceed. This is borne out by the finding that in most cases sectioned for failure to progress in labour, effacement of the cervix had never properly taken place.

Caldeyro-Barcia et al (1974) have produced evidence that fetal hypoxia is more likely to occur if amniotomy is performed early in spontaneous labour than if deferred until dilatation of

dilatation of/

the cervix is well advanced. The same may be true of induced labour and this may become clinically apparant especially in cases that require a prolonged latent phase of cervical effacement because the cervix is unripe. Another advantage in a method of labour induction might be avoidance of the need for amniotomy.

The therapeutic options in the management of the unripe cervix may now be examined. There are four:

1) Carry out elective caesarean section.
2) Delay delivery in the hope the cervix will ripen in the meantime.
3) Employ more suitable methods of labour induction, perhaps avoiding amniotomy and employing prostaglandins.
4) Attempt to produce a ripe cervix before inducing labour.

Options 3 and 4 will be discussed in later chapters but consideration will now be given to options 1 and 2.

Elective Caesarean Section

There are some pregnancies in which, because of deteriorating placental function, the stress of even the easiest of labours would be undesirable. Elective caesarean section is the appropriate management of such cases regardless of the state of the cervix. Logically this would also seem appropriate in cases with marginally better placental function if the

if the/

cervix is unripe. However, to apply such management in a blanket fashion to all patients with an unripe cervix would be unduly radical.

Firstly the maternal risks associated with caesarean section are not trivial (Report on Confidential Enquiries into Maternal Deaths in England and Wales 1970 - 1972). Secondly it should be stressed that while the results in the "unripe group" in the prospective study were extremely poor, by no means all 31 patients had an unsatisfactory outcome. Twenty-one of the mothers were delivered vaginally in a mean time of 12.9 hours, and twenty of the 31 babies had one minute Apgar scores of 7 or better. Had all 31 mothers been delivered electively by caesarean section, substantially more than half would have had the operation unnecessarily. Caesarean section is not yet so safe, either in the short term or in respect of future pregnancies, that it may be performed lightly or without good cause.

Delaying the Delivery

It is a recognised practice in some departments that if the cervix is found to be unripe delivery is delayed to await ripening. Clearly if the indications for induction are trivial such a course would seem sensible. Unfortunately, the results are often disappointing. The data (Figure 3.3) from the study of Bishop (1964) indicate that if the cervix was ripe (score 9-12) labour began within an average of 2 - 3 days, but if unripe

unripe/

(score 0-3) the interval was almost three weeks.

Such a delay might be justified in relatively normal pregnancies (although the dangers associated with prolonged pregnancy would begin to mount); it could not be justified if the indications were pressing. Any improvement in the state of the cervix may be bought at the cost of impaired placental function, even in normal pregnancies allowed to continue long after term. We have personal experience of stillbirths occurring while cervical ripening was awaited. Delaying the delivery is at best a temporary expedient which may not be in the best interests of the mother or her baby.

Furthermore, it may be a mistake to assume that the cervix is unripe simply because the ripening process has been delayed. Clayton (1941, 1953), Stewart and Bernard (1954) and Walker (1959) have all shown that the incidence of abnormal uterine action in labour is increased in pregnancies which continue beyond term. This may be not so much the result of the delayed onset of labour as the cause of it; in other words there may be a fundamental defect in uterine function. This may contribute to unripeness of the cervix and waiting may not cure it.

Since the optimum clinical solution to the problem of the unripe cervix does not lie either in the use of elective caesarean section or in the postponement of induction, it was necessary to find alternative methods of management. The search for such methods is the central theme described in the next three chapters.

CHAPTER 5

AMNIOTOMY AND INTRAVENOUS PROSTAGLANDIN E_2 AS AN ALTERNATIVE TO AMNIOTOMY AND INTRAVENOUS OXYTOCIN

AMNIOTOMY AND INTRAVENOUS PROSTAGLANDIN E_2 AS AN ALTERNATIVE TO AMNIOTOMY AND INTRAVENOUS OXYTOCIN

In the search for a more successful method of induction of labour for the primigravida with an unripe cervix, the first modification investigated was the substitution of prostaglandin E_2 for oxytocin in the standard method of amniotomy and intravenous oxytocin infusion. The literature contained a large number of reports of the use of E and F prostaglandins administered intravenously for induction of labour (Embrey 1969; Beazley, Dewhurst and Gillespie 1970; Embrey 1970; Karim et al 1970; Anderson et al 1971; Beazley and Gillespie 1971; Karim 1971; Kinoshita et al 1971; Roberts and Turnbull 1971; Anderson, Hobbins and Speroff 1972; Elias 1972; Hogaki 1972; Ring 1972; Scher et al 1972; Spellacy and Gall 1972; Vakhariya and Sherman 1972; Vroman et al 1972; Brown et al 1973; Laros, Witting and Work 1973; Naismith, Barr and MacVicar 1973; Spellacy et al 1973; Thiery et al 1973; Witting, Laros and Work 1973; Caballero et al 1974; Thiery et al 1974). Nineteen of these papers described experience with intravenous $PGF_{2\alpha}$ for induction of labour in a total of 893 patients and nine of the reports concerned the use of PGE_2 in 886 patients (500 of whom were contributed by Karim (1971) in a single report). Experience with PGE_1 was limited to 39 patients described in three of the reports and only two papers mentioned the use of $PGF_{1\alpha}$ in each instance for one patient only.

Because the protocols differed widely with regard to

regard to/

indications for induction of labour, parity, gestational age, dosage of prostaglandins, timing of amniotomy, criteria of success and method of recording side effects, it is not possible to draw other than the broadest comparisons and conclusions from these studies. In particular, very few of the authors made any mention of the cervical findings at the time of induction so that no opinion could be formed on the value of prostaglandins in the specific problem of the unripe cervix. Nevertheless, the following conclusions could be drawn:

1) Prostaglandins (especially PGE_2 and $PGF_{2\alpha}$) infused intravenously in combination with amniotomy are effective agents for induction of labour.

2) While fixed dose rate schedules may be effective an escalating dose gives better results.

3) The therapeutic dose range appears narrower than with oxytocin so that uterine hyperstimulation may occur if the dose is too great.

4) Maternal side effects (nausea, vomiting, diarrhoea, pyrexia, shivering, pain and erythema at the site of infusion) may occur with the doses necessary to induce labour. These are more common and troublesome with $PGF_{2\alpha}$ than with PGE_2.

5) PGE_2 and $PGF_{2\alpha}$ appear about equally effective for labour induction at term.

Comparisons of I.V. Prostaglandins with Oxytocin

Ten of the above mentioned reports have attempted to make

to make/

a comparison between either or both prostaglandins and oxytocin. The almost invariable conclusion of these studies has been that prostaglandins appear about as safe and effective as oxytocin in inducing labour. On the other hand, the higher incidence of irritating side effects (around 5% of patients overall) is an important drawback. The only suggested advantage of prostaglandins was the theoretical one of having no anti-diuretic effect similar to that of oxytocin but this is rarely of clinical importance (Roberts et al 1970).

Only one of these studies (Beazley and Gillespie 1971) was conducted on a double blind basis. PGE_2 was compared with oxytocin and the results were virtually identical, but the patients were not matched for factors known to affect labour such as age, parity and gestation and in particular no account was taken of the state of the cervix. Another study (Vakhariya and Sherman 1971) did differentiate on the basis of a cervical score (range 0 - 16) into "difficult" (0 - 5) and "easy" (6 - 16) inductions, but all the patients were multiparous and this factor was therefore probably less important. Fifty patients were classified as difficult inductions and 25 received each drug. Amniotomy was performed when contractions were established and on the rather arbitrary basis of vaginal delivery within $8\frac{1}{2}$ hours of induction, 23 oxytocin cases and 22 $PGF_{2\alpha}$ cases were considered to have had a successful outcome. Only one patient in each group required caesarean section, one because of fetal distress and one because of failure of descent of a breech presentation; this perhaps suggests that an unfavourable

unfavourable/
cervix is a less serious problem in multiparous patients than in primiparas.

In the other studies that compared prostaglandin E_2 and oxytocin, Brown, Hamlett and Hibbard (1973) state that amniotomy was performed at the outset "following pelvic assessment" but no data on the state of the cervix is presented. Karim (1971) makes no mention of the cervical state (nor even maternal age, parity or gestional age) and his failure rate of 33 per cent for oxytocin against 4 per cent for PGE_2 suggests that he could not have been employing oxytocin in a manner designed to ensure its maximum efficiency. The other studies, which compared $PGF_{2\alpha}$ with oxytocin, suffered from similar defects and since our main concern is with PGE_2, these will not be considered further.

In order to examine the possibility that intravenous PGE_2 following amniotomy would be more effective than intravenous oxytocin for the primigravida with an unripe cervix, a double blind trial was designed. The study is described in the following paper.

PGE_2 was preferred to $PGF_{2\alpha}$ for two reasons. Firstly, the two compounds appeared on the face of published evidence to be about equally effective, but PGE_2 was rather freer of side effects. Secondly, although the muscle of the cervix may have little functional importance (page 76) there was some evidence (Embrey and Morrison 1968; Najak, Hillier and Karim 1970; Karim and Ratnam 1974) that PGE_2 might relax the muscle of the

of the/

cervix and lower segment which would clearly be preferable to the opposite effect which had been attributed to $PGF_{2\alpha}$.

The paper described 100 primigravidae with cervical scores of 0 - 6. Because subsequent clinical studies are concerned only with primigravidae with the most unripe cervices (scores 0 - 3) the data for those patients in the series with scores of 0 - 3 have been extracted and are presented separately on page 112.

Data for Patients with Cervical Scores 0 - 3

Thirty-four of the 100 patients had cervical scores between 0 and 3, and 17 of these patients received each drug. The numbers are therefore small but the details of labour, delivery and adverse effects in the two groups are shown in Table 5.1.

Intravenous PGE_2 appeared more effective than oxytocin in achieving cervical effacement and dilatation; the latter drug again being associated with the pattern of "failure to progress" in labour. This was the indication for caesarean section in four of the five oxytocin cases sectioned. The operation was performed in these four cases after a mean of 20.2 hours by which time the mean cervical dilatation was only $3\frac{1}{4}$ cm. The other case was sectioned because of cephalopelvic disproportion after 13.7 hours and a cervical dilatation of $4\frac{1}{2}$ cm.

In the two PGE_2 cases requiring caesarean section, the indication was failure to progress in labour in one case (cervix 4 cm dilated after 16.0 hours) and fetal distress in the other (cervix 7 cm dilated after 11.2 hours).

Although the numbers are small there is some support from these data for the view that the use of PGE_2 produced uterine action that was more efficient than oxytocin in causing cervical effacement and dilatation. Fetal distress and birth asphyxia were also less common. However, the unpleasant maternal side

maternal side/
effects, while never becoming intolerable, were sufficient of a disadvantage to off-set the benefits.

It was originally planned to follow up this study with another using systemic prostaglandin E_2 (intravenous or oral) without amniotomy to investigate the theoretical benefit of intact fetal membranes (page 40). This plan was abandoned after a pilot study of five patients, two who received intravenous PGE_2 and three who received oral PGE_2 tablets. This had demonstrated that the methods were clearly less effective than if combined with amniotomy, and the side effects were worse.

The literature contained 17 reports of the use of oral PGE_2 for term labour induction (Karim and Sharma 1971a, 1972; Barr 1972, 1973; Elias 1972; Filshie 1972; Craft 1973a, 1973b; Kelly, Flynn and Bertrand 1973; Thiery et al 1973b, 1974a; Yip, Ma and Ng 1973; Corson and Bolognese 1974; Elder and Stone 1974; Murnaghan et al 1974; Wilkin et al 1974; Laurensen and Wilson 1975), an experience of over 1,700 patients. As with intravenous studies the protocols varied widely especially in respect of parity, gestational age and whether or not cervical state was considered. Although some authors claimed success even if the cervix was unripe, this was the commonest reason given for failure and did not encourage optimism that oral prostaglandins might provide the solution to the problem. However, the main reason systemic routes of prostaglandin therapy

therapy/

were not pursued further was that investigations of local routes had begun, and were already yielding much more promising results.

The main conclusion from this study, therefore was that there was little to choose between intravenous prostaglandin E_2 and oxytocin for induction of labour in primigravidae. The advantage of prostaglandin E_2 was to achieve better cervical dilatation in the most unfavourable cervices but this was off-set by its increased systemic side effects. It was hoped that by applying prostaglandins locally, the advantageous cervical effects might be increased and the disadvantageous systemic complications reduced. The studies which were undertaken to explore the potential value of local prostaglandins in the unripe cervix are described in the next two chapters.

C H A P T E R 6

DEVELOPMENT AND APPLICATION OF METHODS OF LOCAL (EXTRA-AMNIOTIC) PROSTAGLANDIN ADMINISTRATION FOR INDUCTION OF LABOUR

DEVELOPMENT AND APPLICATION OF METHODS OF LOCAL (EXTRA-AMNIOTIC) PROSTAGLANDIN ADMINISTRATION FOR INDUCTION OF LABOUR

The foregoing chapters have identified the deficiencies of hitherto available methods of induction of labour if the cervix is unripe. Amniotomy and intravenous oxytocin infusion proved unsatisfactory and although intravenous infusion of prostaglandin E_2 appeared capable of stimulating uterine action which was more efficient for cervical effacement and dilatation than that produced by intravenous oxytocin, its use was limited by maternal side effects.

The preceding few years had seen extensive investigation of the use of prostaglandins for therapeutic abortion, notably in the second trimester of pregnancy. While it had been shown that such pregnancies could be successfully terminated by intravenous infusion of PGE_2 (Karim and Filshie 1972) or $PGF_{2\alpha}$ (Karim 1971c) and even by intramuscular (Karim et al 1971) or oral (Karim 1971b) administration of these agents, the dose required by systemic routes was large, so that side effects were very commonly produced (Hendricks et al 1971; Hillier and Embrey 1972).

There are several reasons for this. It is now clear that in most of their physiological roles the primary prostaglandins are synthesised and released at or close to their site of action, and do not behave as circulating hormones (Embrey 1975). Furthermore they are rapidly metabolised in the circulation,

circulation,/

particularly during passage through the lungs (Karim and Rao 1975) so that very large doses are required by systemic routes to achieve effective levels at the target organ, in this case the uterus. This, together with the lack of specificity of these compounds, explains the high level of side effects. Both PGE_2 and $PGF_{2\alpha}$ are known to influence contractility of a wide variety of smooth muscle systems such as those in gut. (Bennett 1972), air passages. (Cuthbert 1973), and blood vessels (Makano 1973). They are also implicated in such processes as pain and inflammation (Vane 1973). It is hardly surprising then that systemic administration for therapeutic abortion resulted in such side effects as nausea, vomiting, diarrhoea, pain and erythema at the site of infusion, and pyrexia as well as occasional instances of headache, visual upsets and tachycardia. Although the dose required for induction of labour is generally much lower, this is less true if the cervix is unripe, hence the incidence of troublesome side effects encountered in the study described in the last chapter.

The logical solution to this problem was to deliver the prostaglandins closer to the site of action. Despite early optimistic reports (Karim and Sharma 1971c) vaginal pessaries proved disappointing for therapeutic abortion, the dose required suggesting that their mode of action involved absorption from the vagina into the systemic circulation (Caldwell et al 1972). Accordingly, side effects were not substantially reduced (Miller and Calder 1971, unpublished observations).

Attention then turned to intra-uterine administration and two techniques were developed namely intra-amniotic and extra-amniotic. Intra-amniotic therapy has proved to be effective for the induction of abortion (Brenner et al 1973), but this technique has obvious disadvantages for induction of labour in the mature pregnancy. The instillation of prostaglandins into the amniotic fluid in the required amounts could induce spasm of the umbilical vessels and impair placental blood flow (Hillier 1970). Furthermore, its use would require amniocentesis which carries the risk of direct damage to the placenta. For these reasons, intra-amniotic therapy has not been considered suitable for induction of labour, and will not be discussed further.

The extra-amniotic route had been used in the past to administer acridine dyes such as aminacrine in order to induce abortion (Nabriski et al 1971). Prostaglandins were first given by this route by Wiqvist and Bygdeman (1970) who were successful in terminating 11 of 12 first trimester pregnancies using repeated extra-amniotic doses of either $PGF_{2\alpha}$ or PGE_2. Independently, Embrey and Hillier (1971) applied a similar technique in second trimester pregnancies. They employed a Foley catheter introduced through the cervix and retained in place by distending the balloon (which lay just above the internal cervical os) with 20 - 40 ml water. Bolus doses of PGE_2 200 µg or $PGF_{2\alpha}$ 750 µg. were given every two hours via the catheter into the extra-amniotic space. Applying this technique to a large series (Embrey, Hillier and Mahendran

(Embrey, Hillier and Mahendran/ 1972) they reported successful abortion within 24 hours in 41 of 61 (67%) who received $PGF_{2\alpha}$ and in 27 of 33 (82%) who received PGE_2. The mean time taken to abortion was 22.4 hours for the series as a whole, but was shorter for PGE_2 (19.5 hours) than for $PGF_{2\alpha}$ (24.1 hours). The dose of prostaglandins necessary to induce abortion was lower than with systemic routes of administration, and side effects were notably reduced.

At Glasgow Royal Infirmary, Miller, Calder and Macnaughton (1972) employed a modification of Embrey's technique for 2nd trimester abortion. Instead of intermittent dosage, the prostaglandins were delivered by a mechanical pump as a continuous infusion. Abortion was successfully induced within 24 hours in 47 of 52 second trimester pregnancies (90%) who received PGE_2 at a rate of 1.5 - 4.5 μg per minute. The mean time to abortion was 15.8 hours and the incidence of side effects was very low. This method also simplified the nursing care of the patients and it remains the method of choice for termination of second trimester pregnancies in Glasgow Royal Infirmary and many other hospitals.

The advantages of the extra-amniotic route over systemic routes of prostaglandin therapy for termination of pregnancy were so obvious both in efficacy and in the absence of side effects that it seemed likely that the same might apply in more advanced pregnancies. It also seemed possible that the unripe cervix

cervix/
at term might have much in common with the cervix in the second trimester, both in its physical characteristics and in its poor response to oxytocin therapy.

Before applying this technique of extra-amniotic prostaglandin treatment to term pregnancies, however, it was first necessary to seek re-assurance about the safety of such an approach. There was no particular anxiety about the drug itself. Prostaglandins had been widely used for labour induction by systemic routes and appeared to be free of serious harmful effects. The uncertainty centred on how the term pregnant uterus would respond to direct application of prostaglandins.

In the first and second trimesters of pregnancy the uterus responds in one of two ways to extra-amniotic prostaglandins (Embrey and Hillier 1971; MacKenzie, Hillier and Embrey 1975). The usual response is a gradual increase in uterine tone and frequent low amplitute contractions which gradually increase (see Figure 6.1). In some cases, however, an immediate rise in uterine tone follows the injection, causing severe pain. This response is more commonly seen if bleeding accompanies insertion of the extra-amniotic catheter, and it has been attributed to rapid systemic absorption of the drug. Although the second pattern is the more extreme, both are associated with a rise in basal uterine tone which would be unacceptable in term labour because of the risk of placental compression and fetal hypoxia.

Whereas it was felt that the response of the uterus to prostaglandins was more likely to be a function of the gestational age than of the route of prostaglandin administration, it was felt essential that the safety of the extra-amniotic method was first demonstrated on advanced non-viable pregnancies. In this way, information would also be gained which would act as a guide to the optimum dosage regimes to be used in viable pregnancies.

Suitable cases for this study were provided by instances of fetal death in utero and anencephaly in late pregnancy. The fetal death cases also provided a useful model to allay another anxiety, namely intra-uterine infection. In the early days of extra-amniotic therapy for induction of abortion, the method was criticised because of the danger of introducing infection into the uterus (Roberts, Cassie and Turnbull 1971). Extensive experience subsequently with the method has not substantiated these fears (Embrey 1975) mainly because the induction - abortion interval is kept short. Nevertheless, the theoretical risk remained and it was felt that it would be re-assuring to show that this complication could be avoided in cases with a dead fetus, potentially those most likely to manifest any intra-uterine infection.

The technique of continuous extra-amniotic infusion of prostaglandins was applied then to cases of fetal death in utero and anencephaly and the early results were reported by Embrey, Calder and Hillier (1974). The method immediately proved highly effective and was subsequently applied in a large series of 72 cases of unsuccessful pregnancy, comprising 50 of fetal

fetal/

death in utero, 13 of anencephaly and 9 of hydatidiform mole.

This experience is described in the paper which follows.

This chapter has described the devlopment and validation of a new method of labour induction. The use of the extra-amniotic route of prostaglandin administration proved to have similar benefits for labour induction, as it had previously done for induction of abortion, notably in reduction of the dose required and accordingly of the side effects encountered. As a routine method of inducing labour at term in cases with a favourable cervix, it appeared to have no particular advantages over existing methods, and it was certainly more complex. On the other hand, it had been shown capable of inducing progressive labour while the fetal membranes were maintained intact and these early studies suggested that it might prove particularly valuable in the management of the unripe cervix. The application of the method in such circumstances is described in the chapter which follows.

C H A P T E R 7

MANAGEMENT OF THE UNRIPE CERVIX IN NULLIPARAE BY LOCAL ADMINISTRATION OF PROSTAGLANDIN E_2

MANAGEMENT OF THE UNRIPE CERVIX IN NULLIPARAE BY LOCAL ADMINISTRATION OF PROSTAGLANDIN E_2

This Chapter describes the results of the methods whose development was described in the previous Chapter when applied to a total of 216 nulliparous women in whom the cervix was very unripe. Two distinct approaches were applied, namely induction of labour by extra-amniotic PGE_2 infusion, and prostaglandin therapy in order to ripen the cervix prior to induction of labour.

INDUCTION OF LABOUR BY EXTRA-AMNIOTIC INFUSION OF PGE_2

Patients

Labour was induced by extra-amniotic infusion of PGE_2 in 95 patients with cervical scores 0 - 3. They are considered under four categories.

i) Sixty-two fullfilled the selection criteria applied in the prospective study of amniotomy and oxytocin infusion described in Chapter 4. They were primigravidae, five feet or more in height, at or beyond 38 weeks gestation with a single fetus presenting by the vertex, who had shown no prior evidence of spontaneous labour. This group were considered to constitute the purest experimental model. The mean cervical score was 2.0.

score was 2.0.

ii) Eleven patients fullfilled these criteria in all respects save the presentation of the fetus which was breech. The mean cervical score in this group was 2.2.

iii) Ten patients fullfilled the criteria of category i) except in respect of stature. They were less than five feet tall, and were to undergo a formal trial of labour. The mean cervical score was 2.1.

iv) Finally, twelve patients were in their second pregnancy, but were nulliparous in the real sense of never having undergone parturition. They had all been delivered by elective caesarean section in their only previous pregnancy. The mean cervical score was 2.2.

All the patients in the series were between 16 and 38 years of age, and had obstetric indications for induction of labour (see Table 7.1).

Method

The method of induction was that described in the paper included in the last Chapter (Calder, Embrey and Hillier 1974) with the following modifications:-

1) A Foley catheter (26 French gauge) was used, and the balloon distended with 20 ml sterile water to retain it in place. A plain Nelaton catheter had been employed in the previous study so that

so that/

the effect of prostaglandin infusion could be assessed independently of the known stimulatory effect (Embrey and Mollison 1967) of a cervical balloon. Having demonstrated the effectiveness of the method there was no need to adhere to this condition, and the added effect of the balloon of a Foley catheter could be usefully exploited. There were four further advantages of this: to introduce a plain Nelaton catheter successfully it was usually necessary for the cervix to admit the catheter plus the operator's finger; in contrast the Foley catheter could be introduced into a more tightly closed endocervical canal and if necessary could be drawn into position by gently beginning to distend the balloon while it was still in the canal. It could thus be used in much less favourable cases, and indeed in our experience it has never proved impossible to insert a Foley catheter. Secondly, the balloon retained the catheter in place - it had otherwise been necessary to tape the catheter to the patient's thigh near the vaginal introitus, and this was not always satisfactory. Thirdly, to ensure that the Nelaton catheter would remain in place, it had been necessary to introduce it for 10 to 12 cm. beyond the internal cervical os, which increased the risks of accidental membrane rupture, or placental separation (ten per cent of patients had to be excluded from the earlier study because of these complications). Fourthly, the Foley catheter was always extruded through the cervix when dilatation had reached a certain stage (around 3 cms.). This was recognised by cessation of the normal intrauterine pressure tracing pattern and when this happened a vaginal examination and amniotomy were usually performed.

2) The second modification concerned the infusion itself. A very cautious approach had been employed in the initial study, both in the concentration of the PGE_2

the PGE_2/

solution, and in its rate of increase. Because the solution was sodilute (1.5 µg PGE_2 per ml) it was necessary to deliver a fairly large volume to achieve the desired response. The average maximum dose required had been around 1.5 µg PGE_2 per minute or 60 ml fluid per hour. This inevitably led to some leak back of fluid and on occasion misled the attendants into supposing the fetal membranes had ruptured spontaneously.

It was decided to employ a solution containing 5 µg PGE_2 per ml. (Even this was cautious - Miller and Mack (1974) went as high as 100 µg/ml). To simplify matters this was infused at an initial rate of 1.0 µg per minute with a maximum permitted dose of 3 µg per minute. This meant a fluid volume of 12,24 or 36 ml per hour, and leakage became much less of a problem.

Using a Hewlett-Packard 8021 A cardiotocograph the same strict fetal monitoring precautions were employed as in the earlier study. Extrusion of the Foley catheter interrupted the recording of intra-uterine pressure and, to restore this, an intra-amniotic catheter was introduced at the time of amniotomy. A fetal scalp electrode was also attached at this time, and direct electronic fetal heart monitoring substituted for the trans-abdominal ultrasonic technique.

Continuous lumbar epidural block was employed when indicated for control of hypertension, or when requested for pain relief, and 69 of the mothers (73%) had this form of analgesia. The indications for induction of labour are shown in Table 7.1.

Results

Details of labour, delivery and morbidity (fetal and maternal) are set out in Table 7.2.

Uterine contractions commenced in all patients within a short time of the start of prostaglandin infusion. The Foley catheter was expelled within 9 hours in all cases (mean 4.1 hours) and amniotomy was performed shortly thereafter. If after a further 2 hours the uterine contractions appeared to have waned, an intravenous infusion of oxytocin was begun using the fully automatic Cardiff Infusion System; this was necessary in 31 of the 95 patients, the remaining 64 progressing to delivery without further stimulation.

All patients were delivered within 24 hours (range 5.5 - 22.7 hours) and the mean birth weight was 3,250 G (range 1,940 - 4,360 G). In only two patients was the lowest dose rate of PGE_2 (1 µg per minute) sufficient; the majority required either 2 µg per minute (37 patients) or the maximum rate of 3 µg per minute (56 patients). The mean total dose in the series was 605 µg (range 200 - 1,250 µg).

Mode of Delivery

A vaginal delivery was achieved in 80 of the 95 patients in the series. Of these, 59 were assisted vaginal deliveries, and 21 spontaneous. The high rate of operative vaginal deliveries (62% of the total) was accounted for by three factors: the inclusion of 9 breech deliveries, the preference for

for/

assisted delivery in cases of previous caesarean section, but mainly by the frequency with which epidural analgesia resulted in delay in the second stage of labour.

Caesarean Section

Caesarean section was performed in 15 cases (16%). The details of the indications for the operation in the different categories are shown in Table 7.3.

In category i) - three of the 62 patients required emergency caesarean section on account of fetal hypoxia, 5.5, 7.1 and 10.2 hours after induction, and at 4 cms., 5 cms. and 8 cms. cervical dilatation. The Apgar scores at one minute were 4, 8 and 4 respectively. Three further cases in this group required the operation because of cephalo-pelvic disproportion after 9.6, 11.5 and 20.2 hours. The cervix was 6 cms. dilated in one of these and fully dilated in the other two, and the Apgar scores after one minute were 5, 6 and 9. In no instance was the operation required for failure to progress in labour.

In category ii) - two of the eleven cases of breech presentation required caesarean delivery. In one, fetal bradycardia developed soon after amniotomy was performed and caesarean section produced a baby with an Apgar score of 4 at one minute. In the other, the cervix had dilated to 9 cm after 13.8 hours but the breech remained high and caesarean section was performed for feto-pelvic disproportion.

disproportion./

The one minute Apgar score was 7.

Three of the ten cases in category iii) (small stature) were delivered by caesarean section, one on account of fetal distress, and two because of disproportion. The fetal distress took the form of profound bradycardia at 5 cm dilatation; the baby had an Apgar score of 8 at one minute. The cases of disproportion were delivered after 11.1 and 14.0 hours at full dilatation and 8 cm respectively. Both babies were in good condition at birth.

In category iv) - four of the twelve patients who had a previous history of caesarean section required to have the operation repeated. In one patient, Type II fetal heart decelerations developed 14.5 hours after induction. On vaginal examination the cervix was found to be 6 cm dilated, and the umbilical cord could be felt beside the presenting part. A healthy infant, Apgar 8 at one minute, was delivered by immediate caesarean section. In a second case, the operation was carried out with the cervix 5 cm dilated after 13.5 hours, following two hours of persistent fetal and maternal tachycardia. The Apgar score of the baby was 9 at one minute, and although the indication for operation is given as fetal distress, an additional factor was undoubtedly anxiety over the possibility of dehiscence of the previous section scar. This was found to be intact. In the third case the cervix reached full dilatation after 15.0 hours, but the presenting part remained above the ischial spines and caesarean section was performed for

performed for/

disproportion. The Apgar score was 8 at one minute.

In the final case labour was induced at term because of static maternal weight, and clinical fetal growth retardation. The cervical score was 1. The Foley catheter was extruded after 7.7 hours and a total dose of 900 µg PGE_2. The cervix was 3 cm dilated and amniotomy released liquor that was slightly blood stained. After a further two hours the contractions were poor and intravenous oxytocin therapy was commenced. Over the next five hours there was little improvement in the contractions, and no progress in cervical dilatation. At the end of this time Type II fetal heart decelerations supervened and so caesarean section was performed. The previous scar in the lower uterine segment was found to have partially dehisced. A live infant weighing 2,680 G was delivered with a one minute Apgar score of 4 (9 at five minutes). The uterus was repaired and the total blood loss was 1,200 ml. Both mother and baby recovered satisfactorily.

Maternal Complications

Apart from the case of partial scar dehiscence just referred to there were no serious maternal complications. There was one case of retained placenta, and a blood loss greater than 500 ml was recorded at eleven deliveries, eight of which were caesarean sections.

A pyrexia greater than 38°C occurred in 12 mothers in the series (Table 7.2) but in most this appeared to be mainly the result of dehydration; in only two were antibiotics exhibited, one of whom had a proven urinary infection and the other was presumed to have intra-uterine infection, although this was never confirmed bacteriologically.

Fetal Complications

There was one perinatal death in the series. The baby, whose mother belonged to category iv) had multiple congenital abnormalities including a diaphragmatic hernia and partial bowel atresia. He died after surgery on the fourth day. None of the neonates showed evidence of infection acquired in utero.

Only four of the neonates (4%) were classified by virtue of an Apgar score below 5 as demonstrating birth asphyxia (Table 7.2). All were delivered by caesarean section and have already been described. All responded well to resuscitation. The mean one minute Apgar score for the series as a whole was 8.3.

No instance of uterine hyperstimulation occurred such as to trigger the hypertonus ("spasm") alarm on the Cardiff apparatus (i.e. an intra-uterine pressure greater than 30 mm Hg sustained for longer than two minutes) nor were there any lesser episodes associated with fetal heart rate changes.

Comment

The results achieved with this method in these cases with highly unripe cervices represented a considerable improvement on previous methods, particularly in respect of the reduced caesarean section rate and the lower incidence of birth asphyxia. The most notable finding was the disappearance (except in the instance of scar dehiscence) of failure to progress in labour as an indication for caesarean delivery

The results for patients in category i) will be fully discussed at the end of this chapter in relation to strictly comparable patients treated by other methods. Meanwhile, consideration will be given to the results in the other categories.

Firstly, breech presentation: it is often suggested that inco-ordinate labour is commoner in breech presentations, perhaps because of a less well-fitting presenting part. The results in the small series of cases presented here were satisfactory, and labour was not prolonged. Perhaps the virtue of intact fetal membranes in early labour has special advantages in breech presentations.

The cases of trial of labour also produced gratifying results. It would be quite wrong to suggest that an efficient method of labour induction could overcome other than the most minor degrees of disproportion, and no such claim is made here. What is suggested is that it allows conduct of a much more satisfactory trial of labour. In all seven cases in the whole

whole/

series who required caesarean section for feto-pelvic disproportion, the cervix was at least 6 cm dilated (in four cases fully dilated) before the diagnosis was established. This meant that the operation could be performed with a large degree of certainty as to that diagnosis.

The implications of this are considerable for the future obstetric management of these patients. When a trial of labour is commenced with an unripe cervix which fails to efface fully or dilate more than a few centimetres, the adequacy of the pelvis for vaginal delivery remains uncertain. This means that in future pregnancies the choice lies between elective caesarean section or a potentially hazardous repeat trial of labour in the presence of a caesarean section scar. It is clearly desirable that the adequacy of the pelvis should be determined during the initial trial of labour by ensuring adequate cervical dilatation. If the adequacy of the pelvis is in doubt and the cervix is unripe, the use of extra-amniotic PGE_2 greatly assists in the achievement of this objective.

PROSTAGLANDIN THERAPY TO RIPEN THE CERVIX BEFORE INDUCTION OF LABOUR

The second part of the Chapter examines the possibility of bringing about a ripe cervix before induction of labour and describes a method of doing so. The desire to make the cervix ripe before induction was not a new one, and other methods have been tried in the past with little success. Prolonged intravenous infusion of oxytocin before amniotomy has been widely employed, but it is tedious for both patient and attendants, and the results are disappointing (Lilienthal and Ward 1971). Oral prostaglandin therapy has also been tried but no clear benefit was demonstrated (Friedman and Sachtelben 1975; Weiss et al 1975).

We developed a different approach as a refinement of the technique described in the earlier part of this Chapter. It arose as the result of two different observations in the earlier experience with prostaglandins for induction of labour and abortion. The first was the observation that when extra-amniotic prostaglandins were used to induce labour, the procedure fell quite distinctly into two parts with amniotomy as the watershed; if after expulsion of the Foley catheter amniotomy was not performed within an hour or two, then the uterine contractions usually waned and clinical labour stopped, but in the meantime an unripe cervix had been converted to a riper one. It was also notable that, although the degree of dilatation at the time of catheter expulsion was fairly constant at around 3 cm, the

the/

interval from amniotomy to delivery varied very widely (3.7 - 18.1 hours), and the factor which seemed to govern this most was the degree of cervical effacement. In other words although the cervix was invariably around 3 cm dilated it was not invariably ripe in a real sense, in particular often remaining thick and uneffaced (Figure 7.1).

The other experience that was utilised was the use of the highly viscous gel methyl hydroxyethyl cellulose ("Tylose") as a vehicle in which to suspend prostaglandins for a sustained release effect. This had already been used by the group with good effect as a single shot method of extra-amniotic prostaglandin therapy for termination of pregnancy(MacKenzie, Hillier and Embrey 1975) and management of fetal death in utero (Calder, MacKenzie and Embrey 1976). Laboratory studies by Dr. Hillier had shown that prostaglandins continued to be released from this gel for up to six hours.

These two considerations encouraged the belief that a prostaglandin containing gel might be employed as a single shot to effect cervical ripening prior to induction of labour. This project was begun in late 1974 and preliminary results were reported at the Third International Congress on Prostaglandins in Florence in May 1975 (Calder, Hillier and Embrey 1975). Subsequently this experience was extended to a series of 121 primiparae with cervical scores 0 - 3 and this is described in the paper which follows.

The indications for induction of labour are not given in the paper but will be found in Table 7.4. One hundred and six of the patients correspond in their selection criteria with category i) in the earlier part of this Chapter, and the remaining 15 comprise 6 in category ii) (breech presentation) and 9 in category iii) (trial of labour on account of small stature). In addition the method was applied in six cases corresponding to category iv) (previous caesarean section) and the data for the different categories is presented separately in Table 7.5. The information from Table III in the paper is illustrated graphically in Figure 7.2. The control group described in the paper are those patients with cervical scores 0 - 3 from the prospective study of amniotomy and oxytocin infusion described in Chapter 4 (page 96). The details of cases delivered by caesarean section are shown in Table 7.6.

Other Studies

The literature now contains nine other reports describing the use of local prostaglandin therapy for induction of labour or cervical ripening. The data from these papers are summarised in Table 7.7. In the first six studies listed the emphasis is, at least in part, on the unripe cervix (three relate to induction of labour and three to pre-induction cervical ripening). In the other two studies the aim is a simplified method of labour induction where the cervix is already ripe. Although all report a fundamentally similar approach there were a number of methodological differences in the treatment routes and regimes, as shown in the Table.

Unripe Cervix - Induction of Labour

Calder and Embrey (1973) reported a small series of seven primigravidae with the most highly unripe cervices (cervical scores 0 or 1) whose labours were induced with extra-amniotic PGE_2 infusion. The gestational age range was 28 weeks to term and all had clamant indications for delivery (severe pre-eclampsia (2), diabetes (2), chronic renal disease, rhesus iso-immunization and fetal growth retardation). There was one perinatal loss : a baby of only 720 G died at 28 weeks gestation a few hours after a delivery which had been necessitated by fulminating pre-eclampsia. The other six babies were all born in good condition with one minute Apgar scores of 8 or better. No evidence of uterine hyperstimulation was seen and this small series is presented here to illustrate the value of the technique in pre-term inductions with the most unpromising features.

Miller and Mack (1974) reported on the use of the technique in 69 patients with a wide spectrum of parity and cervical ripeness. Forty-eight were considered unfavourable (score 0 - 5) and 21 favourable (score 6 - 9). The series included four cases of anencephaly.

The pattern of labour and delivery was similar to other studies (see Table 7.7). The rather high caesarean section rate of 17.4 per cent was mainly due to a high incidence of the operation on account of mechanical problems (11.6%). There were three perinatal deaths in this series but in none could the cause be attributed to the method of labour induction. One

One/

instance of uterine hyperstimulation was recorded resulting from an accidental bolus overdose of PG solution when the catheter was being connected to the infusion pump.

Neuberg (1975) reported his experience using a simplified technique in 37 patients with what he called "uninducible" cervices (scores 0 - 3). He gave bolus doses of PGE_2 in saline extra-amniotically via a Foley catheter. A test dose of 50 µg was followed after 30 minutes by 100 µg and this dose was repeated two hours and again four hours later. Intravenous oxytocin infusion was commenced after a further interval of one hour. The method proved very successful and rather surprisingly no uterine hyperstimulation was reported with PGE_2 therapy alone, although two instances occurred after oxytocin was commenced. The caesarean section rate was 13.5 per cent. The birth asphyxia rate is not recorded but the mean one minute Apgar score was 7.7.

Unripe Cervix - Pre-induction Cervical Ripening

Our reports of the cervical ripening technique using PGE_2 in tylose (Calder, Hillier and Embrey 1975) were followed by reports of other workers' experience with the technique (Shepherd, Sims and Craft 1976; Thiery et al 1977, 1978). Shepherd, Sims and Craft treated 15 patients with cervical scores 0 - 4 (mean 2.1). They also studied a control group who received the gel alone and in neither group was a Foley catheter used. The mean improvement in cervical score in the treatment

treatment/

group was 4.9 against 0.8 for the control group. One patient in each group required caesarean section, and the mean length of induced labour was shorter in the treated patients than in the controls. The number of patients was small, and parous women were included, but this study clearly demonstrated that the value of the technique was mainly due to the action of PGE_2 rather than to any local effect of the tylose gel or a Foley catheter.

Thiery et al have described their experience with the technique in Belgium in two reports (1977, 1978). They have studied a total of 196 normal women at term (cervical score 0 - 4) who were undergoing "elective" induction of labour. This is taken to mean without obstetric inductions, i.e., a very low risk group. They followed the method of Calder, Hillier and Embrey (1975) except in the timing of amniotomy. PGE_2 therapy was given at midnight and, assuming ripening had occurred, amniotomy was performed 7 to 8 hours later in contrast with the 18 hour interval we allowed. In five subjects they felt that cervical ripening had been insufficient to permit amniotomy, and this was deferred while a second dose of PGE_2 gel was given. The mean improvement in cervical score before amniotomy for the whole group was 3.7 for nulliparae and 4.1 for parous women. The mean time from treatment to delivery was 13.9 hours and only nine patients (5%) required caesarean section, all on account of cephalo-pelvic disproportion. These workers did not record the incidence of birth asphyxia as indicated by

indicated by/

a low Apgar score but they reported that there were no untoward perinatal or maternal effects and indeed the purpose of the second study (Thiery et al 1978) was to look specifically for fetal complications.

Very recently MacKenzie and Embrey (1977) have reported a simplified technique of cervical ripening by intra-vaginal PGE_2 in gel. They have employed a very much larger dose of PGE_2 (2.0 or 5.0 mg) in a different gel (2 or 4% sodium carboxymethyl cellulose) given high into the vagina 16 - 18 hours before induction of labour. In a series of 168 primigravidae (cervical scores 0 - 3) they reported results very similar to those obtained using the extra-amniotic route. The mean length of induced labour was 10.5 hours and the rates of caesarean section and birth asphyxia were 12.4 per cent and 8.9 per cent respectively. They reported no maternal or fetal side effects or complications, but since publication of the report they have encountered some instances of uterine hyper-stimulation with the larger dose necessitating emergency caesarean section on at least one occasion (MacKenzie, personal communication).

Ripe Cervix - Induction of Labour

A peripheral development from experience with prostaglandin gels for cervical ripening is also worthy of mention. Because a number of patients were found to have become established in

established in/

labour following therapy and the nature of the resulting labour proved so satisfactory, the technique has been applied as a method of labour induction when the cervix is ripe. Mellows, Sims and Craft (1977) gave 300 µg PGE_2 in tylose extra-amnidtically to 120 patients with cervical scores of 6 or greater. Delivery was accomplished in 75 per cent of cases without further stimulation, and in the remainder after amniotomy and oxytocin therapy. These authors report that following this experience the method has become the routine for labour induction in Queen Charlotte's Maternity Hospital.

In our own department, Kennedy et al (1978) have given 400 µg PGE_2 in tylose endocervically (i.e. between high vaginally and extra-amniotically) to induce labour in 30 women with cervical scores of 6 or greater. They compared these with two other matched groups both treated by amniotomy and followed either by oral PGE_2 or intravenous oxytocin. The method was much superior to amniotomy with oral PGE_2 and compared favourably for efficiency with amniotomy plus intravenous oxytocin. The patients' reactions to the methods of induction were assessed, and the PGE_2 gel technique emerged as the most widely acceptable, perhaps because the resulting labour so closely resembled spontaneous labour.

General Observations from the Experience of the Author and Others on the Efficacy and Safety of Local Prostaglandin Therapy in Term Pregnancies.

All forms of obstetric interference carry some risk and when new techniques are introduced which appear to be very effective,

effective,/
it is vital that their potential risks should be identified and minimised. The primary prostaglandins are uterine stimulants of the most potent kind, and in addition exhibit a multitude of widely differing biological properties. The concluding part of this Chapter is devoted to examining the experience with locally administered prostaglandins in an effort to define how these techniques may be employed with the maximum degree of efficacy and safety.

Over the years obstetric practice has clearly identified the main maternal hazards of labour and induction of labour as intra-partum and post-partum haemorrhage, and the need to resort to caesarean section. All these complications are easily recognised and measurable, and there is no evidence to suggest that, properly used, the methods of local prostaglandin therapy described have increased the risks. Indeed it may be claimed with some justification that they have done the opposite.

The possible risks to the fetus are more imponderable, but before discussing these in detail it may be worth considering in greater depth the importance of the minor methodological variations employed by different authors.

1. Catheter

The value of the additional influence of the balloon of a Foley catheter on the unripe cervix (Embrey and Mollison 1967) has already been referred to. Most authors have employed a

employed a/

Foley catheter if the cervix is unripe and the other advantages of this were discussed on page 132. The balloon size was varied between 20 and 50 ml, however, and although the larger size may allow therapy to be continued until more cervical dilatation is achieved, against this must be set the danger of causing an unstable lie in a fetus with an already high presenting part. A balloon size of 20 ml is probably large enough for most cases. Regardless of the type of catheter used, it is considered important to insert the catheter with the lumen open so that any bleeding provoked within the uterus immediately becomes apparant.

2. Prostaglandin Therapy

The features which have varied most between different studies have been the dose, volume and concentration of prostaglandin therapy. Where a solution has been given extra-amniotically the dose rate has varied between 0.3 and 3.0 µg per minute, the volume of vehicle between 1.8 and 100 ml per hour and the concentration of the solution between 1.5 and 100 µg per ml. Among those using gel therapy the bolus dose has varied between 250 µg and 5.0 mg, the volume between 3 and 12 ml and the concentration between 25 and 500 µg per ml although it should be emphasized that these highest doses and concentrations were given vaginally by MacKenzie and Embrey (1977) and not into the uterus.

Most authors appear to agree on the safe and effective extra-amniotic dose both for induction of labour (about 1 - 3 µg/min) and for cervical ripening (between 250 and 500 µg in gel). When solution is used the concentration is of some

of some/

importance. Reference has already been made (page 133) to the problem of leakage of solution from the system if it is too dilute. On the other hand too concentrated a solution brings the danger of accidental hyperstimulation such as that described by Miller and Mack (1974) which followed an accidental bolus dose while the catheter was being connected to the pump. There would seem no benefit from using so concentrated a solution as the 100 µg/ml they employed. A balance must be struck but a solution of 5 - 10 µg/ml would seem to allow a large enough margin of safety while eliminating leakage problems. (The volume of infusion required with a solution of 10 µg at the maximum dose of 3 µg/min is less than 20 ml per hour).

Neuberg (1975) gave repeated bolus doses of 100 µg PGE_2 in 4 ml solution into the extra-amniotic space and suggested that this was a safe and effective method which avoided the need for complex equipment. There must hardly be a hospital in the land that does not now possess some form of infusion pump and the risk of hyperstimulation with Neuberg's technique would seem to subordinate safety to simplicity and convenience. These risks have recently been stressed by Thiery and Amy (1977) who have condemned the practice of giving bolus doses of prostaglandins in solution to term pregnancies as being frankly dangerous. In the same way, while the vaginal gel technique of MacKenzie and Embrey (1977) has obvious and powerful attractions the problems of hyperstimulation they have recently encountered with the 5 mg dose (page 148) emphasise the need to continue investigations to find the most effective method and dosage with the widest possible safety margins.

Direct Effects on the Fetus

The methods at our disposal are barely adequate to assess harmful influences to the fetus of obstetric procedures. The limitations of the Apgar score and of methods of neurological assessment of the neonate are well recognised and the longer the interval from birth the more difficult does it become to make meaningful developmental assessments because of the multitude of environmental influences.

Nevertheless, the short and long term hazards to the offspring from drugs used to induce labour must continue to be a vitally important area of study. This is particularly so where prostaglandins are concerned because of their diversity of effects on body functions. The data presented in this Chapter and the studies of other authors already reviewed are reassuring in their failure to demonstrate any direct ill-effect of local prostaglandins on the fetus or neonate, asphyxial or otherwise. Thiery et al (1978) made a study of patient's receiving PGE_2 gel for cervical ripening with the express purpose of detecting deleterious effects on the fetus. They carried out routine fetal scalp blood sampling at the time of amniotomy, and again during the second stage of labour to assess the acid-base and lactate-pyrurate status on these samples, and also on samples obtained at the time of delivery from the umbilical artery and vein, and the maternal femoral artery. They also carried out continuous fetal heart recording throughout and Apgar score assessment at birth. They were unable to detect any deleterious effects on the fetus as a result of the use of PGE_2 gel.

It appears that, so long as care is taken to prevent uterine hyperstimulation, the healthy fetus is unlikely to suffer ill-effects from the use of prostaglandins to induce labour. Closer consideration must, however, be given to highly complicated pregnancies in which placental function may be seriously impaired. This is especially so in view of the warning by Brosens, Dixon and Robertson (1974 a, b) that prostaglandins should not be used in cases of pre-eclampsia and essential hypertension. They suggest that the normal vaso-constrictive effect of prostaglandins on the uteroplacental (spiral) arteries (Moghissi and Murray 1970) might be exaggerated in these clinical conditions, increasing the risk of fetal hypoxia. This contention was based on structural changes they had described in the spiral arteries of patients with these hypertensive states (Brosens, Robertson and Dixon 1972). Calder et al (1974) disputed this theory citing electron microscopic evidence on the ultra-structure of the spiral arteries (Sheppard and Bonnar 1974) which suggested that these vessels might become unresponsive to vasoactive agents and was at odds with the findings of Brosens et al 1972. They also reported experience in a series of 23 patients with moderate or severe pre-eclampsia whose labours were induced between 36 and 38 weeks gestation by amniotomy and intravenous PGE_2 or oxytocin given in a double blind fashion, and a further 18 primiparae with unripe cervices also between 36 and 38 weeks gestation induced by continuous extra-amniotic PGE_2. In the first study the only patient who required caesarean section for fetal distress belonged to the oxytocin group. The mean Apgar score at one minute was 7.0

was 7.0/

with oxytocin and 8.1 with PGE_2. In the second study two patients had caesarean sections for fetal distress and the mean Apgar score for the group as a whole was 8.0.

The conclusion was that there was no evidence of any harmful effect of PGE_2 in such pregnancies and this was supported by Jacomb and Hinchley (1974) who reviewed 283 cases of essential hypertension or pre-eclampsia who had received $PGF_{2\alpha}$ or PGE_2 intravenously. The mean Apgar score at one minute was 8.2 and at five minutes 9.4 and only four infants (1.4%) had Apgar scores below 5 at five minutes. Lauerson and Wilson (1975) reported similar findings in cases of pre-eclampsia and hypertension, and also in five cases of maternal diabetes.

Clark, Ryan and Brody (1973) infused $PGF_{2\alpha}$ intra-arterially in pregnant bitches and even with dose rates as high as 100 per minute were unable to demonstrate any increase in the utero-placental vascular tone, and while allowance must be made for species differences, this adds further reassurance as to the safety of the prostaglandins in pregnancy.

Induction of labour has also been implicated as a causative factor in neonatal jaundice, with oxytocin in particular the object of suspicion (Ghosh and Hudson 1972; Davies et al 1973). In order to investigate the possible effect of prostaglandins in this area Calder et al (1974) measured the neonatal bilirubin level on day five in four groups of 30 primigravidae. In the

In the/

first two groups labour was induced by amniotomy and intravenous oxytocin or PGE_2. The third group had extra-amniotic PGE_2 infusion and the fourth laboured spontaneously throughout. The results are shown in Figure 7.3. There was no significant difference between the first two groups but both showed significantly higher levels of bilirubin than the spontaneous group. The results in the group receiving extra-amniotic PGE_2 fell between the spontaneous group and the two amniotomy groups and did not differ significantly from any other group. The results suggested that the cause of neonatal jaundice after induced labour perhaps lies more in the fact of the interruption of pregnancy (causing marginal immaturity) or in early amniotomy than in a direct drug effect. There was certainly no evidence that PGE_2 carried a greater risk of causing neonatal jaundice than existing methods of labour induction.

Finally, Ounsted, Hendrick and Calder (1978) carried out a follow-up study of 235 babies born to primigravid mothers between July 1973 and October 1974 who fell into the same four groups as described in the last paragraph. The babies were examined and the mothers interviewed on the first and fourth days after delivery and again after two months. The observers were not aware of the group to which each mother belonged. The groups cannot be regarded as strictly comparable because of differences in the antecedent obstetric complications but it was re-assuring that no major differences emerged. In particular there were no sequelae attributable to prostaglandin therapy. The incidence

incidence/
of respiratory, cerebral, infective or thermoregulatory problems was evenly distributed among the three induction groups. One hundred and fifty mothers stated a wish to breast feed their babies, and their success in establishing lactation was broadly similar in the four groups.

At the two month examination the average daily weight gain of the babies was the same in all groups. The incidence of feeding problems (usually colic or "wind") was lowest in the intravenous prostaglandin group. Medical problems had been evenly distributed among the four groups.

Using a standard questionnaire the mothers were asked about their babies' responses to their attentions and the interaction between mother and child was observed during the interview. The value of such assessments is uncertain but no differences were found between groups for this factor or for establishment of feeding and sleeping routines. These data do not suggest that the use of prostaglandins had any effect on the subsequent mother-child relationship.

Choice of Technique

The results presented in this chapter confirm the value of the extra-amniotic route of prostaglandin administration in the management of the primipara with an unripe cervix. In

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Table 7.8 these results are presented alongside those obtained using amniotomy and intravenous oxytocin infusion (Chapter 4) and amniotomy and intravenous PGE_2 infusion (Chapter 5) for those patients who fulfil the strict criteria applied to select category (1) patients (see page 130). This excludes patients with obvious sources of intrapartum complications such as those with breech presentations and those of small stature.

It is clear that the use of prostaglandins achieved much superior results than the use of oxytocin. As has been seen in Chapter 5, intravenous PGE_2, while more effective than intravenous oxytocin, was associated with an unacceptable level of maternal side effects in these difficult inductions. No such side effects were encountered when extra-amniotic prostaglandins were used and this would seem to represent the best approach to the problem of the unripe cervix.

The question remains however: which technique is to be preferred, infusion of PGE_2 solution to induce labour, or PGE_2 gel therapy to ripen the cervix beforehand? There is little to choose between the results achieved either in efficacy or safety and the answer would appear to lie in the question of acceptability, both to patients and staff.

The patients appeared generally to prefer the gel ripening technique. They accepted the need for treatment aimed at preparing them for labour and those who went into labour as a

labour as a/

result of the treatment considered this a bonus. Those who did not came fresh to induction the following morning after a night's rest. In contrast, those who had labour induced with PGE_2 infusion from the starting point of an unripe cervix often found the technique disagreeable and the total length of labour was often disappointingly long. This latter problem was overcome with the gel technique by dividing the process into two distinct parts. During the first part the patient did not expect to be making progress in labour and was therefore less likely to become disheartened.

The attendants also preferred the PGE_2 gel technique, mainly because of its simplicity. The need for complex infusion equipment and adjustment of dose is avoided. An indication of this is the wide extent to which the technique has been adopted in other centres. In addition to those studies already referred to (Table 7.7) the technique has been applied to good effect in many hospitals and this inspite of the trouble involved in getting the gel prepared; the pharmaceutical industry have so far been reluctant to produce ready-packed gel containing prostaglandins.

Conclusions

This chapter draws together all the original clinical data presented in the thesis; the next describes the laboratory

laboratory/
studies performed to examine the physiological role of prostaglandins in cervical ripening and parturition.

The overriding conclusion of the clinical studies is that to date insufficient attention has been paid to the state of the cervix in relation to induction of labour, perhaps because of a lack of effective methods of dealing with it. Local prostaglandin therapy provides at least a partial answer to the problem and it is likely that new or improved techniques will be developed in due course. A uniform method of induction of labour has many attractions, but until the normal physiology of cervical ripening and parturition is fully understood and can be accurately reproduced it will remain necessary to apply methods which meet the particular requirements of the individual patient.

CHAPTER 8

LABORATORY STUDIES TO DETERMINE THE PHYSIOLOGICAL ROLE OF THE PRIMARY PROSTAGLANDINS IN CERVICAL RIPENING

LABORATORY STUDIES TO DETERMINE THE PHYSIOLOGICAL ROLE OF THE PRIMARY PROSTAGLANDINS IN CERVICAL RIPENING

This Chapter describes laboratory investigations of the levels of the primary prostaglandins and certain steroid hormones in amniotic fluid and peripheral venous plasma during pregnancy, and labour. The purpose of these studies was to assess the physiological role of the prostaglandins in the processes of cervical ripening and parturition.

The methodology used for the collection and assay of samples is set out in Appendix B.

THE ROLE OF PROSTAGLANDINS IN LABOUR

The first study conducted investigated the levels of F prostaglandins (the assay for E prostaglandins was not then developed in our laboratory) in samples of amniotic fluid and maternal peripheral plasma obtained serially during spontaneous and induced labour. This study is described in the paper which follows.

FURTHER DISCUSSION OF
THE ROLE OF PROSTAGLANDINS IN LABOUR

Studies of Maternal Peripheral Blood

There are major difficulties in obtaining and interpreting data from maternal circulating prostaglandins for the following reasons:-

1) The primary prostaglandins do not behave like conventional hormones and achieve their target via the general circulation. They are released close to their site of action, so that levels detected in the circulation may be a poor reflection of their physiological importance (see page 116).

2) The rate of metabolism of these compounds is very rapid (Embrey 1975) with as much as 90% inactivated by a single passage through the lungs, so that it may be impossible to detect subtle changes in the rate of PG synthesis in the uterus by examining the peripheral blood.

3) Different assay methods (bioassay, gas/liquid chromatography and mass spectrophotometry, and radio-immunoassay) have yielded widely different results in similar situations and the multitude of influences which have a bearing on the different methods make validation of results most difficult.

4) Even accepting the limitations of peripheral levels as a reflection of physiological behaviour, the difficulties are legion in ensuring that the levels in the sample being assayed are the same as those in the maternal circulation when it was collected. Firstly, synthesis and metabolism can be significantly effected by trauma during venepuncture both from the needle and the use of a tourniquet (leading article, Prostaglandins 1972) and this may continue after withdrawal of the blood mainly

mainly/

due to the action of enzymes contained in platelets (Smith et al 1973). These problems may be minimised by collecting the blood into cooled syringes containing PG synthetase inhibitors but E prostaglandins may continue to be generated during storage (Jubiz and Frailey 1974) and the influence of the temperature of the sample at the time of extraction must also be considered (Karim and Hillier 1975).

For these reasons many of the early reports of circulating levels of primary prostaglandins (including those reported and cited in the foregoing paper) are now regarded as being invalid because the levels are erroneously high (Embrey and Hillier 1977). Measurement of the main plasma metabolite may be more valuable and this has been the subject of a study by Green et al (1974). They suggest that plasma levels of 15-keto-13, 14-dihydro $PGF_{2\alpha}$ may be more meaningful than those of the parent prostaglandin because it is not formed during plasma collection and is less rapidly degraded by the lungs. These authors also showed a slight rise in the levels of this metabolite in late pregnancy, and then a much greater increase (10 to 30 fold) during active labour (see Figure 8.2). Hamberg (1974) showed a gradual increase during pregnancy of the major urinary metabolite of $PGF_{2\alpha}$ suggesting a steady rise in prostaglandin production.

Studies of Amniotic Fluid

Amniotic fluid does not suffer from the same limitations

limitations/

as maternal plasma as an area of investigation of prostaglandin activity in pregnancy and labour. The following advantages make it a much more valuable subject of study:

1) It is readily accessible yet it is very close to the centre of activity in the uterus.

2) It may be collected in large amounts or in serial smaller amounts without difficulty.

3) It does not metabolise or synthesise prostaglandins (Keirse, Williamson and Turnbull 1975) so that its prostaglandin content may be a quantitative reflection of the prostaglandin synthesis of tissues in the uterine millieu.

Despite these advantages, an important reservation must be the doubt surrounding the significance of amniotic fluid prostaglandins. Are they there in a passive capacity having spilled into the amniotic fluid during activity elsewhere, or in an active capacity in which the amniotic fluid acts as a reservoir? Whatever the answer to this question and whatever their source, the dynamic fluctuations in prostaglandin levels that occur during labour must reflect changes in the rates of synthesis or metabolism or both, and the higher levels we detected in early spontaneous labour compared with established induced labour, represented one of the first concrete pointers to an active role of prostaglandins in the initiation of labour. The subsequent steep rise in levels of F prostaglandins during the acceleratory phase of labour has been confirmed by Salmon and Amy (1973) and by Keirse, Flint and

Keirse, Flint and/
Turnbull (1974) and shown also to apply to E prostaglandins (Keirse and Turnbull 1973) although these studies relied on single samples of liquor all obtained at the time of amniotomy in large numbers of patients at varying stages of labour (Figure 8.3).

Gestational Changes in Amniotic Fluid Prostaglandins

Salmon and Amy (1973), Hibbard et al (1974), and Hillier, Calder and MacKenzie (1974) showed a rise in F prostaglandins in amniotic fluid in late pregnancy, but before the onset of labour. Our own data for both E and F prostaglandins in 10 patients between 14 and 22 weeks gestation and 42 patients between 38 and 42 weeks gestation are shown in Table 8.1 and in Figure 8.1. In the Figure, the scale of gestation is discontinuous between 22 and 38 weeks, and this, together with the continuing rise between 38 weeks and 42 weeks shown in the figure suggests that, rather than being linear, the rise is slow at first becoming more rapid in the latter weeks of pregnancy. It seems a reasonable hypothesis that this trend might follow the evolutionary trend of uterine contractility during pre-labour (Caldeyro-Barcia 1958).

We were unable to obtain samples for analysis during the time between 22 and 38 weeks gestation in normal pregnancies because during this time amniocentesis is rarely performed except in pathological circumstances, but Dray and Frydman (1975) studied the period between 30 and 39 weeks gestation in 18 subjects.

subjects./

The indication for the amniocenteses was not recorded. Their findings are shown in Figure 8.4 which shows the steepest rise in PGE_2 occurring between 35 and 37 weeks gestation and a doubling in the level of PGE_2 between 35 and 39 weeks. These workers could detect no prostaglandins E_2 or $F_{2\alpha}$ in the early second trimester and they found the rise in $PGF_{2\alpha}$ occurred later and was less marked, in contrast with the almost parallel rise in E and F prostaglandins (allowing for a 5-fold difference in absolute levels) observed in our study (Figure 8.1). Dray and Frydman also suggested that the ratio of PGE_2 to $PGF_{2\alpha}$ became reversed during labour, with $PGF_{2\alpha}$ predominating after 3-4 cm cervical dilatation. This raises the possibility that the more important role of PGE_2 might be to modify the condition of the cervix in late pregnancy while $PGF_{2\alpha}$ is more important as a myometrial stimulant once labour is established.

Tamby Raja et al (1977) have measured E and F prostaglandin levels in amniocentesis samples between 36 weeks and term and have shown a massive and steady rise in both over that time. The mean value for PGF rose from 58 pg/ml at 36 weeks to 4276 pg/ml at term with a corresponding rise in PGE over the same interval from 0.46 ng/ml to 4.26 ng/ml. These authors also found that the levels of PGF obtained at amniotomy in patients induced after term for post-maturity were significantly lower than the levels in amniocentesis samples from patients who laboured at or around term, and in the post-mature patients the levels correlated with the degree of cervical ripeness.

ripeness./

These findings lend further support to the hypothesis that the pregnancy which continues beyond term with an unripe cervix may be endocrinologically abnormal.

The Source of Amniotic Fluid Prostaglandins in Late Pregnancy and Labour

Since prostaglandins were first identified in the amniotic fluid by Karim (1966) much interest has centred on their site of origin. A number of possible sources have been suggested including the decidua, the placenta, the fetal membranes and the fetus itself.

Decidua has long been known to be a rich source of prostaglandins (Karim and Devlin 1967) and Gustavii (Gustavii 1972; Gustavii and Green 1972) has suggested that labour results from release of these when decidual cells are stressed by stimuli such as hypoxia or ischaemia. Disruption of the decidual cells was also shown to be an important process in the mechanism of hypertonic saline induced abortion. The ability of prostaglandins to cross the fetal membranes into the amniotic fluid has been demonstrated by Hillier, Calder and MacKenzie (1974).

The fetal membranes also appear to be a possible source of prostaglandins with the demonstration by Keirse and Turnbull (1976) that the chorion can metabolise and almost certainly synthesise them. This offers an explanation for the important role of amniotomy in induction of labour as well as the

as the/

fluctuations in amniotic fluid levels seen around the time of amniotomy in spontaneous labour in our own studies (Hillier, Calder and Embrey 1974). It may also explain at least in part, the changes seen as a result of local interference in the form of vaginal examination, membrane sweep and catheter insertion (Embrey and Mollison 1967). Mitchell et al (1977) have recently shown that such procedures are quickly reflected by a rise in the circulating levels of 15-keto-13,14-dihydro prostaglandin F (Figure 8.5).

The importance of local stimulation of the lower genital tract in the generation of prostaglandins has already been discussed in Chapter 3 (page 87). One further observation is worth recording here. The use of a cervical vibrator is a popular method accelerating desultory labour in Japan and elsewhere. This often results in rapid dilatation of the cervix while the instrument is applied. During the use of such an instrument we took the opportunity (Calder 1975a) of collecting serial samples of amniotic fluid. The levels of E and F prostaglandins measured before, during and after application of the instrument are shown in Figure 8.6. The fetal membranes had already been ruptured so the source of the increased production of both prostaglandins is uncertain, although the decidua remain the likeliest source.

The role of the fetus in the initiation of parturition is currently the centre of intense investigation, and not surprisingly

surprisingly/
a fetal production of prostaglandins has also been postulated to explain their presence in the amniotic fluid. Challis et al (1974) measured plasma PGF levels in the maternal and fetal circulations at vaginal delivery and elective caesarean section. Although the levels were consistently higher in the fetus than in the mother, this could be explained simply on the basis that the fetal pulmonary circulation, the main site of PG degradation is largely by-passed in utero. The fetal levels were also higher if the mother had laboured and delivered than if she had undergone elective caesarean section but there was no consistent difference in levels between the umbilical artery and vein. A fetal source could therefore not be confirmed and the authors could claim to have shown no more than an increasing level of PGF within the fetal compartment during active labour. The possibility of a fetal contribution has not been ruled out, but by studies on cases of intra-uterine fetal death we have shown (Hillier, Calder and MacKenzie 1974) that such a source was not obligatory for the normal pattern of appearance of amniotic fluid prostaglandins in labour (Figure 8.7). A steady rise in the liquor PGF levels was noted before amniotomy in samples obtained via a trans-abdominal catheter inserted at amniocentesis. The familiar fluctuating pattern was seen following amniotomy followed by a very much greater rise preceding delivery.

Also of interest were our studies on cases of anencephaly. This model is important in the study of fetal endocrinology because of the absence of the fetal pituitary, but although the levels remained lower prior to rupture of the membranes, a sharp

sharp/

rise was again seen thereafter (Figure 8.8).

This rather different pattern is probably more the result of the different physical make-up of the anencephalic fetus (poor presenting part) and the associated hydramnios than of any differences in fetal endocrinology. One could postulate the the rate of PG production in this case may have been very similar to that in previous examples: the slower rise in liquor concentration may be due to a greater dilution effect with hydramnios and the steep rise after amniotomy may be due to the sudden reduction in the liquor volume producing the opposite effect. In addition a sudden change in uterine wall tension may increase the rate of PG synthesis.

AMNIOTIC FLUID PROSTAGLANDINS AND STEROIDS IN RELATION TO CERVICAL RIPENESS AND THE RESPONSE TO LABOUR INDUCTION

A number of observations have been made in this thesis concerning the factors which may control the process of cervical ripening. Some of these appear to be interrelated and the following are highlighted:-

1) Cervical ripening appears to be an integral part of the transition from pregnancy through "pre-labour" to "clinical labour" (Chapter 3).

2) Failure of the primiparous cervix to ripen is associated with a poor clinical response to induction of labour by amniotomy and intravenous oxytocin infusion (Chapter 4).

(Chapter 4).

3) Better results can be obtained in such cases if prostaglandins are used especially by the extra-amniotic route (Chapters 5-7).

4) The primary prostaglandin levels in amniotic fluid rise in late pregnancy perhaps in association with "pre-labour" and cervical ripening (present Chapter).

To further pursue the possible association between these factors, we carried out biochemical studies on a proportion of the patients described in the prospective study reported in Chapter 4. In that study, 125 primiparous women covering the spectrum of cervical ripeness had labour induced between 38 and 42 weeks gestation by amniotomy and intravenous oxytocin infusion, and the clinical outcome was found to be closely related to the degree of cervical ripeness.

In 42 of these 125 primiparas, a sample of maternal venous blood was withdrawn before induction, and when the intra-amniotic catheter was inserted immediately after amniotomy a 10 ml sample of amniotic fluid was collected. This was immediately stored at $-20^{o}C$ together with the plasma from the venous blood sample. Two of the blood samples clotted and were thus unsuitable so that the study was conducted on 40 plasma samples and 42 amniotic fluid samples. The laboratory methods employed in the assays are described in Appendix B.

The levels of oestradiol 17β and progesterone were measured by radio-immunoassay in all 40 plasma samples. For the reasons

reasons/
already stated (page 164) it was decided not to attempt to measure prostaglandins in the peripheral plasma samples. The levels of the primary prostaglandins (E and F) were measured by radio-immunoassay in all 42 amniotic fluid samples and where the availability of samples would allow, oestradiol 17β (40 samples), progesterone (30) and cortisol (25) were also measured. The mean values for all the samples analysed together with the range and standard deviation in each case are given in Table 8.2. The results were then analysed according to the state of the cervix at induction, the sensitivity of the uterus to oxytocin and the length of induced labour. Statistical analysis was carried out using the Mann-Whitney rank sum test for non-parametric data (Siegel 1956).

Cervical State

The cervical score at induction varied between 1 and 11 (mean 6.0 $\pm$ 2.9 S.D.). The cervix was considered to be unripe if the score was 4 or less, intermediate if 5-8, and ripe if greater than 8. The results in the ripe and unripe cases are compared in Table 8.3. The amniotic fluid of those patients with a ripe cervix contained significantly higher levels of both E and F prostaglandins and also of oestradiol 17β than those with an unripe cervix. No significant differences emerged for either of the substances (oestradiol 17β and progesterone) measured in the plasma or for the levels of progesterone or cortisol measured in the amniotic fluid.

The prostaglandin results are shown graphically in Figure 8.9. This shows only a small increase in levels between unripe and intermediate cases, but a much larger rise in ripe cases. This adds further weight to the hypothesis that prostaglandins have a central role in the initiation of labour if it is accepted that cases with a very ripe cervix are on the brink of spontaneous labour. It also suggests that if the prostaglandins are responsible for ripening the cervix the time course of ripening may not be linear but rather gradual in the early stages and more rapid towards the onset of labour. This would not be surprising in view of the observations in other parts of this thesis concerning the evolution of uterine activity, the appearance of prostaglandins in the amniotic fluid, and the pattern of cervical dilatation in labour, all of which seem to follow a similar pattern.

Oxytocin Sensitivity

Because of the use of the Fully Automatic Cardiff Infusion System in all these cases it was possible to obtain an index of the uterine sensitivity to oxytocin in each case. From the description of this apparatus (Appendix A) it will be seen that the dose rate of the oxytocin infusion is determined automatically by the feed-back to the apparatus of the uterine contractile response. Thus when the machine receives the information that the uterine contractility is adequate, no further increase is made in the dose rate (Figure 8.10). A uterus that is very sensitive to oxytocin will reach this point at a low rate of infusion while one that is insensitive

insensitive/
will require a much higher rate, and the final dose rate chosen by the apparatus can be taken as an inverse function of the oxytocin sensitivity of the uterus.

The maximum dose rate reached in each patient varied from 3 to 32 milliunits per minute (mean 13.2 $\pm$ 9.5 S.D.). Those patients in whom the rate remained below 8 mu per minute throughout were considered to be "oxytocin sensitive" and those in whom it rose above 16 mu per minute were considered "oxytocin insensitive". The results in the sensitive and insensitive cases are compared in Table 8.4. The liquor amnii of patients who proved oxytocin sensitive contained significantly higher levels of both E and F prostaglandins, and also of oestradiol 17_{β}. The levels of cortisol in the liquor, oestradiol in the plasma and progesterone from both sources showed no significant differences.

Length of Labour

The time from amniotomy to delivery rangedfrom 2.6 to 27.4 hours (mean 10.4 $\pm$ 5.6). The median time was 8.7 hours. Those labours which lasted less than 6 hours were considered as short, 6-10 hours as intermediate, and more than 10 hours as long. The results for patients with short and long labours are compared in Table 8.5. The levels of both E and F prostaglandins differ significantly for this factor (see Figure 8.11) but no signficant differences were found in any of the other results.

Discussion

Our failure to demonstrate any association between the plasma levels of oestradiol and progesterone and the response to labour induction conflicts with the experience of Johansson (1968) who found that following a standard infusion rate of oxytocin, those patients who showed a rapid response had significantly lower plasma progesterone levels than those who showed a slow or minimal response. However, Shabaan, Jandial and Klopper (1974) could demonstrate no correlation between the plasma level of these placental steroids and the success or otherwise of amniotomy alone in inducing labour.

The results of our amniotic fluid studies are so similar when analysed according to the three factors (cervical score, oxytocin sensitivity and length of labour) that it might be presumed that the same groups of patients represented the extreme ends of the spectrum in each instance. This was not the case. Indeed of the 16 patients who were included under at least one of the "favourable" parameters (ripe cervix, oxytocin sensitive, short labour) only four were found to occur in all three, and similarly only four of the 19 patients who fell into at least one "unfavourable" category (unripe cervix, oxytocin insensitive, long labour) belonged to all three categories.

These two groups of four patients represent the most obvious extremes of the spectrum we are studying, and examination of their prostaglandin values (Table 8.6) shows that they differ

differ/

more widely than any of the hitherto examined groups.

Four patients in the series had caesarean sections and their prostaglandin results are also shown in Table 8.6. The indications for the operation were failure to progress in 2 cases, fetal distress in one and disproportion in the other. Only one of the two cases of failure to progress fell into all three unfavourable categories (the other had an unripe cervix and a long labour, but was intermediate in oxytocin sensitivity). Nevertheless the prostaglandin results in these two cases (Table 8.6) while not quite the lowest recorded in the series (see Table 8.2), were the lowest of any definable group.

While it cannot be claimed that these results demonstrate that prostaglandins are responsible for the normal process of cervical ripening, they at least establish a close link between the two. The possibility must be conceded that the rise in the levels of amniotic fluid prostaglandins and the cervical ripening are both the result of a third factor. The most likely candidate for such a role would appear to be oestradiol 17_{β} (see Chapter 3) which is known to stimulate prostaglandin synthesis in some species (Thorburn, Challis and Currie 1977).

These studies offer an endocrinological explanation for the poor outcome of oxytocin induced labour in the primpara with an unripe cervix, and for the improved results when prostaglandins are used. The patient with an unripe cervix

cervix/

is deficient in endogenous prostaglandin activity, and perhaps also in other factors. The clinical studies described in the foregoing Chapters indicate that steps taken to correct this deficiency by supplying exogenous prostaglandins go at least part of the way towards restoring normality and allowing a satisfactory outcome.

CHAPTER 9

CONCLUSIONS

CONCLUSIONS

"It is a basic tenet of medicine that the nearer a therapeutic manoeuvre approximates to a natural physiological event, the more effective and safer it will be" (Chard 1977).

The phenomenon of cervical ripening in the last few weeks of pregnancy is an integral part of the evolution of labour. The evidence presented in this thesis indicates an obligatory interrelationship between three factors, all of which normally exhibit the same pattern of development. They are imperceptible in early and mid pregnancy, they gather speed during the third trimester and they gain full momentum during labour.

The three factors are:-

1) Uterine contractions.
2) Cervical changes.
and 3) Endogenous prostaglandin production.

The major conclusion of this thesis is that unless this pattern of development is well advanced, induction of labour by conventional means will carry a high failure rate with a significantly increased morbidity for both the mother and her child. In the past the importance of this has tended to be obscured by its relative rarity and by the excellence of the results in the great majority of patients undergoing induction

induction/
of labour. It is none the less an iatrogenic and avoidable occurrence. The circumstances likely to lead to such an outcome may be recognised by a simple clinical examination to assess the degree of ripeness of the cervix.

It has long been the clinical impression of many obstetricians that if the cervix is unripe, induction of labour may be less successful. An essential part of this thesis was the use of a scoring system to assess cervical ripeness and so bring objectivity to a hitherto highly subjective impression.

The first part of the original work described in the thesis had the aim of quantifying this long standing clinical impression (Chapter 4). In the event, the results indicated that the problem of the unripe cervix in the primigravida may be even greater than obstetricians had fully appreciated. They dispelled the belief that had arisen that the use of amniotomy followed by immediate escalating intravenous infusion of oxytocin had overcome most if not all of the problems associated with induction of labour. The overall results were better but there remained a small, hard core of resistant patients in whom the response was unsatisfactory due to prolonged labour, fetal asphyxia and the need for caesarean section. The typical pattern of labour in these cases was of poor progress as judged by cervical effacement and dilatation, in spite of apparently adequate uterine contractions.

The purpose of the subsequent clinical studies (Chapters 5, 6 and 7) was to develop techniques which might improve the results in patients requiring induction of labour in the face of an unripe cervix. Prostaglandins were chosen as likely to be of value because of their ability to induce labour or abortion at any stage of pregnancy regardless of the state of the cervix, and because of experimental evidence that they might play a role in the control of labour.

The major clinical studies investigated the value of intravenous and extra-amniotic prostaglandin therapy for induction of labour in such cases. Intravenous therapy proved effective but it produced disagreeable maternal side effects. This problem was overcome by employing the extra-amniotic route. Side effects were minimal, presumably because systemic therapy was avoided. As a logical extension of this experience a further technique was developed of delivering extra-amniotic prostaglandin therapy as a bolus dose in viscous gel for sustained release. This proved highly effective for ripening the cervix before induction of labour.

These techniques of local prostaglandin therapy achieved a marked improvement in the results in primigravidae where the cervix was unripe, and these clinical findings were reinforced by the laboratory measurements of prostaglandin levels during

during/

pregnancy and labour (Chapter 8). The laboratory results point strongly towards an important role of the primary prostaglandins in the physiology of cervical ripening and parturition.

The main conclusions of the thesis are thus as follows:-

1) The phenomenon of cervical ripening in late pregnancy is an essential part of the normal transition from pregnancy to spontaneous labour.

2) Failure of such ripening is an indication of an abnormality in the endocrine millieu of the pregnancy associated with impaired endogenous prostaglandin production.

3) Induction of labour by conventional means without regard to the condition of the cervix is likely to result in greater morbidity for those in whom it remains unripe.

4) The use of extra-amniotic prostaglandin therapy in such patients, either for induction of labour or for pre-induction cervical ripening, will go some way towards restoring their prospects of a satisfactory labour and delivery.

The results of the research emphasise that we should no longer resign ourselves to philosophical acceptance of a poor outcome of induced labour because the cervix is unripe. Labour and delivery remain potentially dangerous events for both mother and child and these dangers are exaggerated in the patient with an unripe cervix. The approach to the management

management/

of these patients suggested in the thesis requires more effort and inconvenience on the obstetrician's part. It requires that all patients in whom induction of labour is planned should have an examination to ensure that the cervix is ripe, and if it is not, local prostaglandins should be employed. The added inconvenience will be rewarded with better results and increased safety for the patients.

The search must continue for a fuller understanding of the physiology of the cervix and the uterus and for improved techniques of managing the problem of the unripe cervix. Preliminary experiments with local oestradiol therapy (Gordon and Calder 1977) have indicated that this may reduce the resistance offered by cervical collagen; the potential roles of relaxin and collagenase remain almost completely unexplored. In time the use of a combination or a sequence of agents may be beneficial, but not until we fully understand the complex processes of cervical ripening and parturition can be expect to provide optimal care for mother and child.

T H E U N R I P E C E R V I X

a thesis presented in two volumes by

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based on research conducted between
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DEPARTMENT OF
OBSTETRICS AND GYNAECOLOGY
UNIVERSITY OF GLASGOW

FEBRUARY 1978

V O L U M E II

TABLE OF CONTENTS

VOLUME II

A P P E N D I X A

CLINICAL METHODS

The specialised clinical techniques which were developed during the course of the research are described in the main text of the thesis. This appendix is confined to description of the patients who participated, the system of data collection, and the equipment employed for drug infusion and intra-partum monitoring.

Patients

All patients described in the thesis were resident in the Oxford area and were delivered in the specialist units of the John Radcliffe Hospital, Maternity Department. The large majority were primigravidae since the problems associated with an unripe cervix are greater and more frequent in such patients. By concentrating on primigravidae variable factors due to parity were eliminated and where comparisons were made between different methods of management (Chapter 7) the following strict criteria of selection were employed to further exclude factors which might bias such comparisons: primigravidae of five feet or more in height with a single fetus presenting by the head, who were between 38 and 42 weeks gestation, and had shown no evidence of spontaneous labour.

Consent

All patients who participated in the innovative techniques

techniques/

described or who provided samples of blood or amniotic fluid, gave full and informed consent to so doing. The research projects described in the thesis were all approved by the Ethical Committee of the Oxford Area Health Authority.

The Cervical Score

Throughout the studies, with the exception of those cases of fetal death in utero, and anencephaly (since the station of the presenting part could not be accurately assessed), the state of the cervix was assessed using a scoring system based on that described by Bishop (1964) but slightly modified (see Figure 3.3 for original system and modified system). The score comprises points awarded for each of five features: cervical dilatation, cervical effacement (or length), the consistency of the cervix and its position (i.e. posterior - towards the sacrum, intermediate or anterior - towards the pubic symphysis), and finally the level of the fetal presenting part relative to the pelvis (the station). At the outset of these studies the following modifications to the Bishop system were made:-

1) Dilatation: The Bishop system expressed this as "0", "1-2", "3-4" or "5-6" cms. Thus a dilatation of 2.5 cm could not be scored since it fell between 1 and 2 points. We therefore modified assessment of dilatation to "less than 1", "1-2", "2-4", "more than 4". (If the dilatation was assessed as

assessed as/

exactly 2 cm, one point was awarded).

2) Effacement: Bishop expressed this as a percentage, but this was felt to be insufficiently precise especially since it was not clear what 0 or 100 per cent represented. We therefore replaced this by length in cm, thus "more than 4", "2-4", "1-2" and "less than 1".

3) Position: Bishop awarded 2 points for an anterior cervix and 1 point if intermediate. Since we considered this the least important factor, we decided to award no points if the cervix was posterior, otherwise 1 point was awarded.

No alterations were made in scoring Consistency or Station, but one result of the modifications was that the maximum possible score was reduced from 13 to 12. All cervical scores were assessed personally by the author so that inter-observer error was eliminated.

Data Collection

This scoring system was incorporated into a report form which was used in every case in the trial. A copy of this report form is to be found at the end of this appendix. The central section is in the form of a partograph on which cervical dilatation was charted (upwards on the chart) as well as cervical effacement and descent of the presenting part (downwards on the

on the/

chart). The value of charting effacement in this way lies in the fact that in cases of induced labour with an unripe cervix, no dilatation or descent may occur for several hours after induction and during this time effacement may be the only index of progress.

Intra-partum Management

Almost all the patients in the studies were nursed during labour by the research midwifery sister who recorded all relevant data. In general vaginal examinations were made every three to four hours, either by the author or in his absence by the research sister.

Equipment

a) Drug Infusion

Throughout the studies the Fully Automatic Cardiff Infusion System was employed for drug infusion (Figure 4.2). When intravenous oxytocic therapy was given (Chapter 4 - prospective study, Chapter 5, Chapter 7 - after cervical ripening) the amplitude of the uterine contractions was recorded by means of a fluid filled manometer catheter introduced into the amniotic cavity via the cervix at the time of amniotomy. This was connected to a strain gauge pressure transducer. The infusion rate of the drug was then controlled automatically by the "closed-loop" system whereby the uterine response is allowed to modify the speed of the infusion pump. The infusion

infusion/

pump consists of a motor driving a peristalic pump with six rollers which is applied to a silicone rubber section of the intravenous infusion giving set. There are two methods of control of the dose rate. This can either be set and adjusted by hand or it can be advanced automatically. When oxytocin is employed, 10 units in 500 ml infusion fluid allows a dose range of 1 - 32 milliunits per minute.

When the automatic mode is employed the initial rate of 1 mu per minute is increased logarithmically by the action of a servo motor which controls the pump speed. Left unmodified the dose is steadily increased on a logarithmic scale in which it doubles every 12.5 minutes and would reach 32 mu per minute after 62.5 minutes. The pharmacological basis for the use of logarithmic increment has been defined by Scott (1972).

If the "closed-loop" system is not employed the midwife is responsible for switching the apparatus to a steady rate of infusion when she considers that labour is established. When the "closed-loop" system is employed the rate is controlled by the uterine response as illustrated in Figure 8.8. The dose rate increases until the first occasion on which the intra-uterine pressure rises above 30 mm Hg. This event causes the servo motor to switch off and the dose rate then remains constant. The servo motor again switches on when the intra-uterine pressure has remained below 30 mm Hg for more than two minutes. The dose rate is thus adjusted until the situation is reached when

when/
contractions of 30 mm Hg or greater are occurring regularly with latent intervals of less than two minutes, by which time the appropriate dose rate has been found and the servo motor remains switched off.

In addition the apparatus incorporates several safety mechanisms whereby infusion of the drug is immediately discontinued if there is danger of overdosage or malfunction. Thus if the drug reservoir empties or the recording catheter becomes blocked the pump is switched off and an alarm sounds. Also if uterine spasm occurs and the pressure remains above 30 mm Hg for longer than two minutes or above 80 mm Hg for longer than ten seconds, the machine switches off. These latter alarms provided a built in device for detecting uterine hyperstimulation and for the purposes of our studies (Chapters 5, 6 and 7) we defined this complication as a pattern of intra-uterine pressure such as would trigger these alarms.

The apparatus was also used exclusively for extra-amniotic infusion of prostaglandins (Chapters 6 and 7). Prior to amniotomy the intra-uterine pressure signal was recorded from the extra-amniotic space and this was linked to the alarm systems, but the "closed-loop" system was not employed for extra-amniotic prostaglandin therapy. The servo motor was not employed, the dose rate being adjusted by hand.

b) Intra-partum Monitoring

Intra-partum monitoring of the fetal heart rate and uterine contractility was performed in every case using a Hewlett-Packard 8021A Cardiotocograph which was purchased with research funds. In addition to the facility for direct fetal heart recording from an electrode placed on the fetal scalp, this had an ultrasonic facility for external fetal heart recording from a transducer placed on the maternal abdomen and this was invariably employed in cases with intact fetal membranes. The monitor also incorporated intra-uterine pressure measurement by means of a strain gauge transducer and this was simply linked to the one on the Cardiff Infusion System by a fluid filled catheter so that the intra-uterine pressure signal was available to both machines.

nduction of labour trial

lame _____ Series number _____

lospital number _____ Date _____

\ge _____ Parity _____ Drug allocation _____

.D.D. _____ Gestation _____ Route of administration _____

ure/ unsure Indication for induction _____

lationality _____ Marital status _____ Social class _____

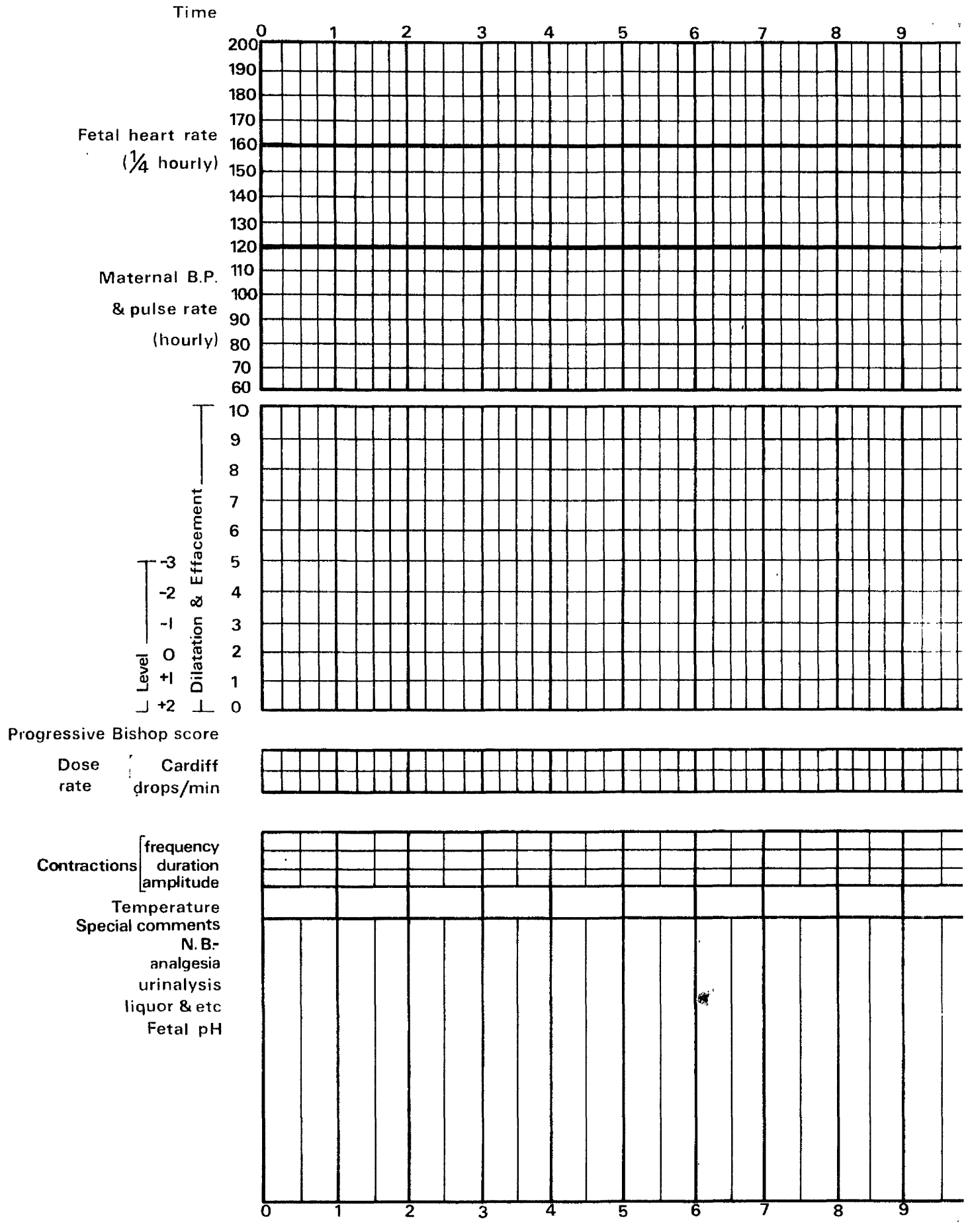
leight (inches) _____ Weight (lbs) _____ Shoe size _____ Blood group _____

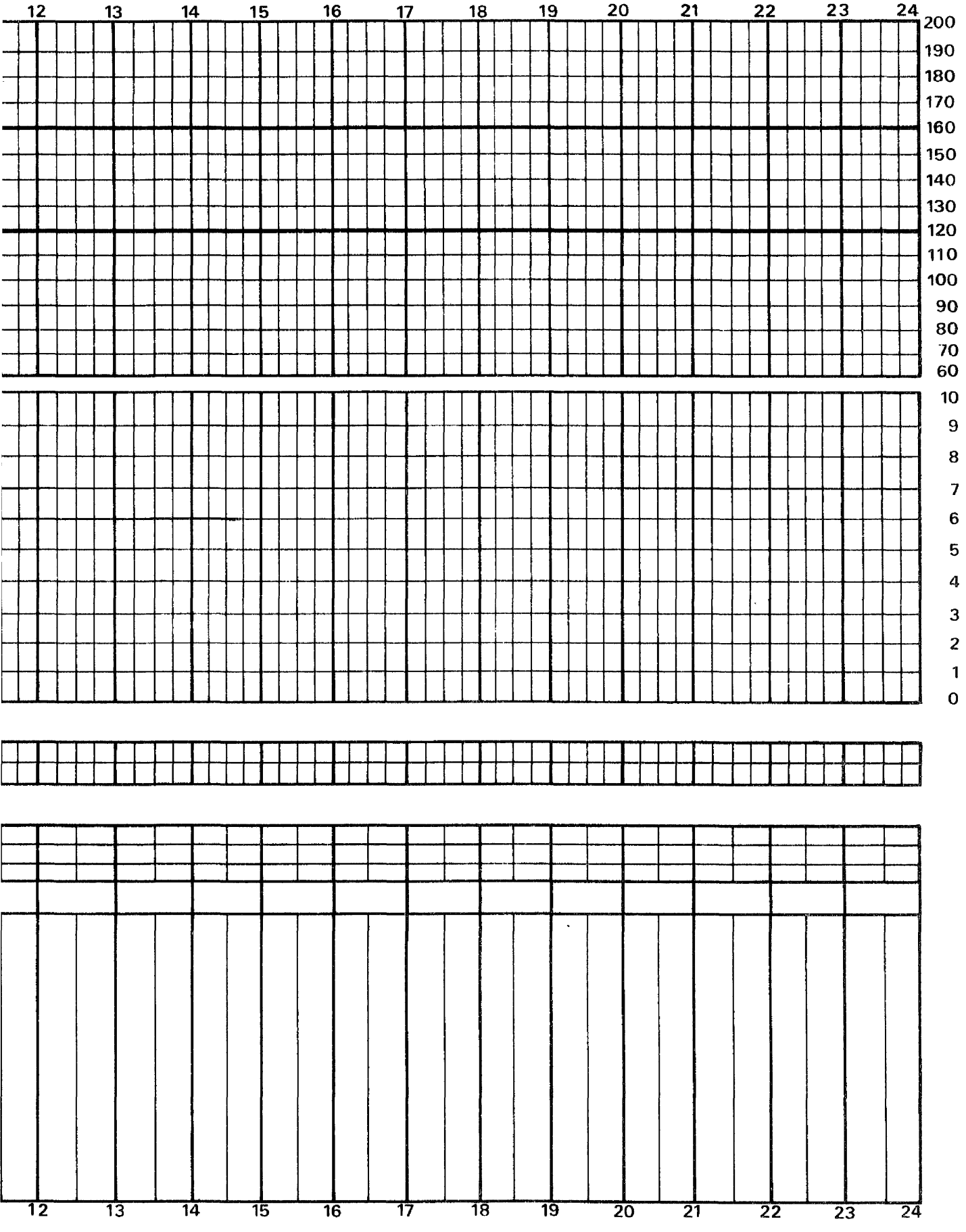
ervical assessment:		0	1	2	3
	Dilatation (cms)	less than 1 ___	1–2 ___	2–4 ___	more than 4 ___
	Length (cms)	more than 4 ___	2–4 ___	1–2 ___	less than 1 ___
	Consistency	firm ___	average ___	soft ___	___
	Position	posterior ___	mid ___ anterior	___	___
	Level	0–3 ___	0–2 ___	0–1; 0 ___	+ ___
					Total score ___

	Date	Time	
mniotomy	_____	_____	Hind / fore
rug commenced	_____	_____	Liquor

ime of delivery Duration of 2nd stage

Labour record

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8
7
6
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4
3
2
1
0

Results

Outcome of labour _____ A./S.B. _____

Weight of infant (gms) _____ Apgar score (1) _____ (5) _____

Description of labour _____

_____ Blood loss at delivery _____

Evidence of fetal distress _____

_____

Fetal pH _____ Time interval after induction _____

Evidence of occipito-posterior position _____ Infant B.P.D. _____

Pelvimetry results _____ Degree of moulding _____

Summary of analgesia _____

Dosage summary _____ Total dosage _____

Pre-amninotomy dosage & time _____ Total treatment time _____

Induction / labour Interval _____ Induction / delivery interval _____

Assessment of results

A P P E N D I X B

LABORATORY METHODS

This appendix describes the techniques used for the collection and storage of biological samples and the assay of prostaglandins and steroids in biological fluids for the studies described in Chapter 8.

Collection of Samples

The following procedures were adopted for collection of samples:

Maternal Plasma:

10 ml samples of maternal blood were withdrawn from a peripheral vein and transferred to a tube containing lithium heparin as an anticoagulant. The blood was centrifuged at 3,000 r.p.m. for 15 minutes, the plasma decanted off into plain tubes and immediately frozen and stored at - 20°C until assay.

Assays were performed on maternal plasma samples for progesterone and oestradiol in the study described on page 172, and for prostaglandin F_{α} in the study described in the paper included at page 163. As has been pointed out in the text (page 165) the measurements of plasma prostaglandins are now considered invalid because of prostaglandin synthetase activity during sample collection.

Amniotic Fluid:

Amniotic fluid samples were collected into plain

plain/

containers which were immediately frozen and stored at -20°C. In five instances (three in spontaneous labour plus the cases of anencephaly and fetal death) serial samples were obtained before amniotomy via a trans-abdominal catheter introduced at amniocentesis. These cases had all had a previous amniocentesis for diagnostic purposes and the catheters were introduced at the same point. A fine epidural type polythene catheter was used. The lumen volume of the catheter was less than 1 ml, so the first 2 ml was discarded at each sampling, the next 5 ml being taken as the sample.

Serial samples in all other cases were obtained via a transcervical polythene catheter introduced at the time of amniotomy. The lumen volume of this catheter was about 4 ml, so the first 10 ml was discarded each time and the following 5 ml taken as the sample. The single samples in which prostaglandins and steroids were measured in the last study described in Chapter 8 (page 172) were all collected (10 ml) via the same type of catheter at the time of amniotomy.

PROSTAGLANDIN ASSAYS

The methods used for the prostaglandin assays were based on those described by Hillier and Dilley (1974). They consisted of extraction and separation of the prostaglandins by chromatography on silica gel microcolumns and radioimmunoassay of the E and F compounds using highly selective antisera. All the assays were performed in duplicate.

Antisera

The antiserum to $PGF_{2\alpha}$ had been raised in rabbits and was supplied by the Upjohn Company. The PGE_2 antiserum was also raised in rabbits and was provided by the Worcester Foundation for Experimental Biology. The cross reactivities of these antisera with other prostaglandins and metabolites are shown in Table B.1.

Extraction Procedure

The prostaglandins were extracted from the samples as follows:-

A tracer of ^{3}H-PG 3,000 d.p.m. was added to a 1 ml aliquot of the sample (^{3}H-PGE_2 for the E assay and ^{3}H-$PGF_{2\alpha}$ for the F assay). 5 ml petroleum ether was then added and the tube vortexed before centrifuging at 2,000 r.p.m. for 4 - 5 minutes. The upper petroleum spirit layer was then decanted off and discarded. 3 ml of an extraction mixture containing isopropanol, ethyl acetate and 0.1 N. hydrochloric acid in the ratio 3 : 3 : 1 was then added to the tube which was again vortexed before the addition of 2 ml of ethyl acetate saturated with water and 3 ml of water saturated with ethyl acetate. The tube was again vortexed and centrifuged at 2,000 r.p.m. for 5 minutes. The upper organic phase was then pipetted off onto approximately 0.3 G anhydrous sodium sulphate to remove superficial water. The organic phase was then transferred to a 5 ml glass tube and after a further washing of the sodiumsulphate with 1 ml ethyl acetate the combined organic phase was evaporated to dryness under a stream of nitrogen at 45°C.

Column Chromatography

Micro columns were prepared using Pasteur pipettes with an internal diameter of 0.5 cm and a working length of 9 cm. These were plugged with Whatman GF/B glass fibre paper and the tightness of the packing adjusted so that the ultimate solvent flow through the column was between 0.2 and 0.3 ml per minute under the maximum solvent head which included a 10 ml reservoir. This range of flow rate gave reproducible separation and recoveries. Silica gel (Kieselgel 0.05 - 0.2 mm Merck 7 - 325 mesh) 0.75 G was slurried in Analar redistilled chloroform and loaded into the column to a height of 4 - 4.5 cm. Glass fibre paper (Whatman GF/C) was placed on top of the silica gel to prevent disturbance of the surface.

The evaporated extract was reconstituted in 0.1 ml of 1% methanol in chloroform and loaded onto the column. A second and third washing with 0.1 ml of 1% methanol in chloroform and 0.1 ml of chloroform respectively was used to ensure maximum transference of extract to the column.

The elution characteristics of the different groups of prostaglandins were initially determined using tritiated prostaglandins A, E and F_α added separately or together to test samples (see Hillier and Dilley 1974). This established that the groups could be separated by the following elution

elution/

sequence : 3 ml chloroform; 7 ml 1.5% methanol in chloroform (A and B prostaglandins); 9 ml 3.5% methanol in chloroform (E prostaglandins); 5 ml 15% methanol in chloroform (F_α prostaglandins). Each solvent volume was allowed to descend by gravity to the surface of the silica gel before addition of the next solvent system.

The results of an experiment to determine the recoveries of the different prostaglandin groups from amniotic fluid and tissue are shown in Figure B.1. The recoveries of the A, E and F groups from the columns were respectively 40%, 51% and 60% with amniotic fluid and 62%. 52% and 100% with tissue.

Radioimmunoassay Procedure

The lyophilized prostaglandin antisera were dissolved in phosphate buffer (pH 7.4); an initial dilution of approximately 1 in 500 was used giving a final dilution of 1 in1500 for the incubation mixture. The PG fractions from the column were evaporated to dryness and reconstituted in 5 ml phosphate buffer. A fifth part of this was counted in dioxan based scintillation fluid to estimate the recovery from the extraction and separation procedures. 50 µl, 100 µl and 200 µl of the reconstituted extract were incubated with 100 µl of the PG antiserum for 30 minutes at room temperature.

temperature./
The incubation volume was made up to 300 µl in each case using phosphate buffer.

The tubes were then placed in ice and approximately 10,000 d.p.m's of ^{3}H-PG label were added. The tubes were then vortexed and incubated on ice at 4°C for a further 60 minutes. 100 µl of 0.5% gelation solution in phosphate buffer was then added followed by 1 ml of dextran coated charcoal to separate free and bound fractions. The tubes were vortexed and stood in ice for a total of ten minutes from the moment of adding charcoal to the last tube and then centrifuged at 4 °C at 3,000 r.p.m. for 5 minutes.

The supernatant was decanted into 10 ml dioxan based scintillation fluid, shaken and counted in the scintillation counter.

Standard curves were constructed with each assay using 0, 10, 25, 50, 70, 100, 150 and 200 pg of the PG in question and the amount of PG in each sample was calculated from the standard curve and expressed as ng/ml of fluid after appropriate correction for dilution and recovery.

The reproducibility of the assay for PGF_{α} is shown in Figure B.2. The separation method used simply separated the prostaglandins into their major subgroups and no further

further/

separation, for instance of $F_{2\alpha}$ and $F_{1\alpha}$, was made. For this reason the results are expressed as either PGFα or PGE concentrations or alternatively as $PGF_{2\alpha}$ or PGE_2 equivalents.

STEROID ASSAYS

The assays for progesterone, oestradiol 17_β and cortisol were all performed under the direction of Dr. A.B.M. Anderson using the techniques in routine use in the research laboratory. These were radioimmunoassay procedures using highly specific antisera raised in sheep to bovine serum albumin conjugates of the steroids in question. The minutiae of the techniques will not be discussed further here.

TABLES

T A B L E 2.1

Figures derived from the Clinical Report of the
Queen Mother's Hospital, Glasgow,
for the 2 year period 1968 - 1969.

GENERAL STATISTICS

Total Number of Births	6,001	
Perinatal Mortality Rate	29.5 per 1,000 live and stillbirths.	
Spontaneous Vertex Delivery	4,167	(69.4%)
Asisted Breech Delivery	171	(2.8%)
Operative Vaginal Delivery (Forceps + Vacuum)	1,190	(19.6%)
Caesarean Section	473	(7.8%)
Elective Caesarean Section	147	(2.5%)
Induction of Labour	1,559	(25.4%)

TABLE 2.2

Figures derived from the Clinical Report of the
Queen Mother's Hospital, Glasgow,
for the 2 year period 1968 - 1969.

BREAKDOWN OF INDUCTION OF LABOUR

Method of Induction	Number	Delivered in 24 hrs.	Delivered by C.S.	C.S. for Failed Ind.
"O.B.E." and buccal 'pitocin'*	166 (11%)	83 (50%)	13 (7.8%)	4 (2.4%)
Amniotomy without oxytocin	462 (30%)	422 (91%)	55 (11.9%)	18 (3.9%)
Amniotomy and Buccal oxytocin	540 (35%)	422 (78%)	34 (6.3%)	10 (1.9%)
Amniotomy and intravenous oxytocin	391 (25%)	127 (32%)	64 (16.4%)	24 (6.1%)
ALL METHODS	1,559 (100%)	1,054 (68%)	166 (11%)	56 (3.6%)

(* "O.B.E." consisted of oral castor oil followed by a hot bath and a soap and water enema).

TABLE 2.2

T A B L E 2.3

POTENTIAL HAZARDS OF INDUCTION OF LABOUR

	Prematurity	Fetal
	Jaundice	Fetal
	Hypoxia	Fetal
	Infection	Fetal
	Haemorrhage	Fetal
Maternal	Caesarean Section	
Maternal	Uterine Rupture	
Maternal	Amniotic Embolism	
Maternal	Dissatisfaction	

T A B L E 2.4

Occurrence of prostaglandins in human tissues and fluids.

Source	Prostaglandins
Seminal fluid	E, F, A, B and 19 hydroxy derivatives
Menstrual fluid	E, F
Endometrium	E, F
Amniotic fluid	E, F
Maternal blood	E, F
Decidua	E, F
Fallopian tube	E, F
Umbilical and placental vessels	E, F
Fetal circulation	F
Aqueous humour	E
Adult blood	E, F, A
Urine	E, F
Gastric juice	E
Gastric mucosa	E
Eccrine sweat	E
Kidney	A, E
Skin	E, F
Lung	E, F
Thymus	E
Thyroid	E, F
Nervous tissue	E, F
Cardiac muscle	E
Gingival tissue	E
Cerebrospinal fluid	F

(Karim and Rao 1975)

T A B L E 2.5

Some areas of biological involvement of prostaglandins.

Central nervous system function.
Meiosis.
Control of intraocular pressure.
Bronchoconstriction; bronchodilatation.
Control of blood pressure.
Gastrointestinal motility and secretion.
Pancreatic function.
Renal blood flow.
Inhibition of platelet adhesiveness and aggregation.
Inflammation.
Pain.
Lipid metabolism.

(Karim and Rao 1975)

T A B L E 3.1

Measurements of the length of the cervix (internal-external os) in the non-pregnant and pregnant subjects.

Category	Number of Subjects	Mean Cervical Length (mm ± S.D.)
Non-pregnant	5	44.9 ± 9.8
Less than 12 weeks pregnant	2	45.5 ± 10.6
12 - 14 weeks pregnant	11	45.3 ± 9.3
15 - 18 weeks pregnant	10	44.3 ± 6.3
19 - 22 weeks pregnant	2	44.0 ± 8.4

(Calder and McManus 1978, unpublished observations)

TABLE 3.2

Measurements of the diameter of the endocervical canal in non-pregnant and pregnant subjects.

Category	Number of Subjects	Mean Cervical Diameter (mm ± S.D.)
Nulliparas		
Non-pregnant	13	7.6 ± 1.1
8 - 9 weeks pregnant	20	8.2 ± 1.2
10 - 11 weeks pregnant	21	8.6 ± 0.8
12 or more weeks pregnant	5	9.3 ± 1.1
Multiparas		
Non-pregnant	30	8.0 ± 1.0
8 - 9 weeks pregnant	24	8.5 ± 1.0
10 - 11 weeks pregnant	22	9.3 ± 1.0
12 or more weeks pregnant	7	9.9 ± 0.8

(data from Johnstone, Boyd, McArthy and McClure Brown 1974)

TABLE 3.3

Cervical findings in primigravidas at 32 weeks gestation in relation to the time of onset of spontaneous labour.

Onset of Labour	External os Admits 1 Finger	Internal os Admits 1 Finger
Before 38 weeks	100%	100%
38-39 weeks	70%	55%
40-41 weeks	55%	20%
41 weeks or later	40%	10%

Data of Anderson and Turnbull 1969.

TABLE 4.1

Retrospective study of primigravid labour
John Radcliffe Hospital, Oxford.
March - August 1974.

MODE OF ONSET OF LABOUR AND OUTCOME

Type of Labour	No.	Delivered within 12 hours	Mean length (hours)	Caesarean section	Birth Asphyxia
Spontaneous throughout	274	213 (78%)	9.4	7 (2.6%)	8 (3.0%)
Spontaneous Augmented	86	59 (69%)	10.3	6 (7.0%)	5 (5.8%)
Induced	537	462 (86%)	8.8	63 (11.7%)	34 (6.3%)
ALL	897	734 (82%)	9.1	76 (8.5%)	47 (5.2%)

TABLE 4.2

Retrospective Study:
Cases delivered by Caesarean Section.

PRIMARY INDICATION FOR CAESAREAN SECTION

	Fetal Distress	Disproportion	Failure to progress	Other	All Indications
Spontaneous Labour	5	7	0	1	13
Induced Labour	21	18	22	2	63
TOTAL	26	25	22	3	76

TABLE 4.2

TABLE 4.3

Retrospective Study:
Cases delivered by Caesarean Section.

PRIMARY INDICATION FOR CAESAREAN SECTION

	Fetal Distress	Disproportion	Failure to progress	Other
Mean Time in labour (hours)	8.6	13.1	16.0	7.4
Mean Cervical dilatation reached (cms) ·	4.0	6.1	3.7	5.9
Mean 1 minute Apgar score	5.5	7.3	6.0	8.4
Birth Asphyxia (%)	50	32	45	0

TABLE 4.3

TABLE 4.4

Retrospective Study:
Cervical state at the time of induction in cases subsequently requiring caesarean section and in control group.

	PRIMARY INDICATION FOR CAESAREAN SECTION					
	Fetal Distress	Disproportion	Failure to progress	Other	Total	Control Group
Cervix ripe	3	4	0	1	8	18
Cervix intermediate	8	8	6	1	23	31
Cervix unripe	10	6	16	0	32	14
TOTAL	21	18	22	2	63	63
Mean approximate cervical score	4.2	5.2	2.6	7.5	4.0	5.9

TABLE 4.4

TABLE 4.5

Prospective study of induction of labour in primigravidas.

INDICATIONS FOR INDUCTION OF LABOUR

Hypertensive States	63
Suspected Placental Insufficiency	27
Prolonged Pregnancy	22
Other (Maternal Age, Diabetes) ..	13
TOTAL	125

TABLE 4.6

Prospective Study of induction of labour in primigravidas.

DETAILS OF LABOUR AND DELIVERY

Cervical State	Induction Delivery Interval (Hrs: Mean ± S.D.)	Mode of Delivery		
		Caesarean Section	Forceps	Spontaneous
Unripe Scores 0-3 (n=31)	14.9 ± 5.5	10 (32%)	16 (52%)	5 (16%)
Intermediate Scores 4-7 (n=69)	8.9 ± 3.0	3 (4%)	38 (55%)	28 (41%)
Ripe Scores 8-12 (n=25)	6.4 ± 2.2	0	11 (44%)	14 (56%)
All Patients (n=125)	10.2 ± 5.0	13 (10%)	65 (52%)	47 (38%)

TABLE 4.7

Prospective study of induction of labour in primigravidas.

CASES DELIVERED BY CAESAREAN SECTION

Primary Indication for Caesarean Section	Number	Mean Cervical Score	Mean Induction Delivery Interval (hours)	Mean Cervical Dilatation Achieved (cms)
Disproportion	2	4.0	10.5	5.5
Fetal Distress	4	2.5	13.5	4.0
Failure to Progress	7	1.7	23.6	3.5

TABLE 4.8

Prospective study of induction of labour in primigravidas.

MATERNAL AND FETAL MORBIDITY

	Pyrexia in Labour ($38^{\circ}C$ or greater)	Birth Asphyxia (Apgar Score at 1 minute 4 or less)	Mean Apgar Score at 1 minute ($\pm$ S.D.)
Unripe Scores 0-3 (n=31)	10 (32%)	7 (23%)	6.6 ± 2.5
Intermediate Scores 4-7 (n=69)	2 (3%)	4 (6%)	8.0 ± 1.5
Ripe Scores 8-12 (n=25)	0	0	8.6 ± 1.3
All Patients (n=125)	12 (10%)	11 (9%)	7.8 ± 1.9

TABLE 4.8

TABLE 4.9

Analysis of the constituents of the cervical score in relation to length of labour.

POINTS AWARDED FOR EACH FACTOR

	Labour longer than Median	Labour shorter than Median	Ratio
Dilatation	70	101	1.4
Length	63	141	2.2
Consistency	43	91	2.1
Position	33	50	1.5
Level	17	62	3.6

T A B L E 5.1

Data for patients from double blind comparison of intravenous PGE_2 and oxytocin with cervical scores 0 - 3.

	PGE_2	Oxytocin
Number of Patients	17	17
Induction/Delivery Interval (hours $\pm$ S.D.)	12.6 $\pm$ 2.9	13.3 $\pm$ 4.1
Caesarean Section	2	5
Forceps	12	10
Spontaneous	3	2
Birth Asphyxia	1	3
Maternity Pyrexia	8	5
Pain/Erythema at Infusion Site ..	14	0
Vomiting	2	1

T A B L E 7.1

Induction of labour by extra-amniotic PGE_2 infusion.

INDICATIONS FOR INDUCTION	
Hypertensive States	40
Prolonged Pregnancy	25
Placental Insufficiency ...	22
Other	8
Total	95

T A B L E 7.2

Induction of Labour by extra-amniotic PGE_2 infusion.

DETAILS OF LABOUR, DELIVERY AND MORBIDITY

	CEPHALIC PRESENTATION (CATEGORY (1))	BREECH PRESENTATION (CATEGORY (2))	SMALL STATURE (CATEGORY (3))	PREVIOUS CAESAREAN SECTION (CATEGORY (4))
Number of Patients	62	11	10	12
Mean Cervical Score	2.0	2.2	2.1	2.2
Mean Time To Catheter Expulsion (Hours ± S.D.)	4.3 ±1.5	3.8 ±1.1	3.7 ±1.2	3.7 ±1.1
Mean Amniotomy-Delivery Interval (Hours ± S.D.)	8.8 ±3.4	9.4 ±2.9	7.6 ±2.7	6.1 ±2.4
Mean Induction-Delivery Interval (Hours ± S.D.)	13.6 ±4.0	13.7 ±4.0	11.9 ±3.0	10.2 ±3.2
Mode of Delivery:				
Caesarean Section	6	2	3	4
Assisted Vaginal Delivery	40	9	4	6
Spontaneous Vaginal Delivery	16	0	3	2
Maternal Pyrexia	7	1	1	3
Birth Asphyxia	2	1	0	1
Mean Apgar Score:				
1 Minute	8.4	7.5	9.0	8.0
5 Minutes	9.8	9.9	10.0	9.8

T A B L E 7.3

Induction of labour by extra-amniotic PGE_2 infusion.

INDICATIONS FOR CAESAREAN SECTION

	Cephalic Presentation (Category 1)	Breech Presentation (Category 2)	Small Stature (Category 3)	Previous Caesarean (Category 4)	All Categories
Fetal Distress	3	1	1	2	7
Feto-Pelvic Disproportion	3	1	2	1	7
Failure to Progress	0	0	0	1	1
Total	6	2	3	4	15

TABLE 7.4

Prostaglandin gel therapy to ripen the cervix before induction of labour.

INDICATIONS FOR INDUCTION OF LABOUR	
Hypertensive States	67
Prolonged Pregnancy	22
Suspected Placental Insufficiency .	16
Other (Maternal Age, etc.)	16
Total	121

TABLE 7.5

Prostaglandin gel therapy to ripen the cervix before induction of labour.

DETAILS OF LABOUR, DELIVERY AND MORBIDITY

	CEPHALIC PRESENTATION (CATEGORY (1))	BREECH PRESENTATION (CATEGORY (2))	SMALL STATURE (CATEGORY (3))	PREVIOUS CAESAREAN SECTION (CATEGORY (4))
Number of Patients	106	6	9	6
Mean Cervical Score:				
Before Treatment	2.3	2.5	2.2	2.5
After Treatment	6.3	6.6	6.1	6.5
Improvement in Score	4.0	4.1	3.9	4.0
Amniotomy-Delivery Interval: Hours (Mean ± S.D.)	10.9 ±4.8	10.0 ±2.8	8.8 ±2.7	9.4 ±2.2
Mode of Delivery:				
Caesarean Section	10	0	7	1
Assisted Vaginal Delivery	65	6	2	4
Spontaneous Vaginal Delivery	31	0	0	1
Maternal Pyrexia:	4	0	1	0
Birth Asphyxia:	7	1	0	0
Mean Apgar Score:				
1 Minute	7.9	8.9	8.7	9.2
5 Minutes	9.3	9.7	9.8	10.0

T A B L E 7.6

Prostaglandin gel therapy to ripen the cervix before induction of labour.

INDICATIONS FOR CAESAREAN SECTION

	Cephalic Presentation (Category 1)	Small Stature (Category 3)	Previous Caesarean Section (Category 4)	All Categories
Fetal Distress	4	1	1	6
Cephalo-Pelvic Disproportion	4	6	0	10
Placenta-Praevia	1	0	0	1
Failure to Progress	1	0	0	1
Total	10	7	1	18

TABLE 7.7

TABLE 7.7

(OPEN OUT)

LOCAL PROSTAGLANDIN E_2 THERAPY

Summary of other published reports

Authors	Number of Patients (Primiparas)	Aim	Cervical Score	Route of Administration	Type of Catheter	Vehicle	Dose	Concentration	Intravenous Oxytocic Added After Amniotomy	Length of labour (hours)	Caesarean Section	Birth Asphyxia
Calder & Embrey (1973)	7 (7)	Induction of Labour	0, 1	Extra-Amniotic	Foley (50 ml)	Saline	Infusion 0.5-2.0 g/min	3 g/ml	5 (Oxytocin)	13.1	0	1 (14.3%)
Miller & Mack (1974)	65 (43)	Induction of Labour	0-9	Extra-Amniotic	Foley (30-50 ml)	Saline	Infusion 1.5-3.0 g/min	50-100 g/ml	23 (Oxytocin)	12.8	12 (17.4%)	11 (18.5%)
Neuberg (1975)	37 (34)	Induction of Labour	0-3	Extra-Amniotic	Foley (45 ml)	Saline	Repeated Bolus Doses of 100 g	25 g/ml	38 (Oxytocin)	14.6	5 (13.5%)	Not Stated
Shepherd, Sims & Craft (1976)	15 (11)	Pre-Induction Cervical Ripening	0-4	Extra-Amniotic	Nelaton	Gel (Tylose)	Bolus 250 g	25 g/ml	Not Stated	Not Stated	1 (6.7%)	Not Stated
Thiery et al (1977, 1978)	196 (139)	Pre-Induction Cervical Ripening	0-4	Extra-Amniotic	Foley (20 ml)	Gel (Tylose)	Bolus 250 or 500 g	75 g/ml	58 (PGE_2)	13.9*	9 (4.6%)	Not Stated
MacKenzie & Embrey (1977)	168 (168)	Pre-Induction Cervical Ripening	0-3	Vaginal	Nelaton	Gel (Carboxy-methyl-cellulose)	Bolus 2.0 or 5.0 mg	200-500 g/ml	112 (Oxytocin)	10.5	21 (12.5%)	15 (8.9%)
Mellows, Sims & Craft (1977)	120 (38)	Induction of Labour	6-11	Extra-Amniotic	Nelaton	Gel (Tylose)	Bolus 300 g	25 g/ml	30 (Oxytocin)	8.7	2 (1.7%)	Not Stated
Kennedy, Quinn, Howie & Calder (1978)	30 (15)	Induction of Labour	6-9	Endo-Cervical	Nelaton	Gel (Tylose)	Bolus 400 g	80 g/ml	7 (Oxytocin)	8.1	4 (13.3%)	1 (3.3%)

* In the Studies of Thiery et al, amniotomy was performed routinely 7 - 8 hours after PGE_2 therapy and the figure given represents the time from PGE_2 therapy to delivery.

TABLE 7.8

Comparison of results in comparable primiparae with unripe cervices (scores 0 - 3; category (1) selection criteria) managed by four different methods. Composite data from Tables 4.6, 4.8, 5.1, 7.2 and 7.5.

	METHOD OF MANAGEMENT			
	Amniotomy + Intravenous Oxytocin	Amniotomy + Intravenous PGE_2	Extra-Amniotic PGE_2 Infusion	PGE_2 Gel Cervical Ripening
Number of Patients	31	17	62	106
Induction-Delivery Interval (Hours; Mean ± S.D.)	14.9 ±5.5	12.6 ±2.9	13.6 ±4.0	10.9 ±4.8
Amniotomy-Delivery Interval (Hours; Mean ± S.D.)	14.9 ±5.5	12.6 ±2.9	8.8 ±3.4	10.9 ±4.8
Caesarean Section Rate	32%	12%	10%	9%
Maternal Pyrexia Rate	32%	47%	11%	4%
Birth Asphyxia Rate	23%	6%	3%	7%

TABLE 8.1

Gestational change in amniotic fluid levels of E and F prostaglandins.

	Gestation Period	
	14-22 wks.	38-42 wks.
Number of Samples	19	42
PGE Equivalents (ng/ml; mean ± S.D.)	0.103 ± 0.091	3.868 ± 3.314
PGF Equivalents (ng/ml; mean ± S.D.)	0.026 ± 0.017	0.673 ± 0.750

All patients were primiparous.
The samples in the second trimester cases were obtained by abdominal amniocentesis and those around term were collected at the time of amniotomy for induction of labour.

TABLE 8.1

TABLE 8.2

Amniotic fluid prostaglandins and steroids and plasma steroids in late pregnancy. (all values are ng/ml).

Substance	Number Measured	Range Of Values	Mean ± S.D.
Liquor Prostaglandin E	42	0.27 - 13.93	3.87 ± 3.31
Liquor Prostaglandin F	42	0.11 - 3.25	0.67 ± 0.75
Liquor Oestradiol 17β	40	0.18 - 1.50	0.56 ± 0.31
Liquor Progesterone	30	10.6 - 47.0	21.7 ± 8.3
Liquor Cortisol	25	13.8 - 52.3	31.9 ± 8.8
Plasma Oestradiol 17β	40	8.1 - 34.2	16.8 ± 6.1
Plasma Progesterone	40	75 - 265	137.5 ± 40.1

TABLE 8.3

Amniotic fluid prostaglandins and steroids and plasma steroids in late pregnancy.
Analysis of results in relation to cervical state.
(all ng/ml;
number of estimations shown in brackets).

Substance	Ripe Cervix	Unripe Cervix	p Value*
Liquor Prostaglandin E	6.27 ± 3.66 (10)	2.77 ± 1.67 (15)	<0.005
Liquor Prostaglandin F	1.54 ± 1.03 (10)	0.36 ± 0.13 (15)	<0.001
Liquor Oestradiol 17_β	0.74 ± 0.32 (9)	0.49 ± 0.24 (14)	<0.01
Liquor Progesterone	26.2 ± 7.4 (6)	17.2 ± 5.9 (7)	N.S.
Liquor Cortisol	36.8 ± 6.4 (5)	23.8 ± 5.2 (9)	N.S.
Plasma Oestradiol 17_β	14.3 ± 3.2 (9)	16.3 ± 5.9 (14)	N.S.
Plasma Progesterone	137.4 ± 44.3 (9)	129.2 ± 35.2 (14)	N.S.

(* MANN-WHITNEY RANK SUM TEST)

TABLE 8.4

Analysis of results in respect of oxytocin sensitivity.
(All ng/ml; number of estimations shown in brackets).

Substance	Oxytocin Sensitive	Oxytocin Insensitive	p Value*
Liquor Prostaglandin E	5.76 ± 3.89 (11)	1.60 ± 0.99 (7)	< 0.005
Liquor Prostaglandin F	1.26 ± 1.10 (11)	0.28 ± 0.10 (7)	< 0.005
Liquor Oestradiol 17_β	0.64 ± 0.29 (9)	0.32 ± 0.11 (7)	< 0.01
Liquor Progesterone	23.4 ± 7.6 (9)	18.4 ± 5.9 (6)	N.S.
Liquor Cortisol	35.4 ± 6.3 (5)	26.7 ± 5.6 (6)	N.S.
Plasma Oestradiol 17_β	13.4 ± 4.3 (10)	16.2 ± 5.6 (7)	N.S.
Plasma Progesterone	131.8 ± 43.6 (10)	144.4 ± 44.5 (7)	N.S.

(* MAN-WHITNEY RANK SUM TEST).

TABLE 8.5

Results analysed by length of labour.
(all ng/ml; numbers of estimations shown in brackets).

Substance	Short Labour	Long Labour	p Value*
Liquor Prostaglandin E	7.13 ± 4.85 (9)	2.47 ± 1.83 (14)	<0.01
Liquor Prostaglandin F	1.27 ± 0.99 (9)	0.33 ± 0.15 (14)	<0.005
Liquor Oestradiol 17_β	0.70 ± 0.33 (8)	0.37 ± 0.14 (14)	N.S.
Liquor Progesterone	25.8 ± 8.9 (5)	17.3 ± 5.1 (11)	N.S.
Liquor Cortisol	37.7 ± 14.4 (5)	27.9 ± 5.0 (10)	N.S.
Plasma Oestradiol 17_β	16.0 ± 4.3 (8)	14.0 ± 3.0 (14)	N.S.
Plasma Progesterone	146.6 ± 55.4 (8)	121.2 ± 30.2 (14)	N.S.

(* MANN-WHITNEY RANK SUM TEST).

TABLE 8.6

Amniotic fluid prostaglandin levels in clinically extreme groups (see text) and in cases which required caesarean section. (all ng/ml).

	Number of Subjects	PGE equivalents	PGF equivalents
Ripe cervix/sensitive uterus/short labour: (mean ± S.D.)	4	9.91 ± 2.68	1.94 ± 0.94
Unripe cervix/insensitive uterus/long labour: (mean ± S.D.)	4	1.34 ± 0.55	0.28 ± 0.08
Caesarean section (all indications): (mean ± S.D.)	4	2.34 ± 1.35	0.37 ± 0.24
Caesarean section (failure to progress): (individual results)	2	1.47; 0.92	0.15; 0.22
Values for whole series (mean ± S.D.)	42	3.87 ± 3.31	0.67 ± 0.75

T A B L E B.1

CROSS REACTIVITY OF PROSTAGLANDIN ANTISERA

	PGF antiserum	PGE antiserum
$PGF_{2\alpha}$	100%	1.6%
$PGF_{1\alpha}$	64%	-
PGE_2	7%	100%
PGE_1	-	128%
15 Keto $PGF_{2\alpha}$	0.3%	-
PGA_2	0.0001%	1.8%
PGB_2	-	0.28%

FIGURES

FIGURE 2.1

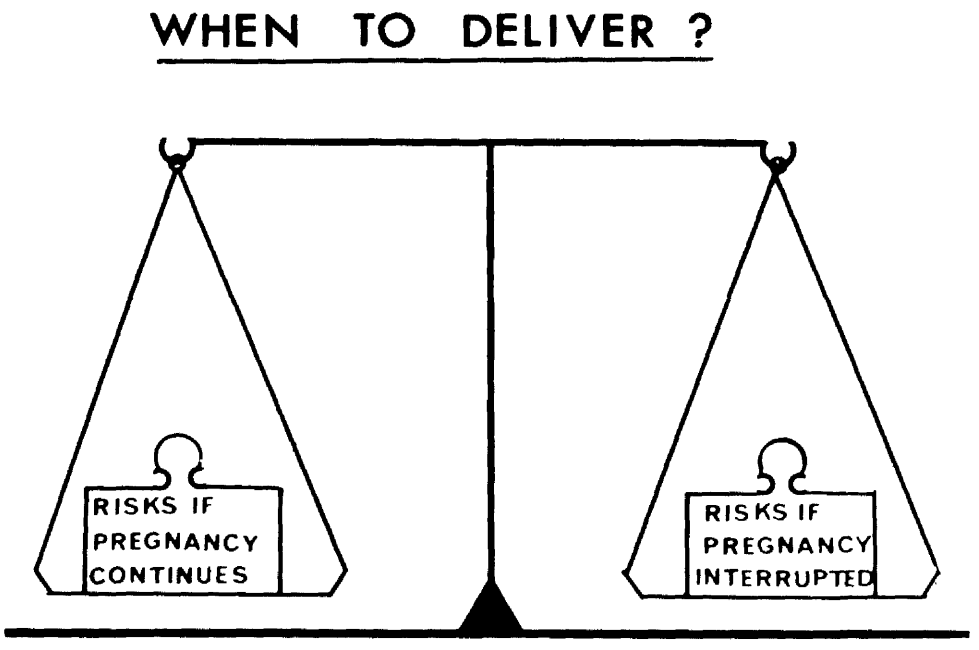
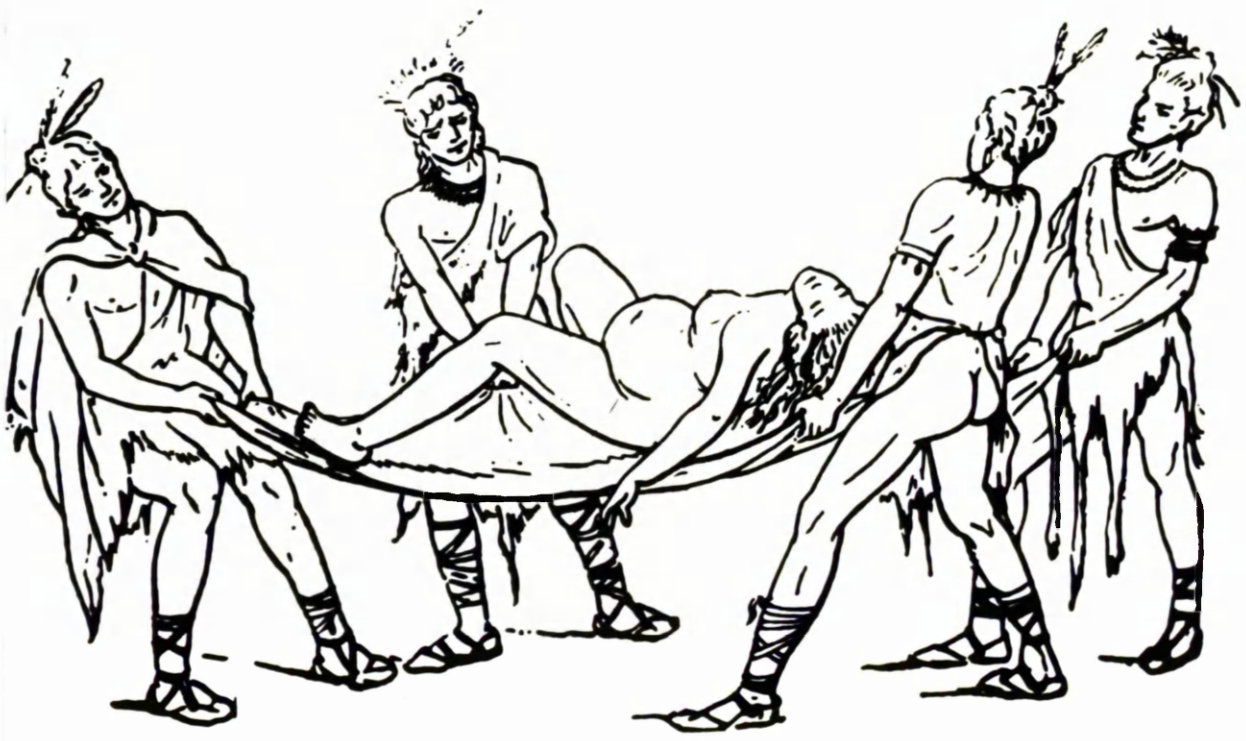

WHEN TO DELIVER ?
RISKS IF PREGNANCY CONTINUES
RISKS IF PREGNANCY INTERRUPTED

FIGURE 2.2a



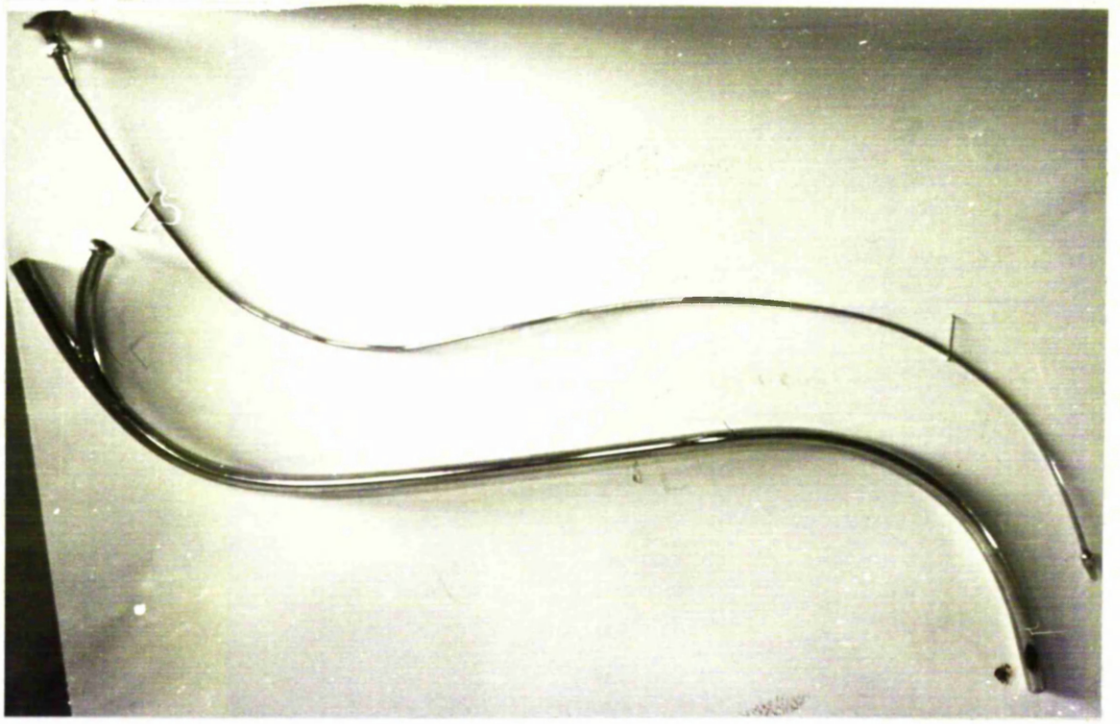
Induction of Labour: a method employed by Canadian Indians. The patient was tossed in a blanket, held at each corner by a brave.

FIGURE 2.2a

F I G U R E 2.2b

Induction of Labour: a method employed in earlier times in Cochin China (now Vietnam). The accoucheur balances himself with a pole while standing on the shoulders of the kneeling patient.

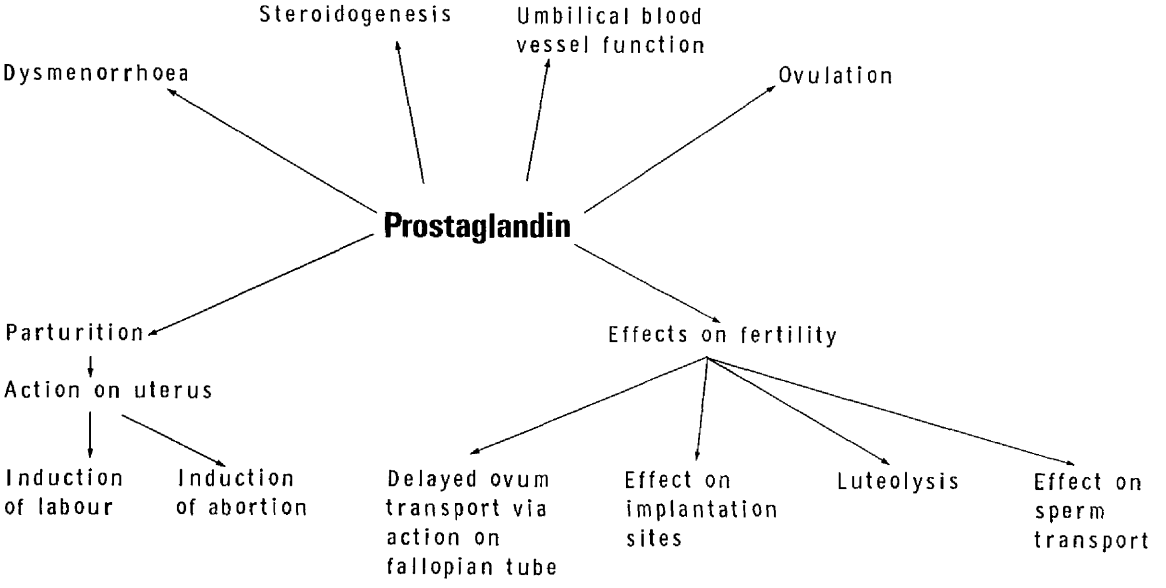
F I G U R E 2.3



THE DREW-SMYTH CATHETER

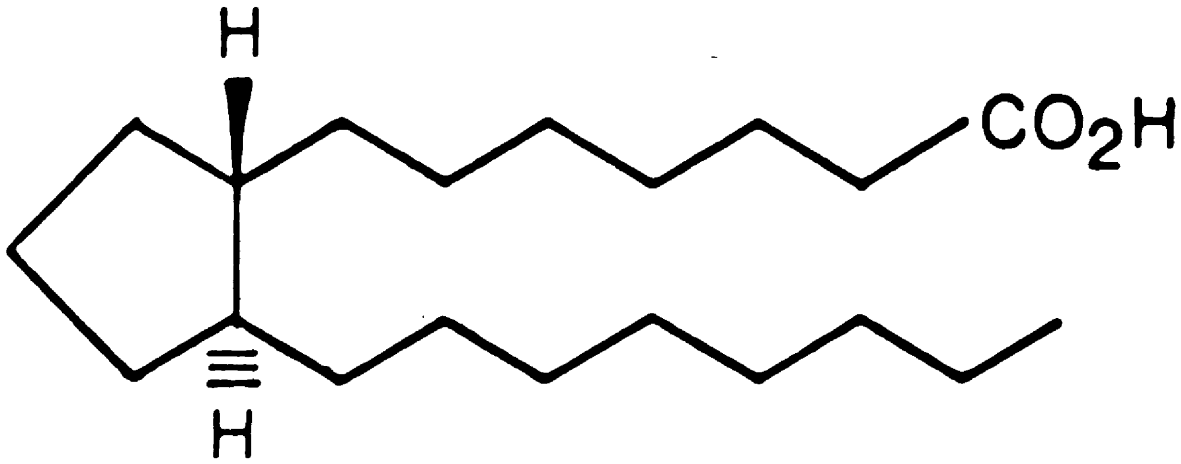
(The stillette has been removed from the lumen of the catheter).

FIGURE 2.4



Established and postulated roles of prostaglandins in human reproduction.
(Embrey 1975).

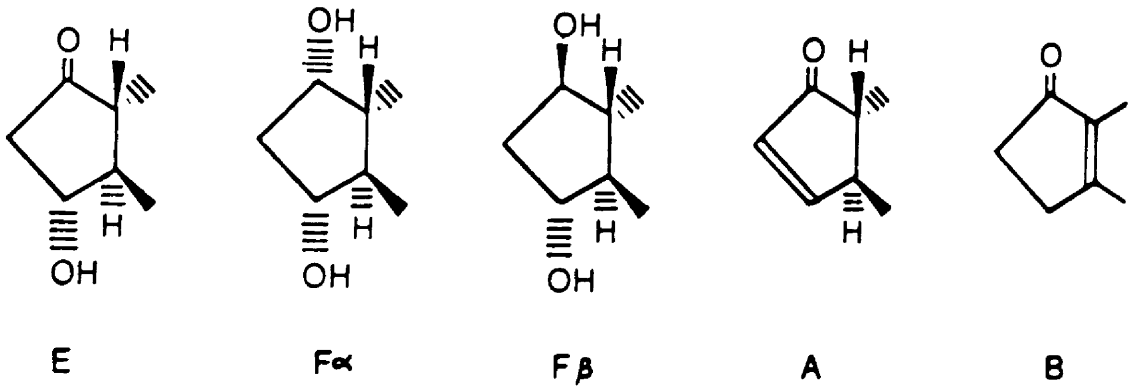
F I G U R E 2.5



PROSTANOIC ACID: Basic structure from which all prostaglandins are derived.

FIGURE 2.5

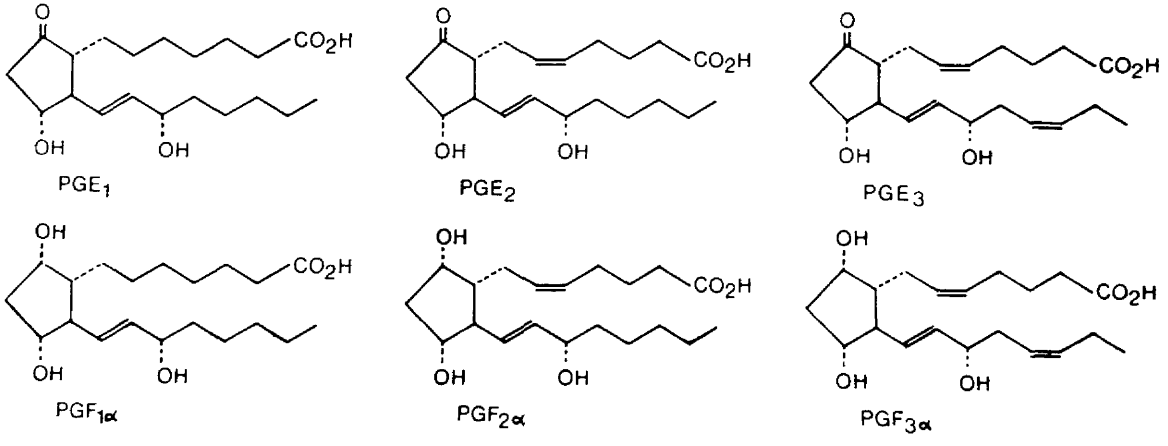
FIGURE 2.6



Structural differences between prostaglandins of the E, F, A and B series.

FIGURE 2.6

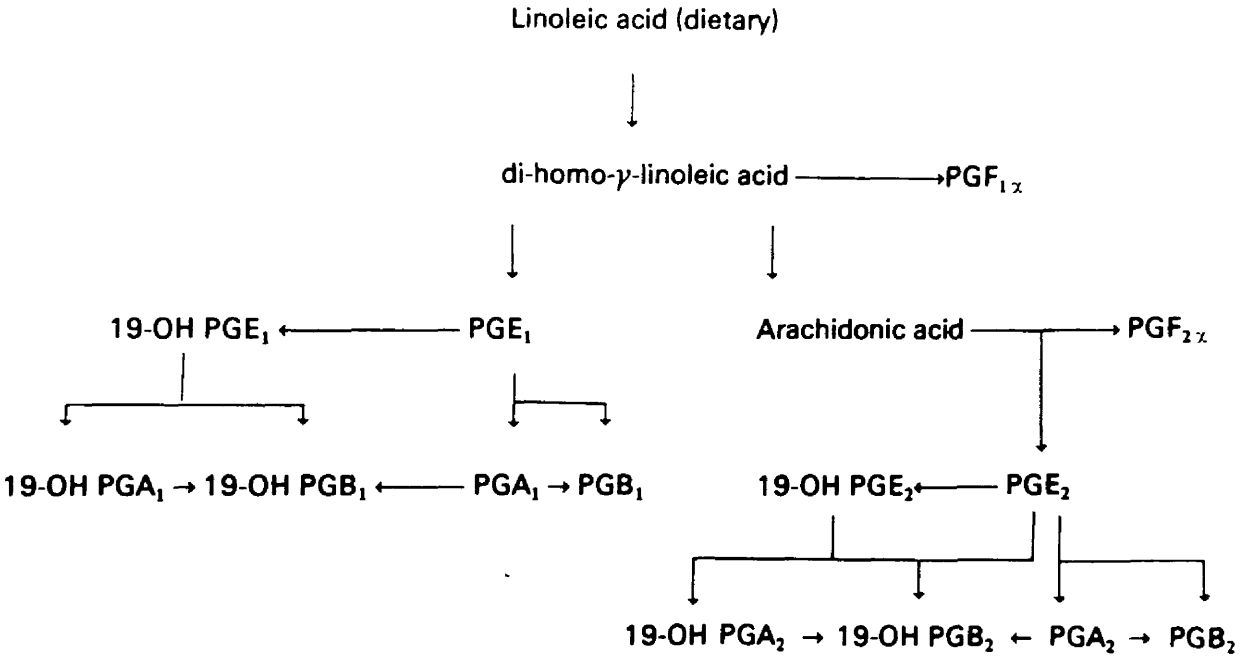
FIGURE 2.7



Chemical structures of the primary prostaglandins.

FIGURE 2.7

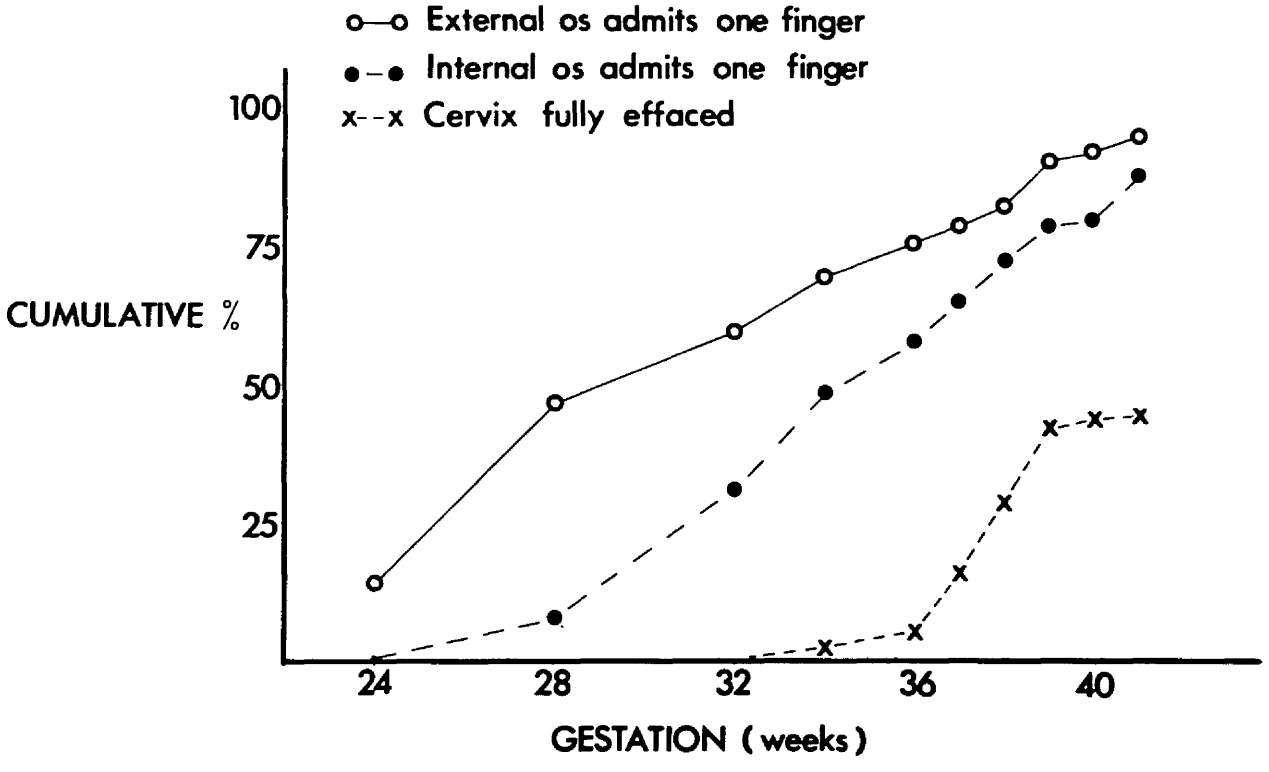
F I G U R E 2.8



Outline of main pathways of prostaglandin biosynthesis.

FIGURE 2.8

F I G U R E 3.1



Gestational changes in the cervical findings in primigravid women.
(drawn from data of Anderson and Turnbull 1969).

FIGURE 3.1

FIGURE 3.2

PELVIC SCORE

	0	1	2	3
Dilatation (cms)	0	1-2	3-4	5-6
Effacement (%)	0-30	40-50	60-70	80
Consistency	firm	average	soft	
Position	posterior	mid	anterior	
Level	0-3	0-2	0-1;0	+
				Total Score

(Bishop 1964)

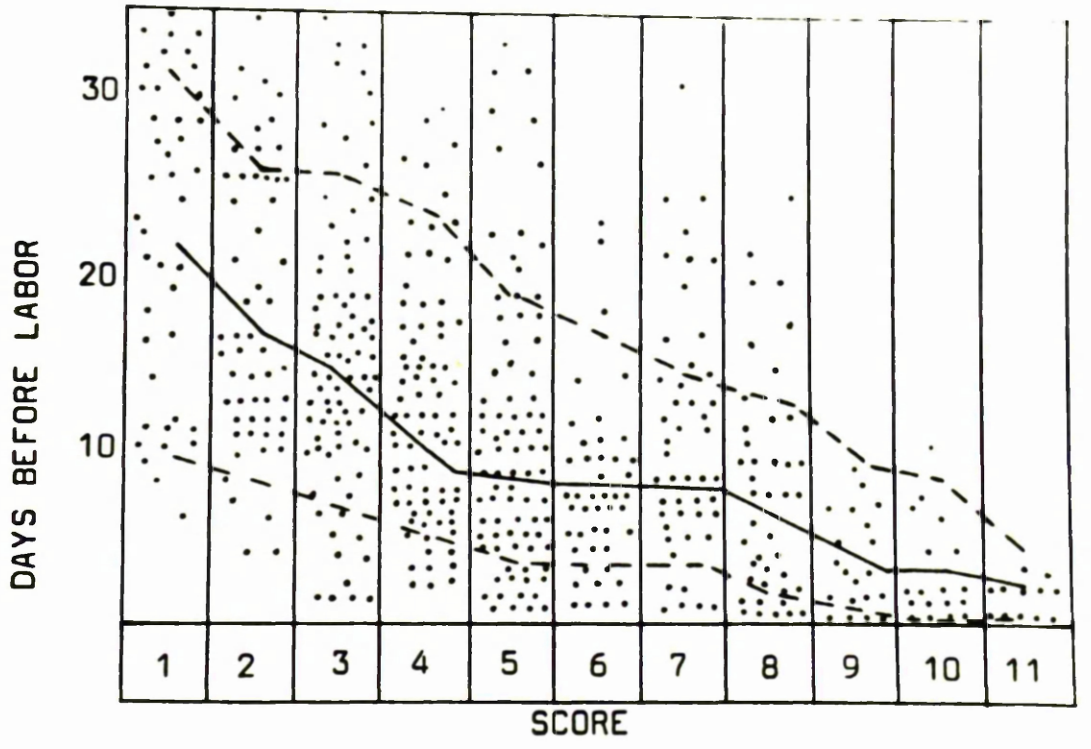
CERVICAL SCORE

	0	1	2	3
Dilatation (cms)	less than 1	1-2	2-4	more than 4
Length (cms)	more than 4	2-4	1-2	less than 1
Consistency	firm	average	soft	
Position	posterior	mid-anterior		
Level	0-3	0-2	0-1;0	+
				Total Score

(Calder , Embrey and Hillier 1974)

Scoring system originally proposed by Bishop (1964) and modified system (Calder et al 1974) used throughout clinical studies.

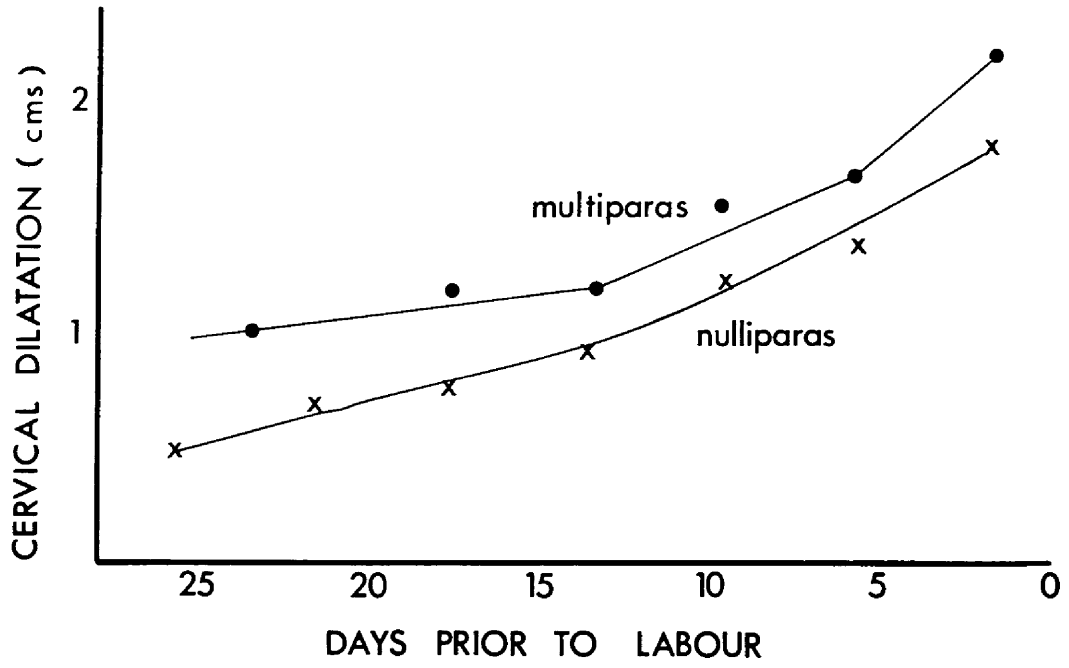
FIGURE 3.3



Pelvic (cervical) score related to the delay before the spontaneous onset of labour (Bishop 1964).

FIGURE 3.3

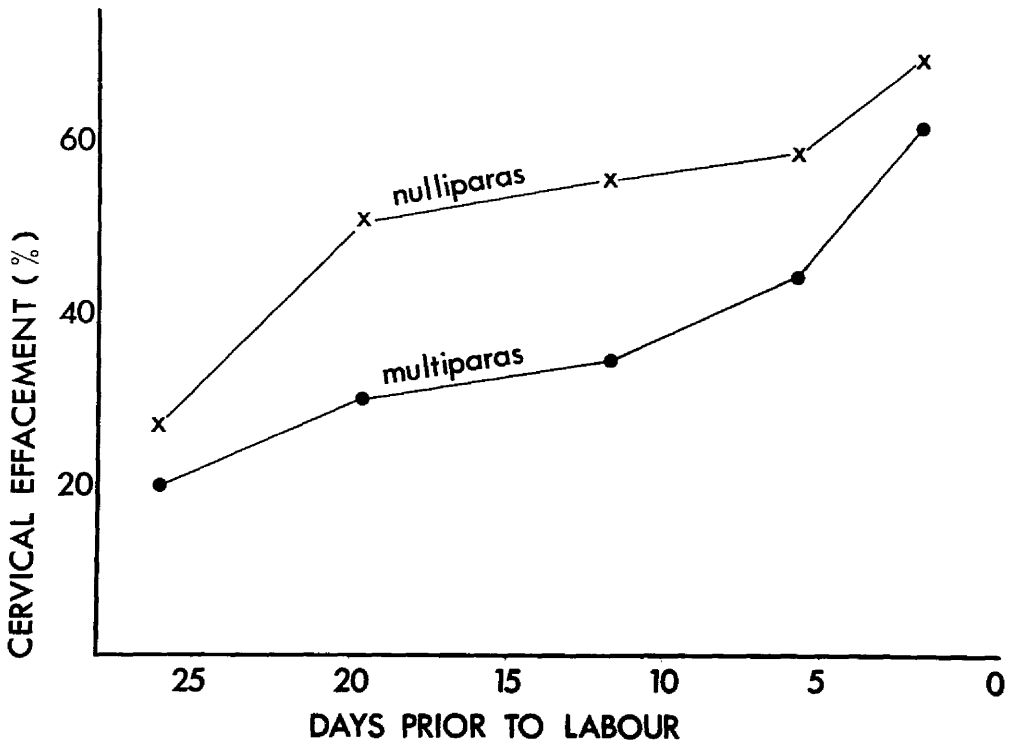
FIGURE 3.4



Pattern of cervical dilatation during the last four weeks of pregnancy (Hendricks, Brenner and Kraus 1970).

FIGURE 3.4

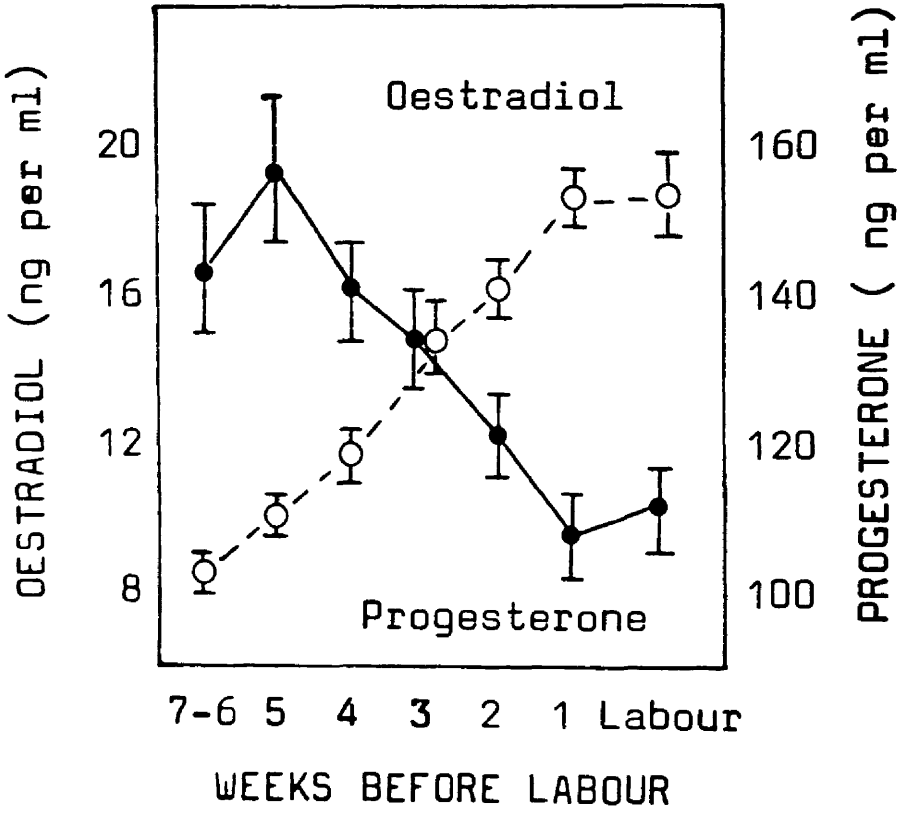
FIGURE 3.5



Pattern of cervical effacement during the last four weeks of pregnancy (Hendricks, Brenner and Kraus 1970).

FIGURE 3.5

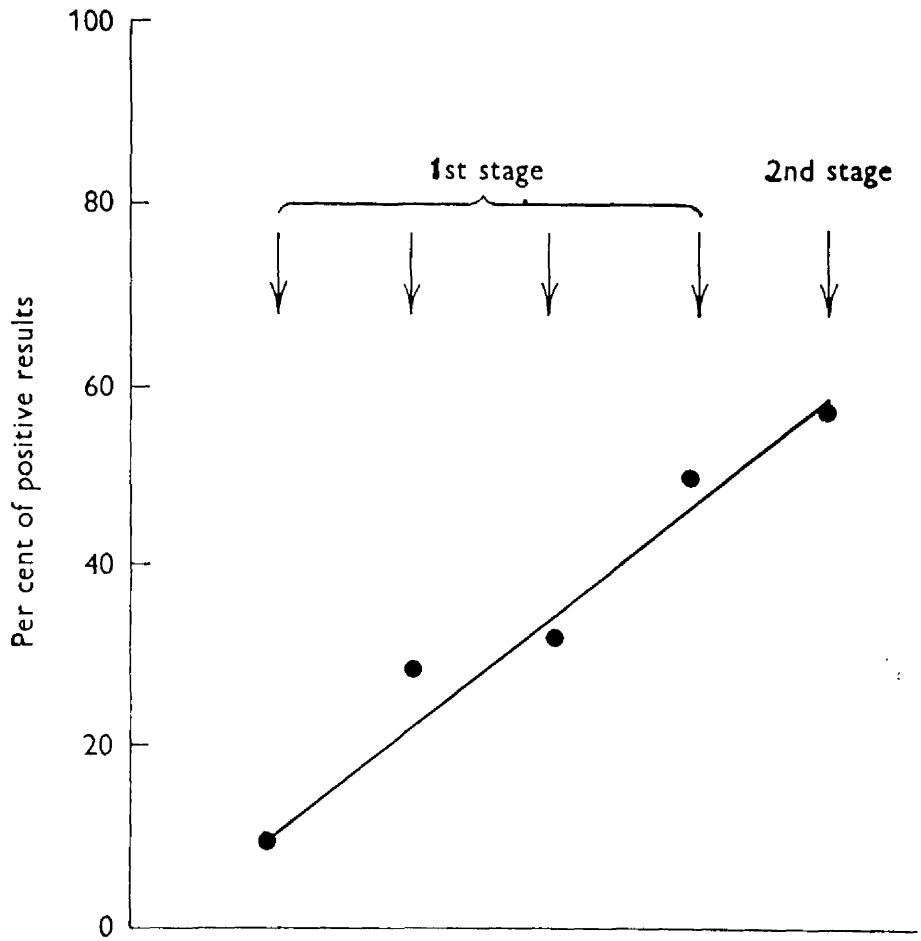
FIGURE 3.6



Changes in plasma progesterone and oestradiol levels before and during labour (Turnbull et al 1974).

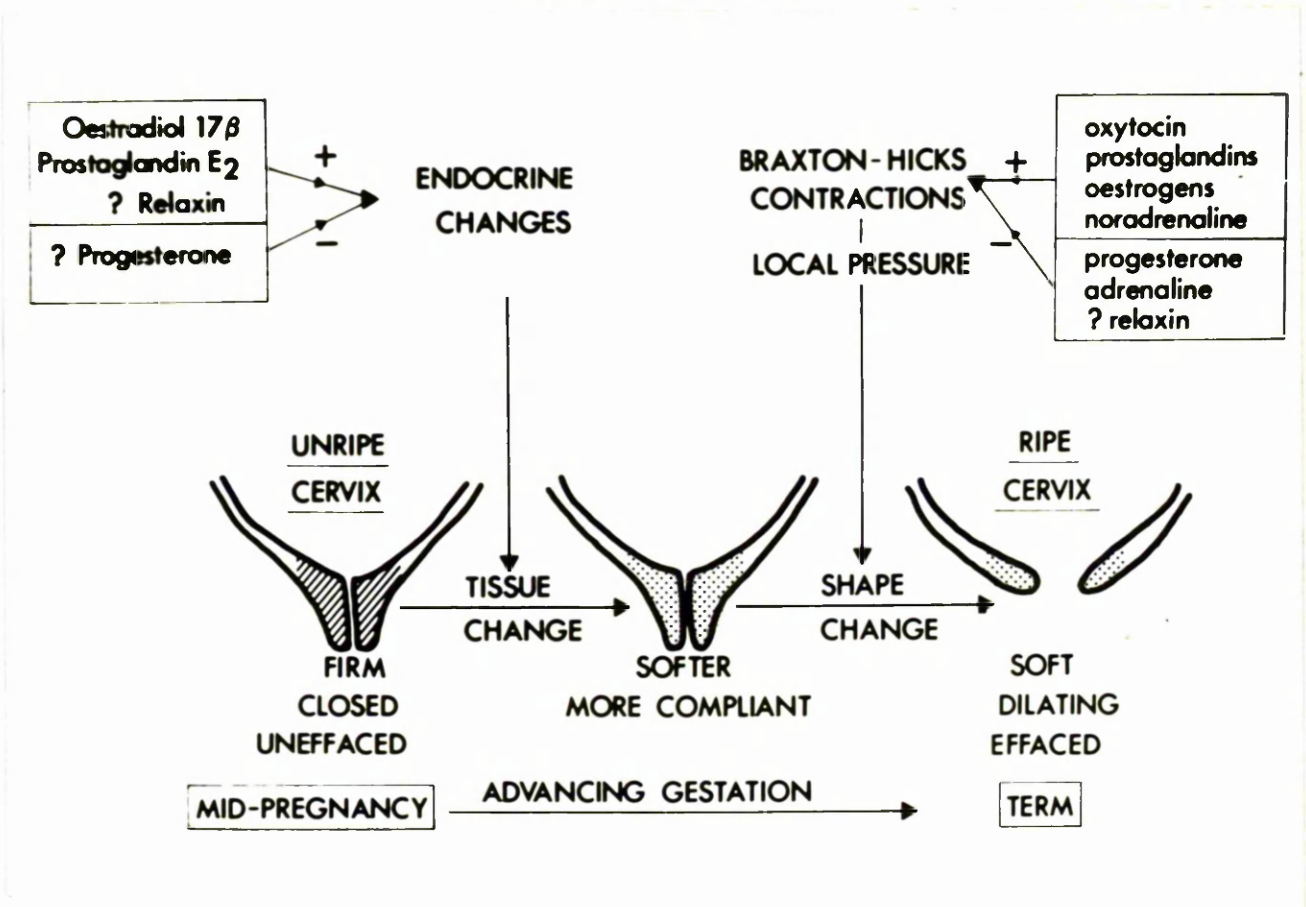
FIGURE 3.6

F I G U R E 3.7



Detection of oxytocin in the maternal circulation (Chard 1973).

F I G U R E 3.8



Schematic representation of the factors which may control cervical ripening.
(It should be noted that the tissue change and the shape change probably occur concurrently).

FIGURE 3.8

DISTRIBUTION OF PATIENTS BY CERVICAL SCORE

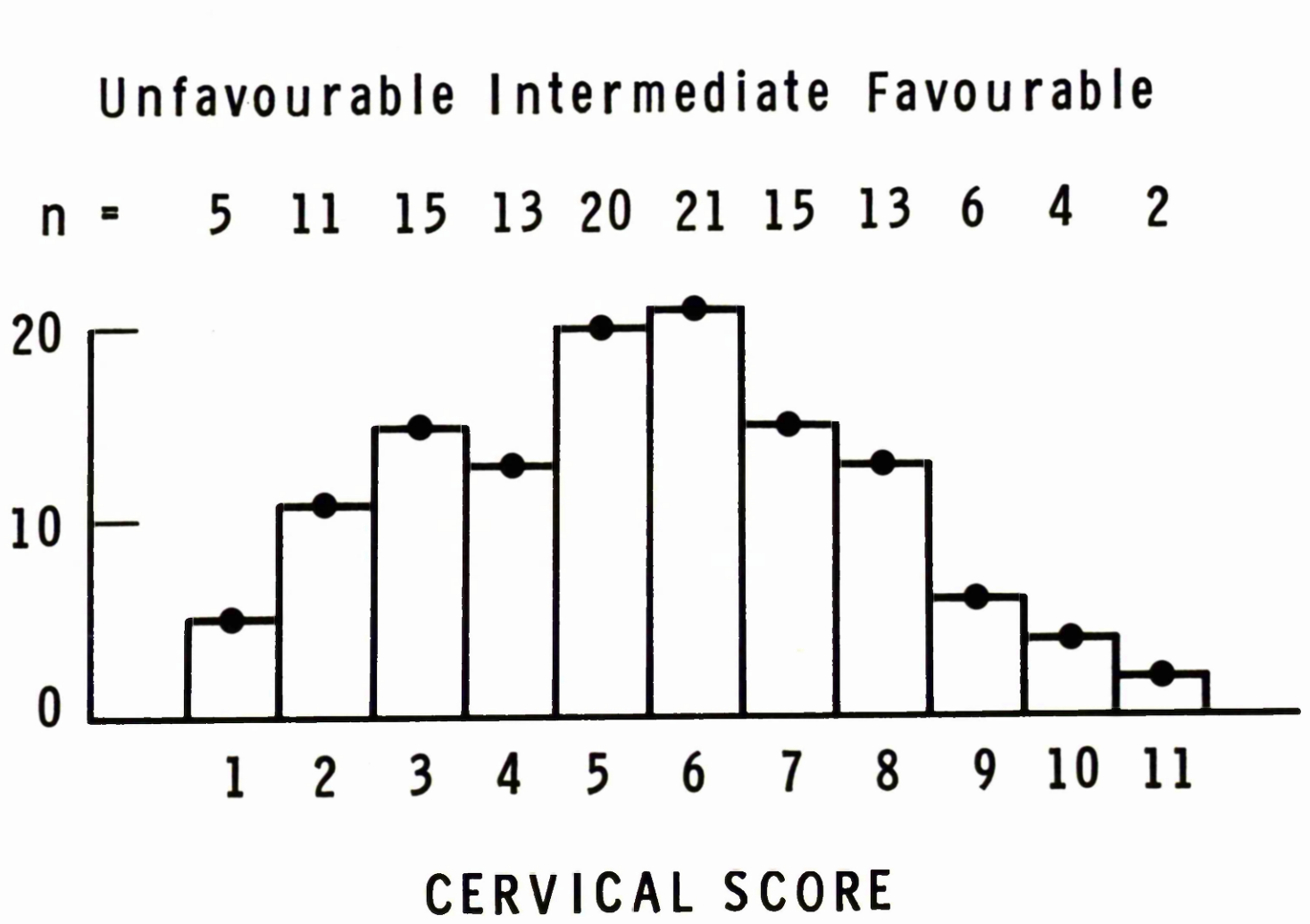
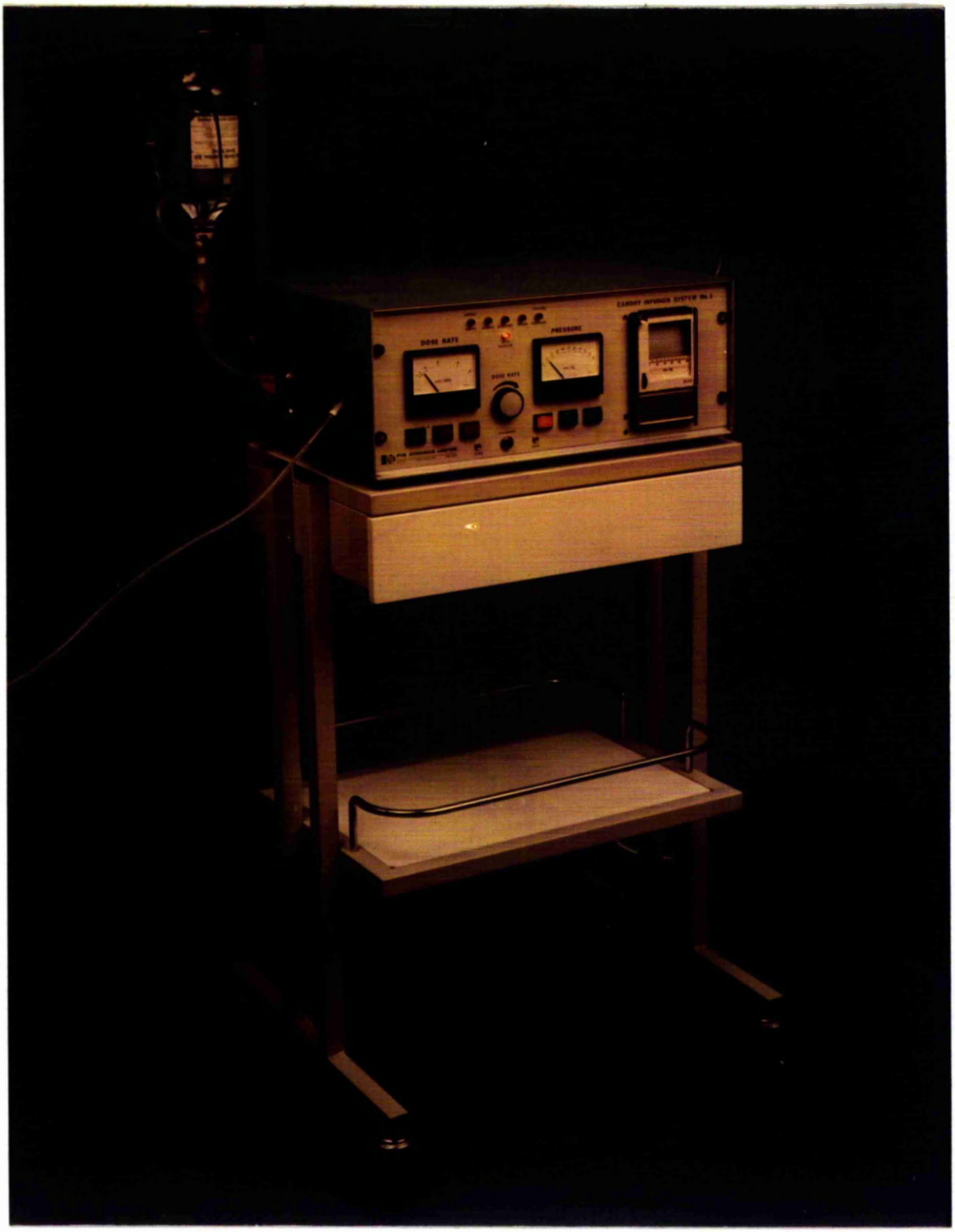
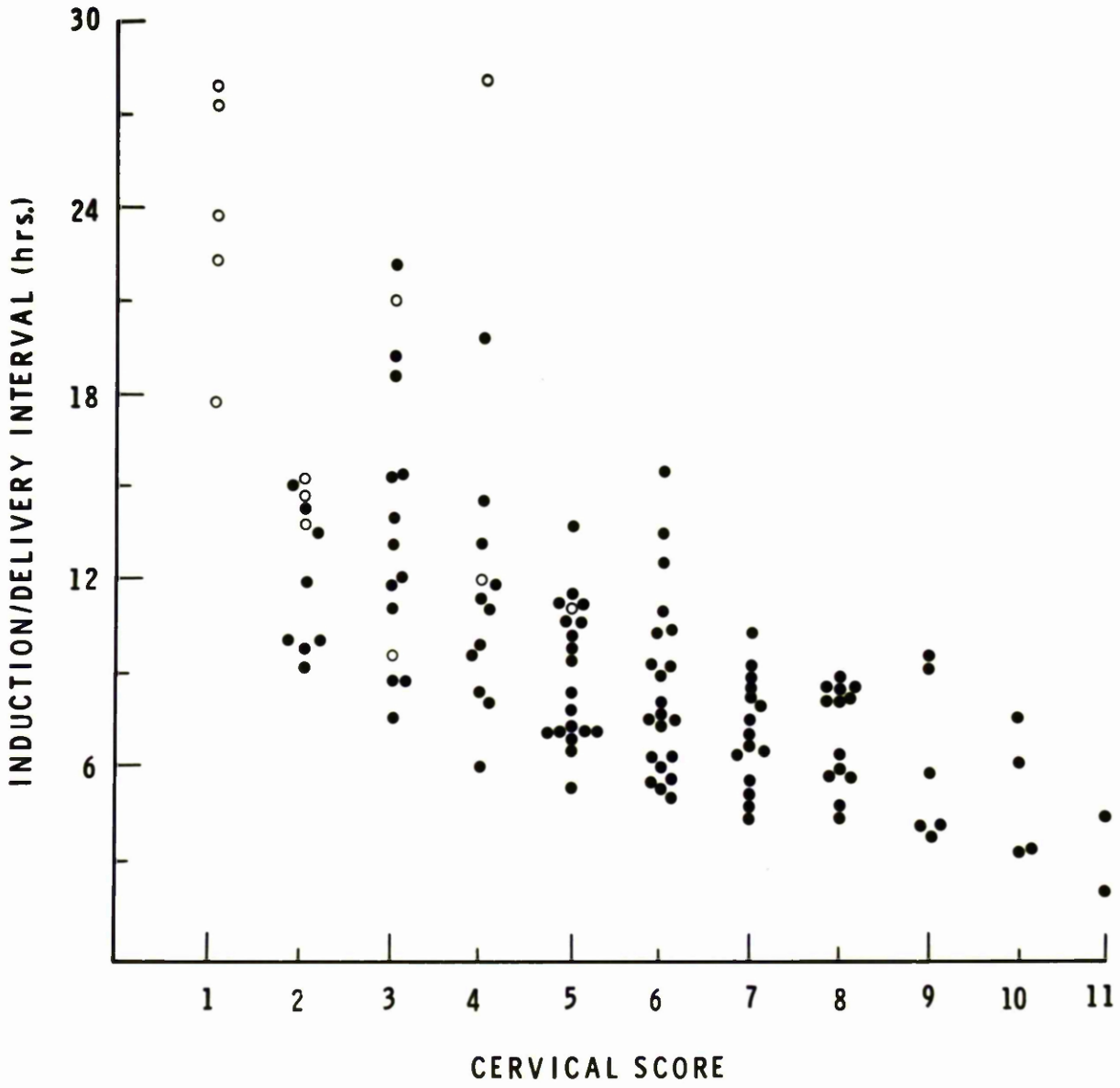


FIGURE 4.1

F I G U R E 4.2



THE FULLY AUTOMATIC CARDIFF INFUSION SYSTEM

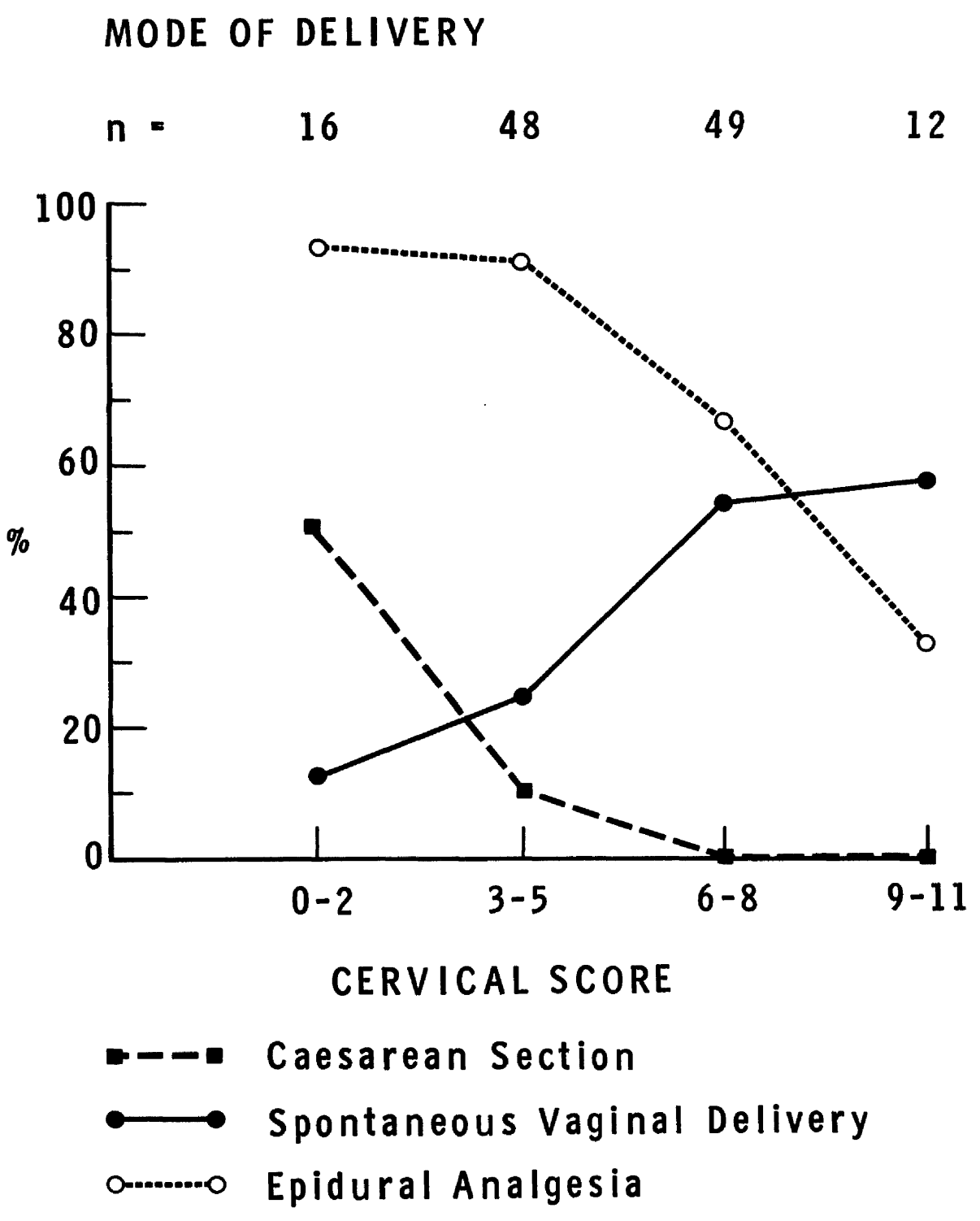


F I G U R E 4.3

Prospective Study: induction/delivery interval related to cervical score at induction (open circles represent cases delivered by caesarean section.)

Figure 4.3

FIGURE 4.4



Mode of delivery related to cervical score (the rate of forceps delivery was fairly constant at around 50 per cent).

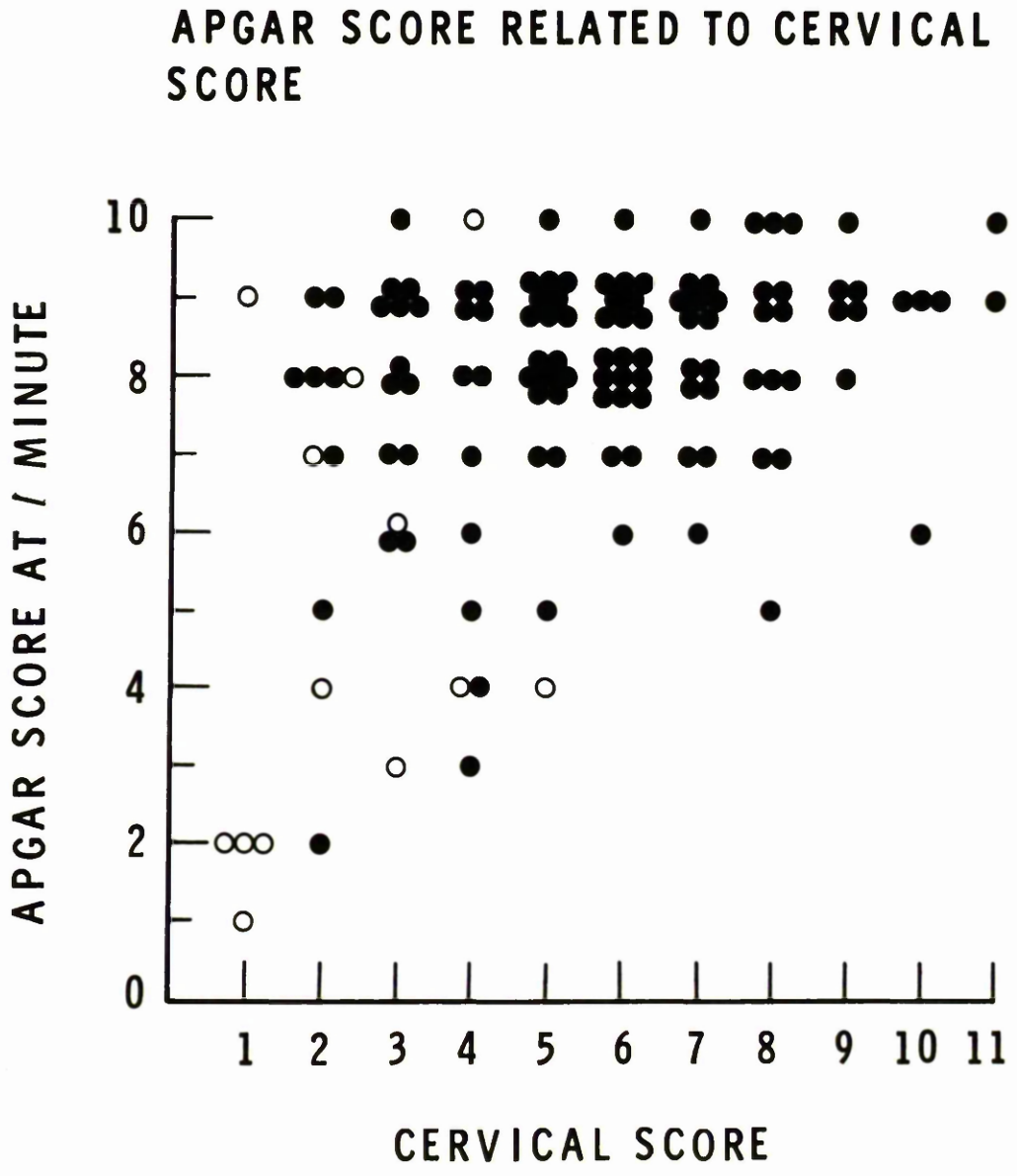
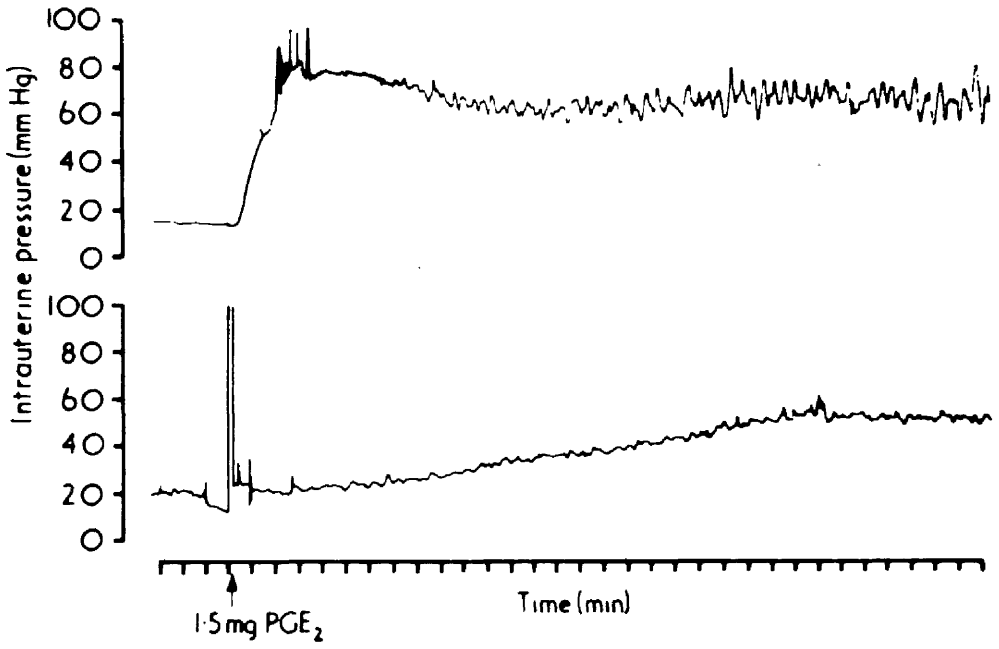


FIGURE 4.5

Prospective Study:
One minute Apgar score related to cervical score at the time of induction of labour.
(Open circles represent cases delivered by caesarean section).

FIGURE 4.5

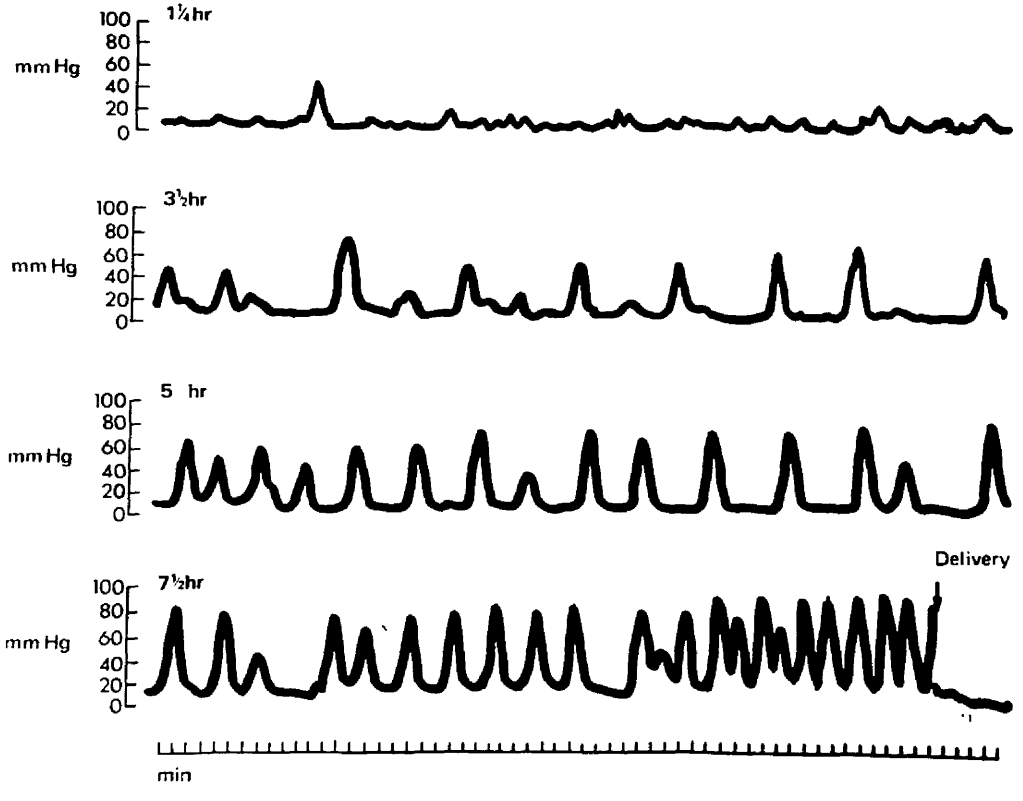
F I G U R E 6.1



Different types of uterine response to extra-amniotic prostaglandin administration in early pregnancy (from MacKenzie, Hillier and Embrey 1975).
The lower tracing shows the more usual response.

FIGURE 6.1

F I G U R E 6.2



Sections of the intra-uterine pressure record from a patient undergoing induction of labour by extra-amniotic PGE_2 infusion at 36 weeks gestation on account of intra-uterine death of the fetus. (Embrey, Calder and Hillier 1974).

FIGURE 6.2

F I G U R E 7.1

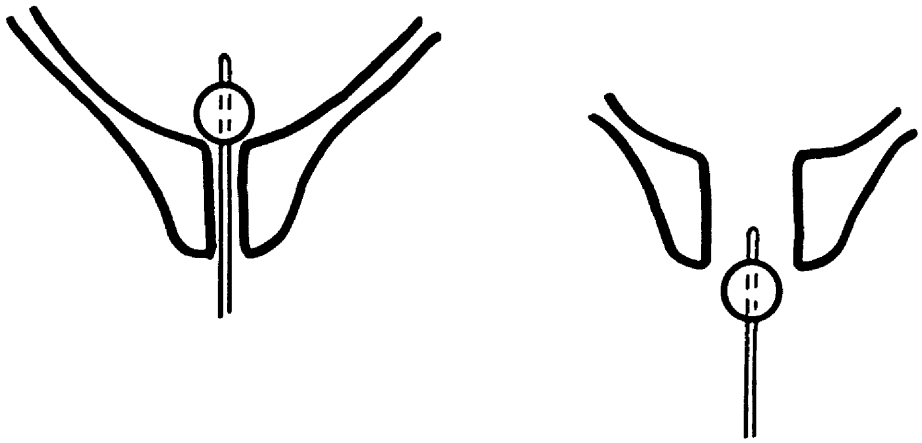
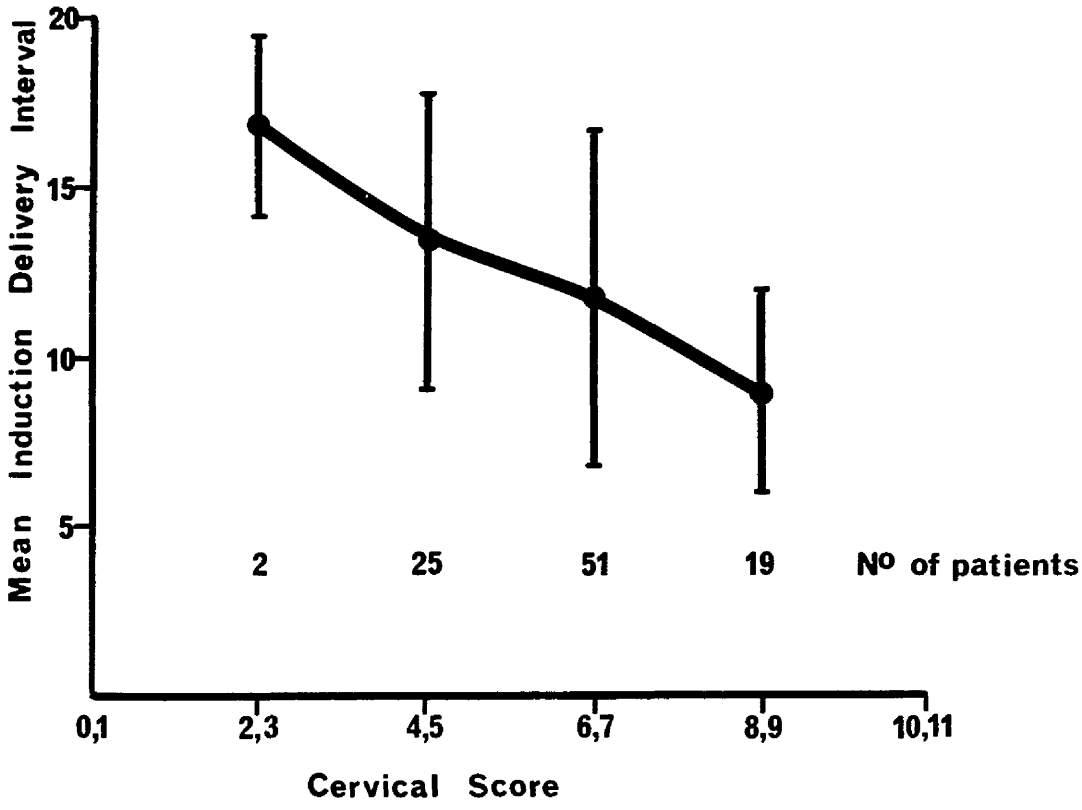


Illustration of the usual pattern of change in the unripe cervix to allow expulsion of a Foley catheter, viz. dilatation but little effacement of the cervix.

FIGURE 7.1

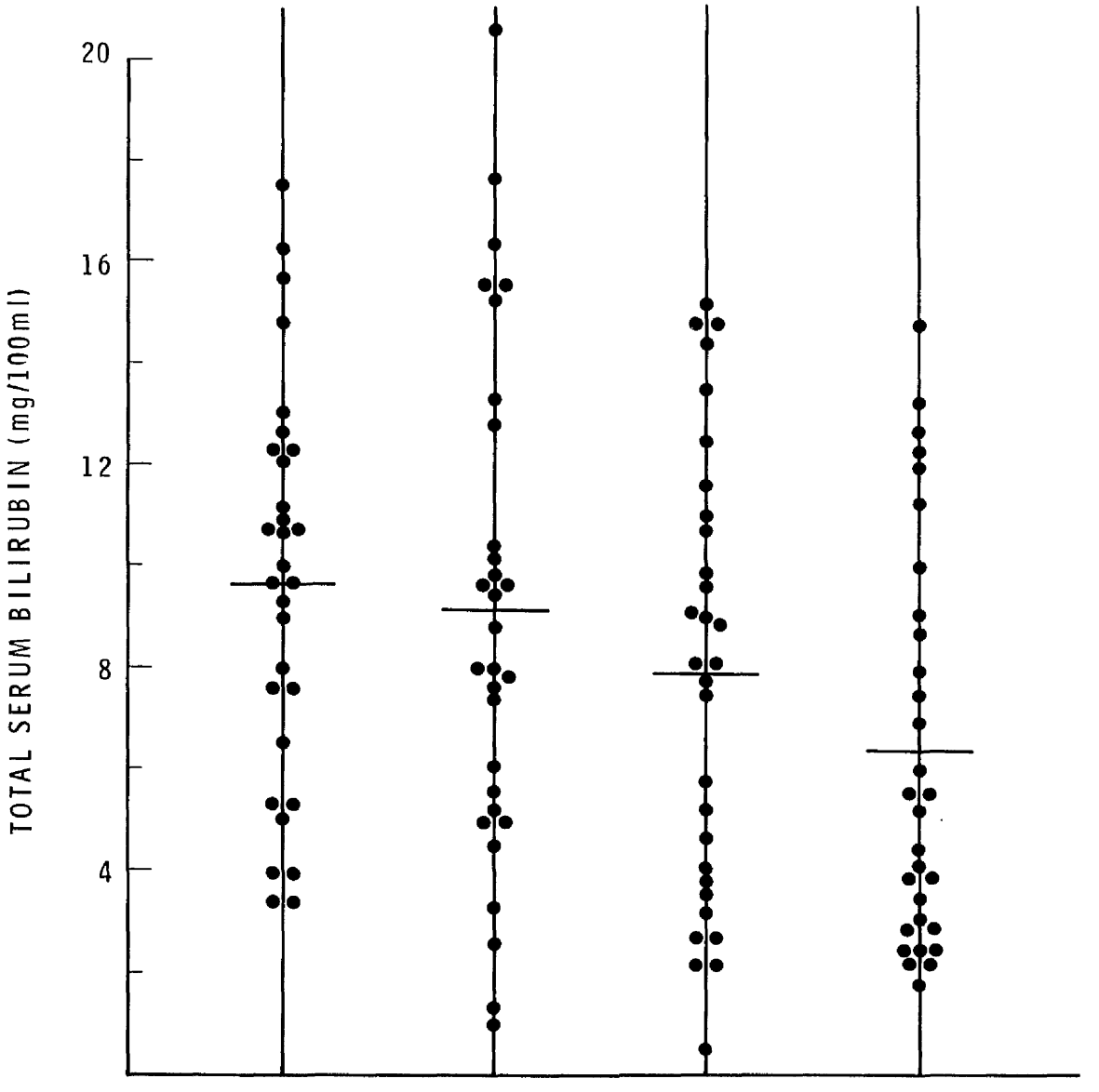
F I G U R E 7.2



Induction delivery interval plotted against the cervical score at the time of amniotomy, i.e., following ripening therapy.
(data from Calder, Embrey and Tait 1977).

FIGURE 7.2

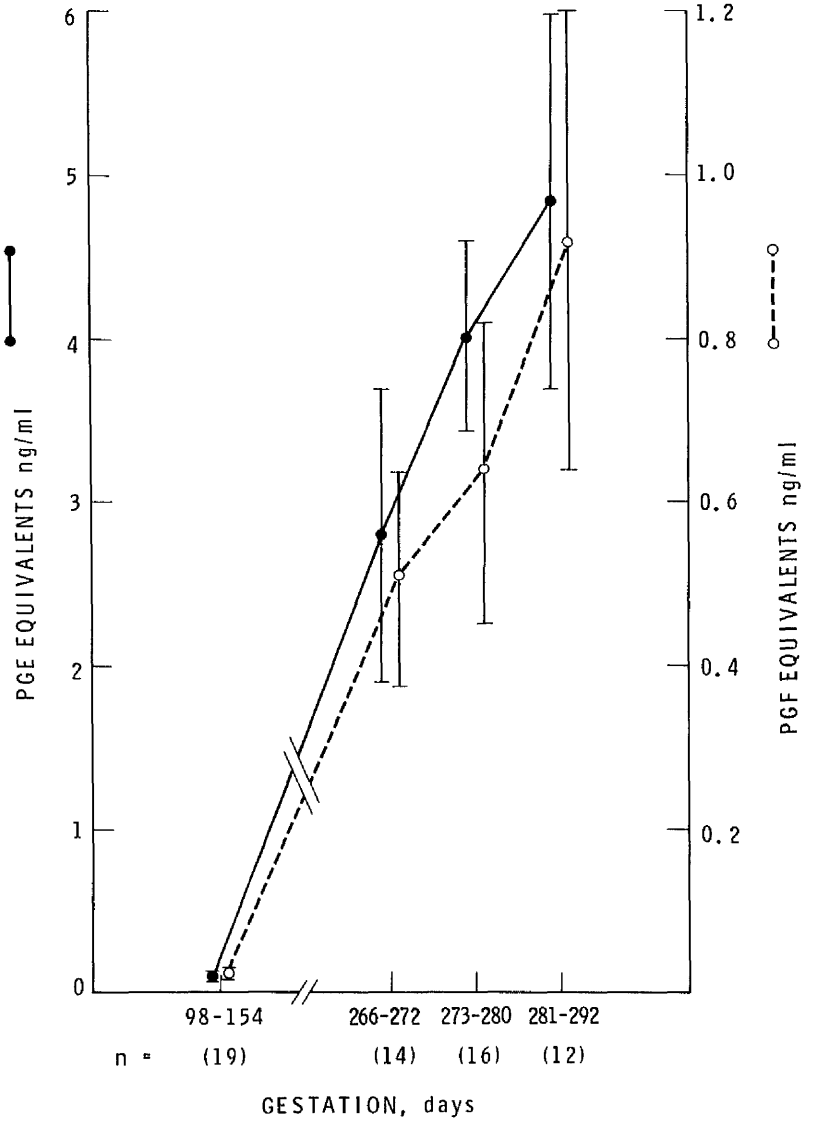
FIGURE 7.3



	Group A Intravenous Oxytocin	Group B Intravenous Prostaglandin E_2	Group C Extra Amniotic Prostaglandin E_2	Group D Spontaneous
Mean	9.6	9.1	7.9	6.4
S.D.	±3.9	±4.9	±4.4	±3.9

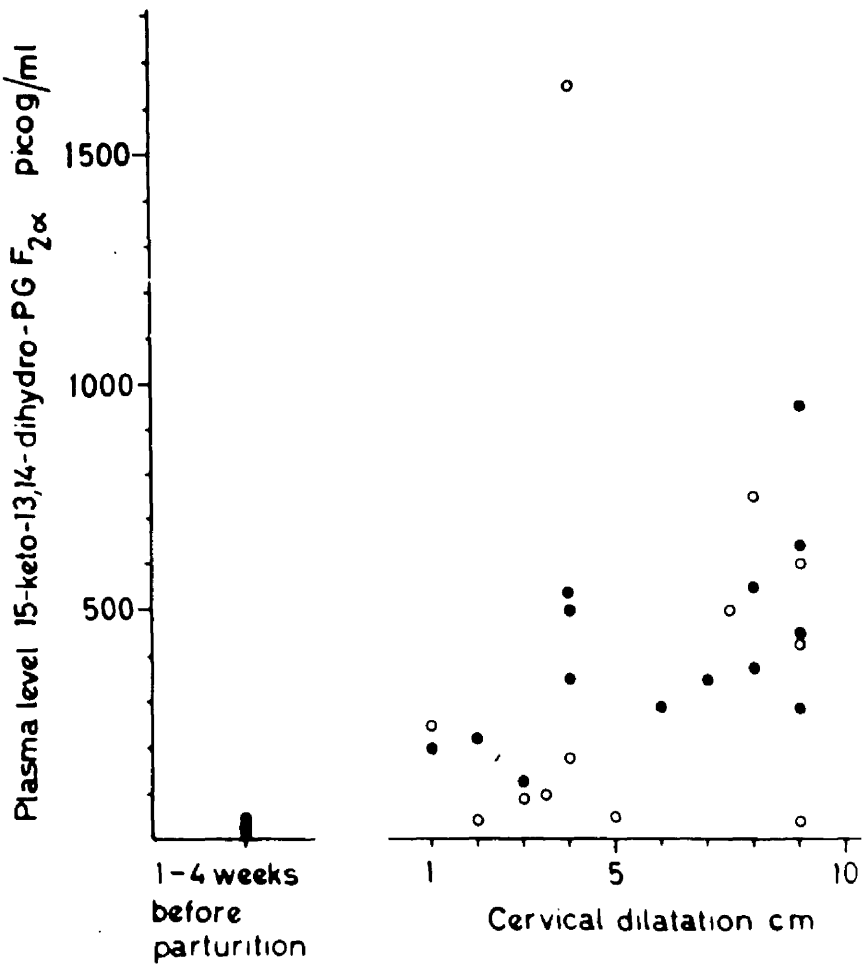
Serum bilirubin levels on day 5 from neonates of primiparous mothers whose labours were induced by one of the three methods shown or spontaneous. The horizontal bars represent the mean in each group (Calder et al 1974).

FIGURE 8.1



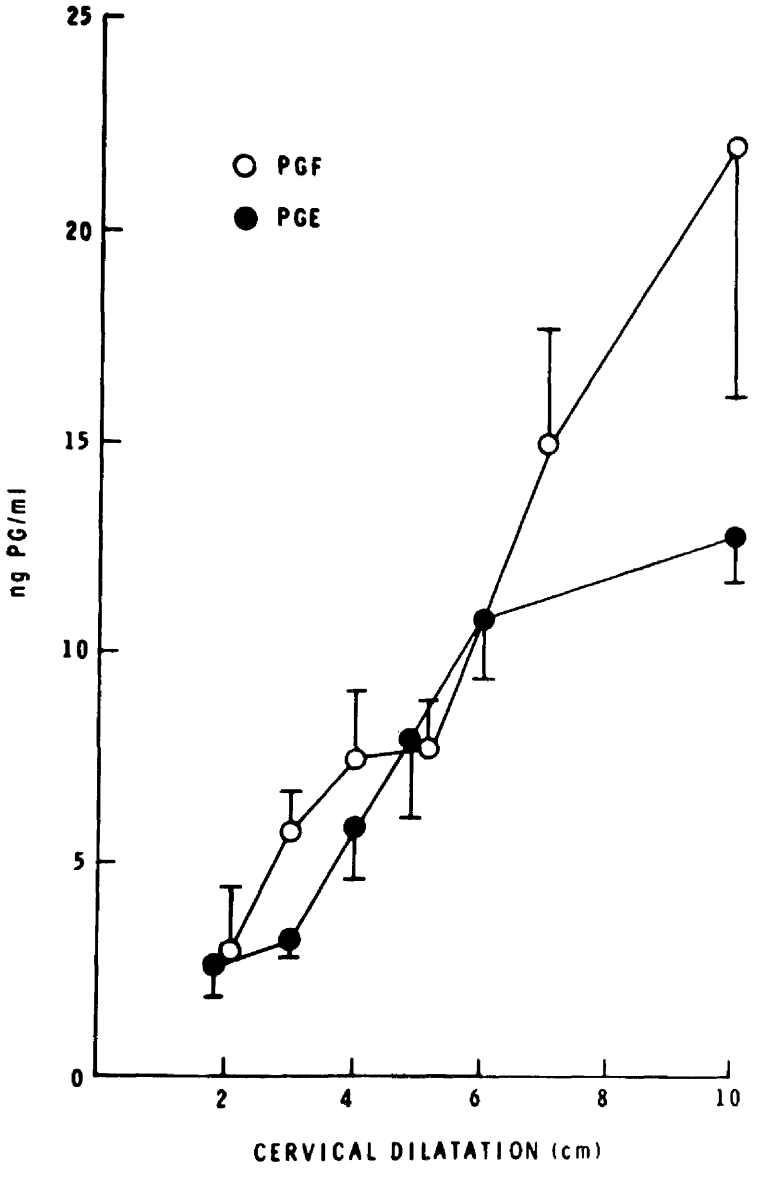
Changes in the amniotic fluid content of prostaglandins E and F in primigravidas as gestation advances. (Vertical lines indicate S.D.).

FIGURE 8.2



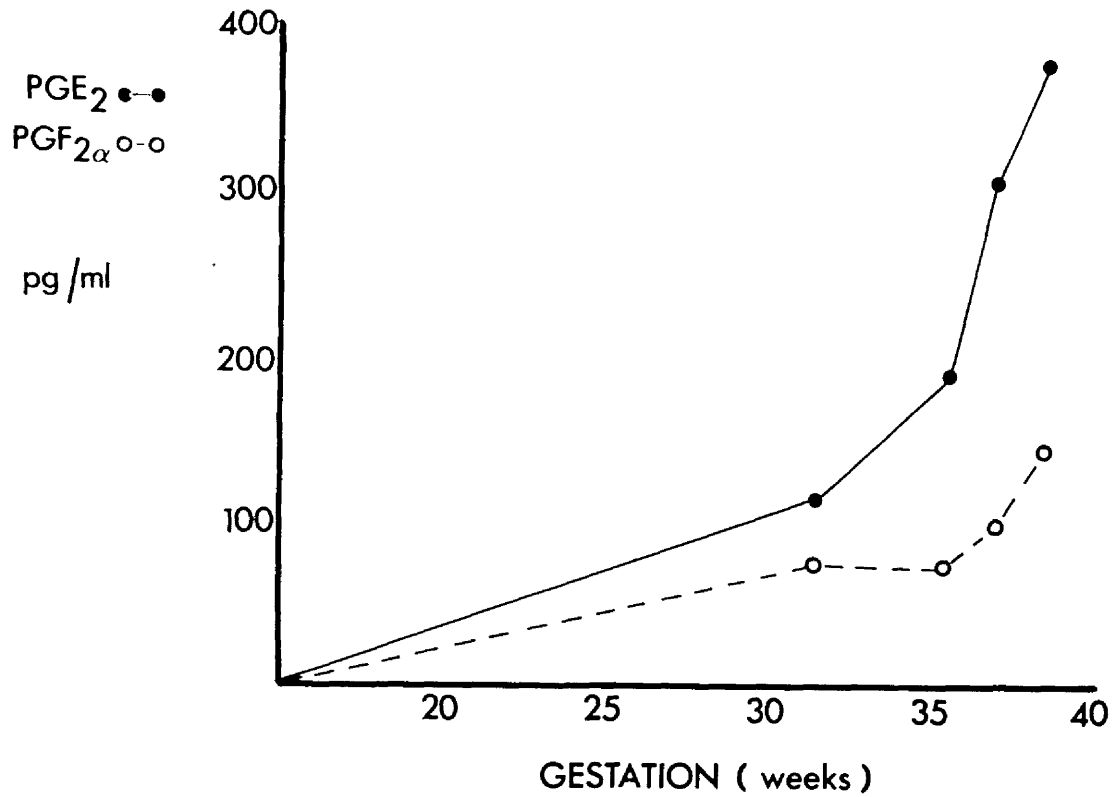
Levels of 15-keto-13,14-dihydro $PGF_2\alpha$ in the maternal circulation before and during labour.
(Green et al 1974).

FIGURE 8.3



Amniotic fluid levels of E and F prostaglandins at different stages of spontaneous labour.
(Kierse, Flint and Turnbull 1974).

FIGURE 8.4

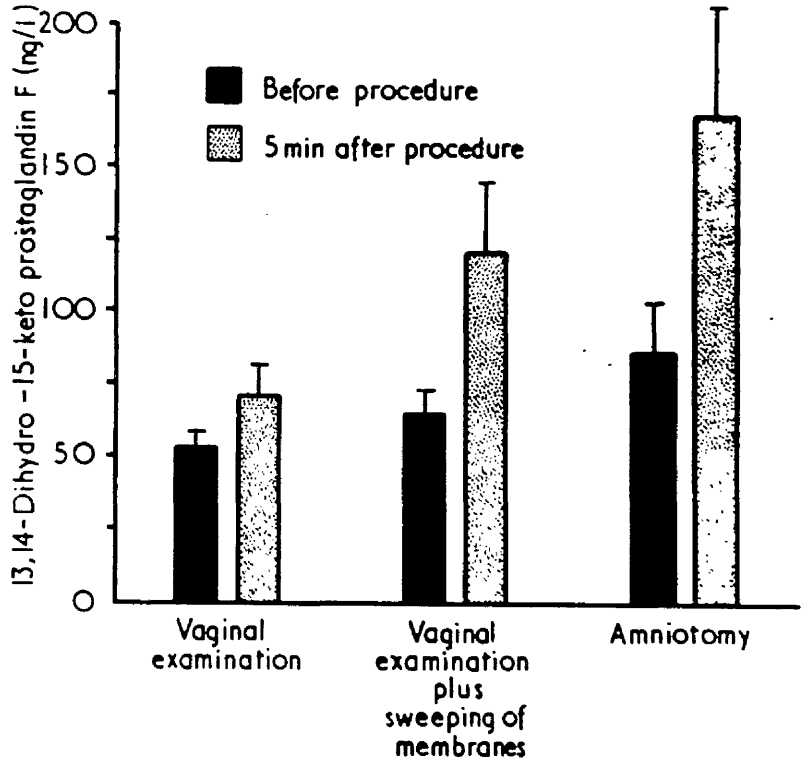


Changes in amniotic fluid PGE_2 and $PGF_{2\alpha}$ in amniotic fluid with advancing gestation (data from Dray and Frydman 1975).

Samples were obtained by amniocentesis.

FIGURE 8.4

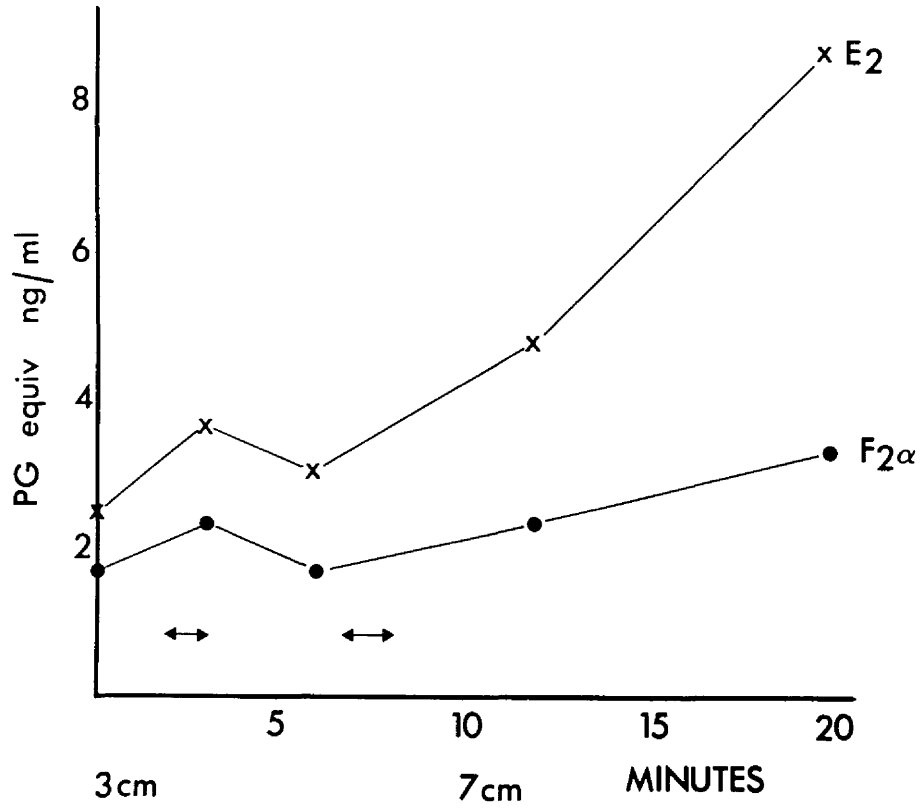
F I G U R E 8.5



Circulating levels of 15-keto-13,14-dihydro PGF before and after vaginal examination, sweeping of the membranes and amniotomy.
(Mitchell et al 1977).

FIGURE 8.5

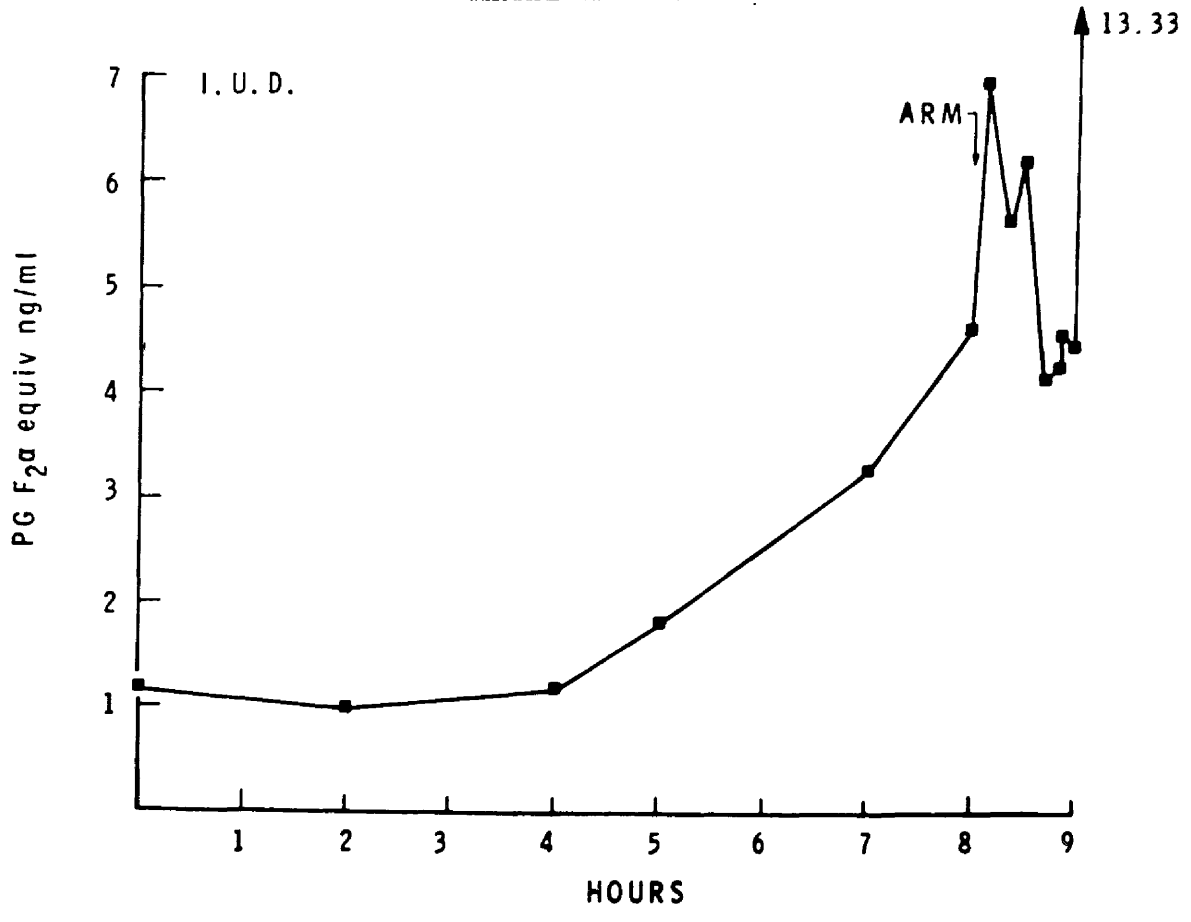
FIGURE 8.6



Levels of PGE_2 and $PGF_{2\alpha}$ in serial amniotic fluid samples from a patient stimulated with a cervical vibrator during labour. As a result of two applications of the instrument (indicated by the arrows) for 60 and 90 seconds the cervical dilatation increased from 3 to 7 cm (Calder 1975a).

FIGURE 8.6

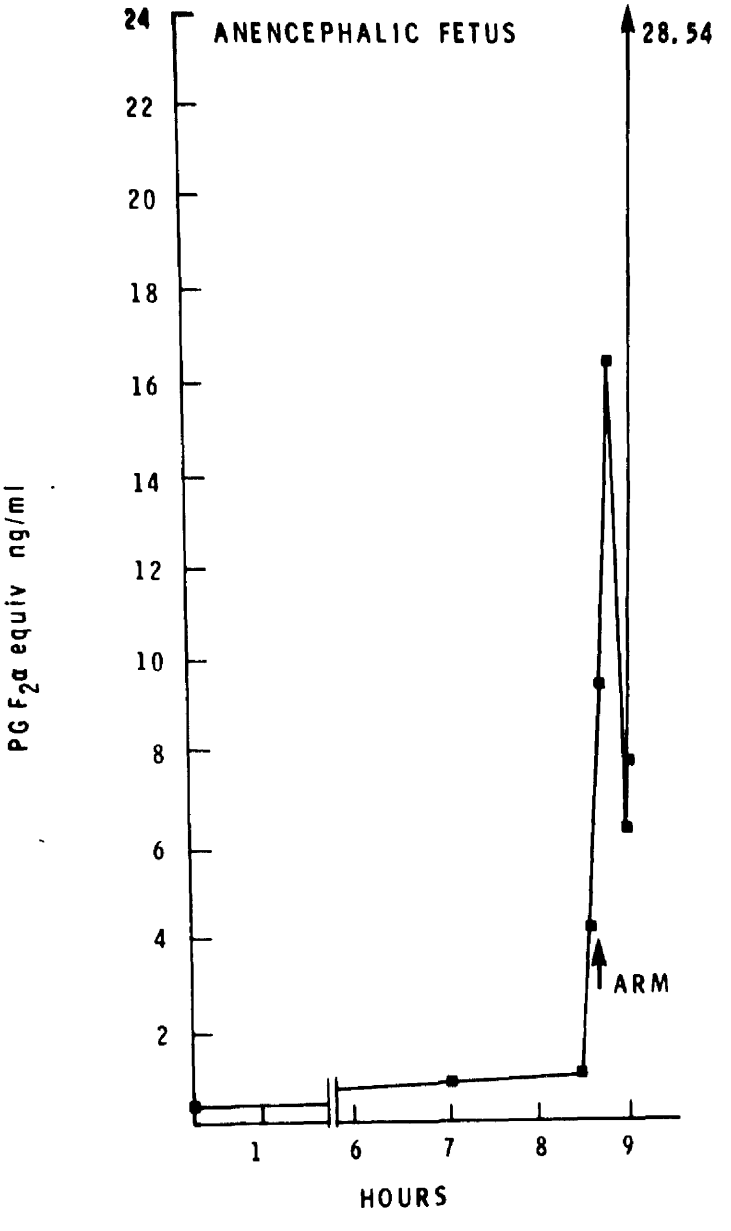
F I G U R E 8.7



Prostaglandin F levels in amniotic fluid from a case of intra-uterine fetal death during labour (Hillier, Calder and MacKenzie 1974).

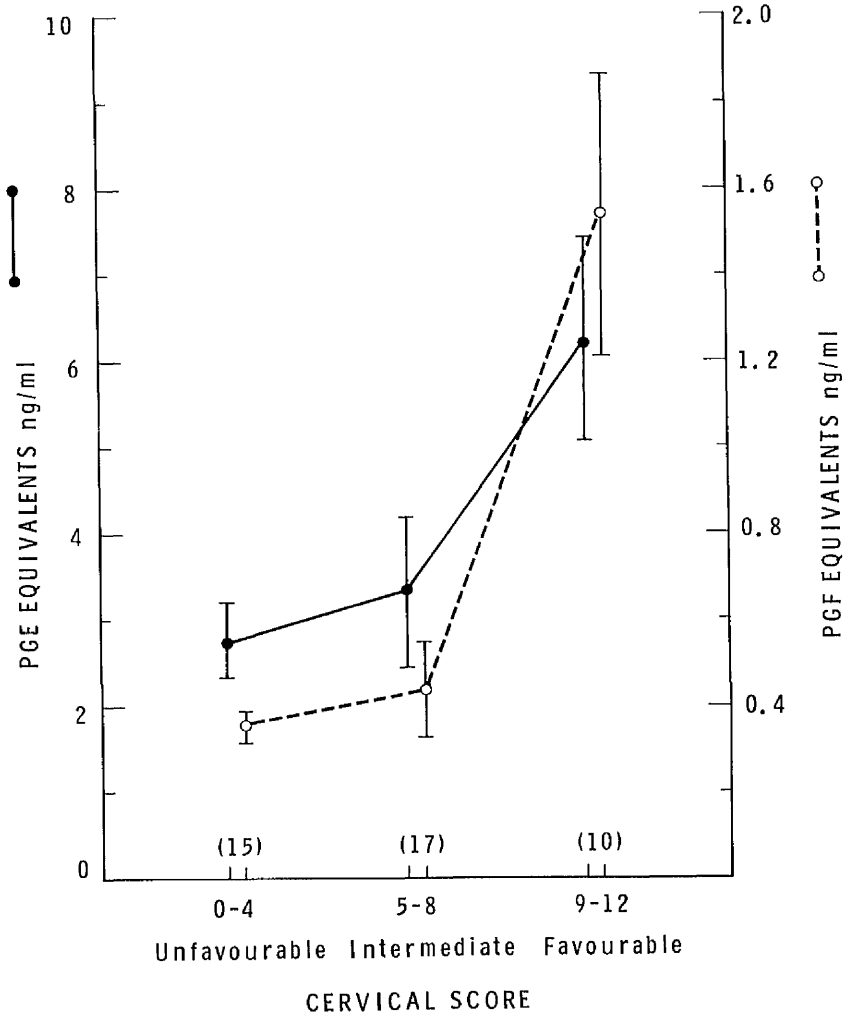
FIGURE 8.7

FIGURE 8.8



Amniotic fluid levels of prostaglandin F during labour in a case of anencephaly
(Hillier, Calder and MacKenzie 1974).

FIGURE 8.9



Levels of E and F prostaglandins in amniotomy samples of amniotic fluid in 42 primigravidae.
Results related to cervical score.
(Vertical lines indicate S.D.).

F I G U R E 8.10

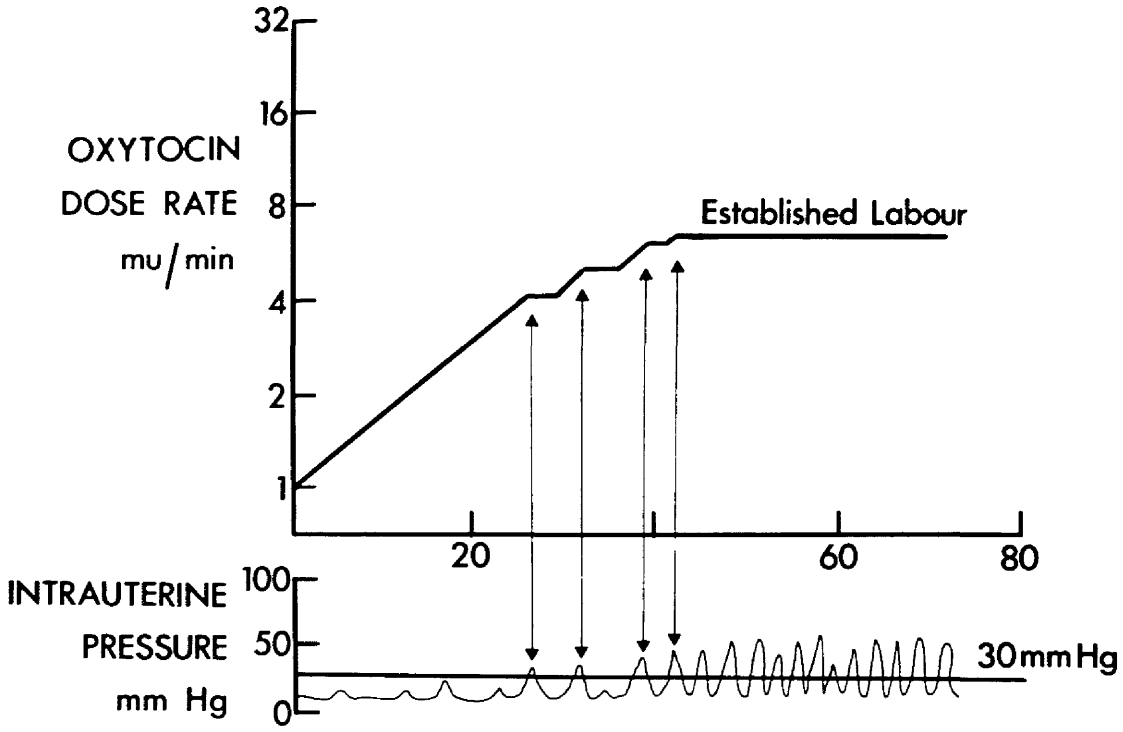
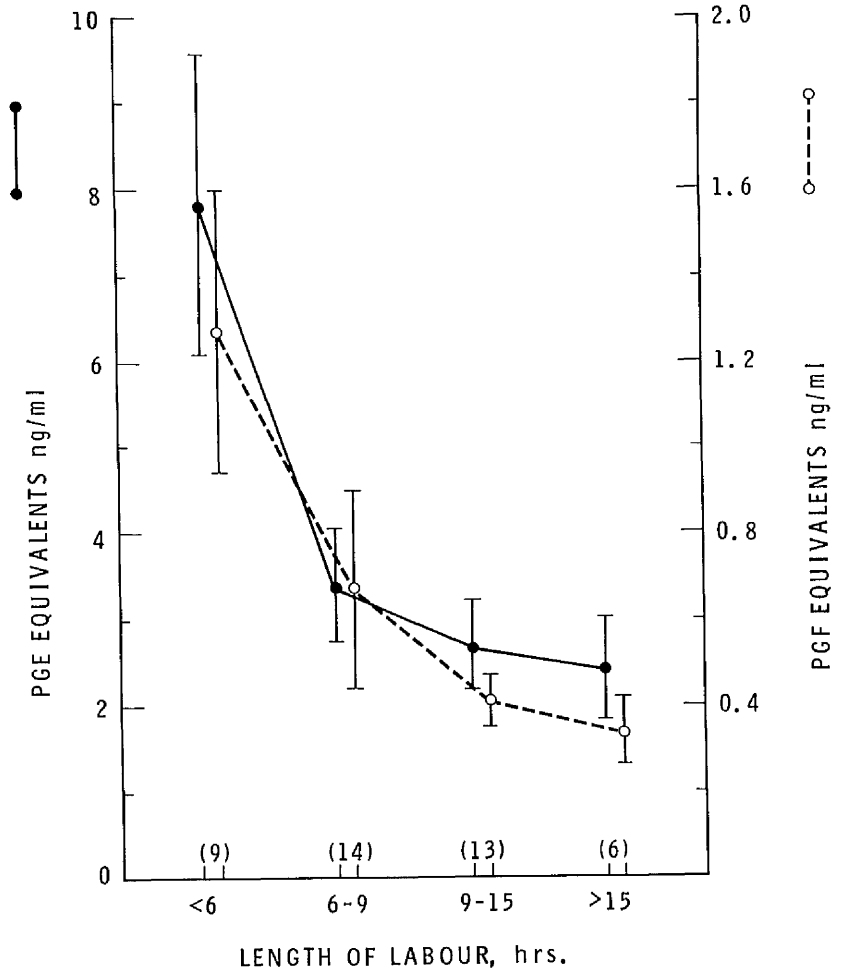


FIGURE 8.10

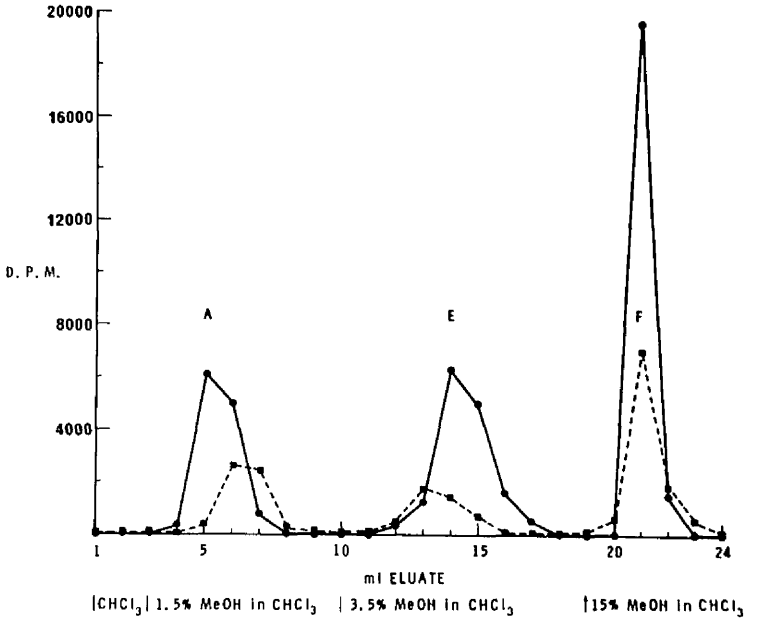
Schematic representation of the mode of operation of the Fully Automatic Cardiff Infusion System. The dose rate of oxytocin is controlled by the feedback from the intra-uterine pressure signal.

F I G U R E 8.11



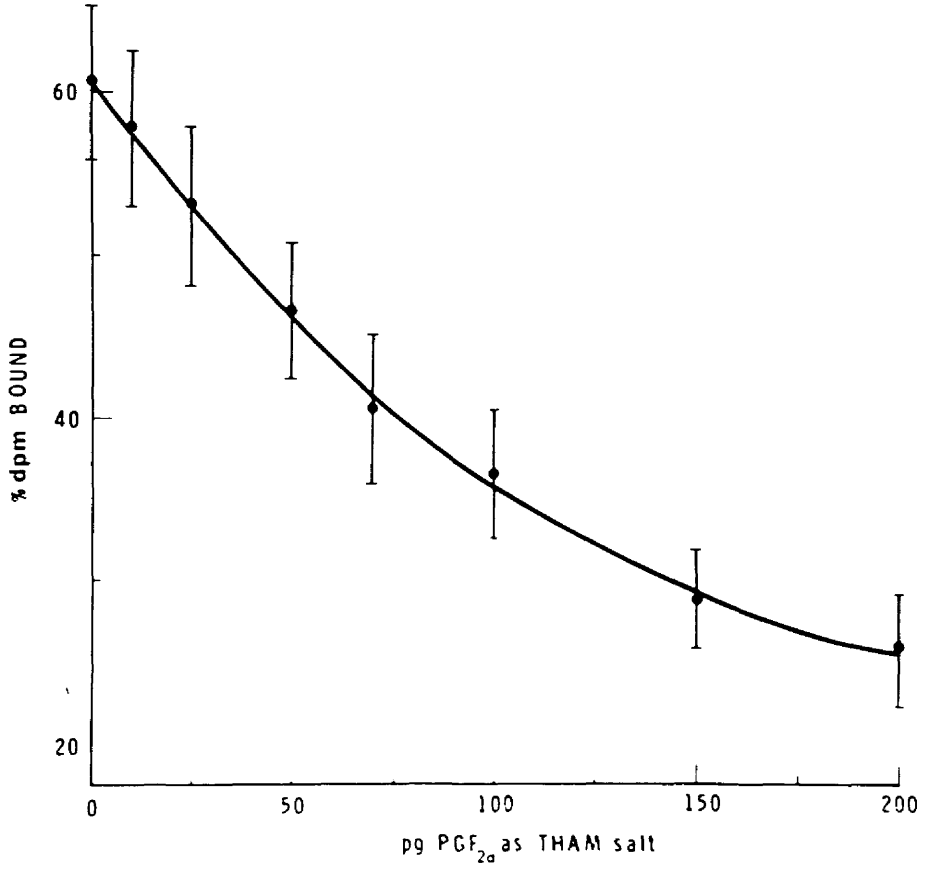
Amniotic fluid levels of E and F prostaglandins in amniotomy samples from 42 primigravidas.
Results related to subsequent length of induced labour.
(Vertical lines indicate S.D.).

F I G U R E B.1



Chromatographic separation of prostaglandins on silica gel microcolumns: the continuous line represents biological fluid and the dotted line tissue. The amounts of ^{3}H-PG added to the fluid before chromatography were: 3H-PGA, 32,960 d.p.m; ^{3}H PGE_2 29,390 d.p.m; ^{3}H-$PGF_{2\alpha}$ 35, 080 d.p.m.

FIGURE B.2



Radioimmunoassay of PGF. Displacement of ^{3}H $PGF_{1}\alpha$ (approx. 10,000 d.p.m. added) from PGF antiserum (dilution 1:500) by increasing amounts of $PGF_{2}\alpha$ Each point is the mean (± 1 S.D.) of ten assays performed in duplicate.

FIGURE B.2

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