THE ROLE OF PROSTAGLANDINS IN SPONTANEOUS AND INDUCED LABOUR

By

JONATHAN SCHER, M.B., Ch.B., M.R.C.O.G.

A thesis

Submitted to the University of Cape Town for the Degree of Doctor of Medicine

July 1974

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

University of Cape Town

"Although much has been learnt in recent years, the physiological functions of the prostaglandins remain obscure. Certainly their significance in labour can only be a matter of conjecture, their therapeutic value, if any, will be determined only after more extended study".

Embrey, M.P. (1969). The Effects of Prostaglandins on the Human Pregnant Uterus. The Journal of Obstetrics and Gynaecology of the British Commonwealth, Volume 76, pp. 783-789.

ACKNOWLEDGEMENTS

The candidate wishes to express his gratitude and indebtedness to the following persons :

Professor D.A. Davey, Head of the Department of Obstetrics and Gynaecology, University of Cape Town, without whose invaluable supervision, guidance and continuous encouragement this investigation could not have been carried out,

Dr. Peter Baillie, Senior Specialist, Department of Obstetrics and Gynaecology, University of Cape Town, for his invaluable supervision and suggestions,

Professor L. Eales, Professor of Clinical Medicine, University of Cape Town, for allowing the routine renal investigations to be performed by his laboratories,

Dr. Susan Jessop, research registrar, for performing the routine renal investigations and for her valuable advice in planning the fluid balance studies,

Dr. J.G. Burger, Superintendent of Groote Schuur Hospital, and Dr. A.W. Falconer, Superintendent of the Cape Peninsula Maternity Services, for allowing access to patients,

Miss D.H. Monk, Chief Matron of the Cape Peninsula Maternity Services, University of Cape Town, for allowing my intrusion into the labour wards under her care, viz. Groote Schuur Hospital, Mowbray Maternity Home, Peninsula Maternity Hospital and Somerset Hospital,

Miss Barbara Hendrie for her invaluable and expert nursing supervision and long hours she spent with my patients,

Mr. Peter Derriman, of the Department of Mathematical Statistics, University of Cape Town, for supervising the transfer of data on to Univac punch cards,

Miss Christine Vader, Statistician of the Department of Gynaecology, for her assistance,

Dr. Henk Rall of the Upjohn Company Ltd., for his continuing assistance, encouragement and prostaglandin supplies,

Mrs. Althea Baillie, not only for the conscientious manner in which she typed this thesis, but for encouraging its completion throughout its course,

Miss S. Katcher, Chief Librarian, University of Cape Town Medical School Library and her staff, in particular Miss G. Jacobsohn, for their tolerance regarding overdue items,

The numerous obstetric registrars and midwives for their help in channelling the patients used in this study.

The candidate further acknowledges the generous financial support of the following companies towards administrative expenses:

Upjohn, Johannesburg

Sandoz, Johannesburg

The patience, understanding and constant encouragement of my wife, Brenda, during the long hours of this study are acknowledged with gratitude.

SUMMARY OF CONTRIBUTION TO KNOWLEDGE OF THIS INVESTIGATION

The present investigation was undertaken in order to assess the clinical effects of prostaglandins and to evaluate their role in present modern day obstetrics. To this end pertinent clinical and laboratory studies were carried out. This has not been done before in the Republic of South Africa. It is considered that the following contributions to knowledge have been made:

1. In comparable patients prostaglandin $F_{2\alpha}$ and oxytocin are equally effective in labour induction at term.

2. Prostaglandin $F_{2\alpha}$ is more effective in labour induction where the cervix is unripe and amniotomy is performed.

3. Amniotomy statistically significantly increases the success rate of induction of labour where prostaglandin $F_{2\alpha}$ is used as the oxytocic agent.

4. Amniotomy statistically significantly accelerates labour in both prostaglandin $F_{2\alpha}$ and oxytocin induction, using labour parameters for comparison which have been devised and are described in the text.

5. Comparable titration schedules of prostaglandin $F_{2\alpha}$ and oxytocin have been devised for labour induction.

6. Prostaglandin $F_{2\alpha}$ is not antidiuretic when used to induce patients with classical pre-eclampsia as compared with oxytocin.

7. Prostaglandins are implicated in the acceleratory phase of normal labour.

8. The only statistically significant side effect produced by prostaglandin $F_{2\alpha}$ when compared with oxytocin is a transient red line in the skin along the area draining the site of the intravenous infusion.

9. Prostaglandin $F_{2\alpha}$ does produce a coordinate form of labour if certain precautions are adhered to.

10. Effacement of the cervix in the latent phase has been measured and may be used in order to predict the rate of progress in the first stage of labour in primigravidae. The results are presented in the text.

INDEX

PART 4

PART 5

PART 1

INTRODUCTION AND REVIEW OF THE LITERATURE

1.1 INTRODUCTION

Folk lore in certain parts of Africa, including Liberia, Zambia and in parts of the Congo, suggests that prostaglandins have been in use clinically in obstetrics for centuries. In these parts it is said that if a woman's labour is prolonged her husband is summoned and a delicate potion is prepared using an aliquot of his seminal fluid. The potion is then administered orally and is reported to have accelerated the course of labour.

From a pharmacological standpoint, however, the pharmacodynamic effects of extracts from seminal fluid and male accessory organs were discovered by Goldblatt (1933, 1935) of St. Thomas's Hospital, London and Von Euler (1934).

They independently found that this material contains a blood pressure-lowering factor and that it stimulates different smooth muscle organs. Von Euler (1936) later demonstrated that these effects were due to a lipid-soluble substance with acidic properties, which he called prostaglandin (Von Euler, 1935). He called it by this Greek word as he thought it originated from the prostate gland. He stated that 'the ether and water soluble substance, which has the effect of lowering blood pressure and stimulating various isolated smooth muscle organs is provisionally named prostaglandin'.

Ironically enough this is a misnomer, for in 1959 it was shown, by fractionation of ejaculates, that the source of prostaglandin was the seminal vesicles and not the prostate gland (Eliasson, 1959).

1.2 HISTORICAL BACKGROUND

In 1935 M.W. Goldblatt wrote 'the possibility that seminal plasma may have functions other than those of nutrition of the spermatozoom and of mechanically sweeping out the latter from the urethra is suggested by recent work of Von Euler (1934) and Goldblatt (1933)'.

The former worker employed human seminal fluid whilst the latter used both the native fluid and extracts made with aqueous alcohol and aqueous acetone. Goldblatt (1935) showed seminal plasma and extracts to have powerful oxytocic activity on the uterus of the virgin guinea-pig in a 30cc bath of oxygenated Tyrode solution. He could not ascribe a role to this substance in human seminal fluid which produced strong vasodilatation and stimulation of smooth muscle, but he felt it improbable for it simply to be an excretory product without physiological function. 'The composition of seminal plasma is so peculiar when compared with other body fluids and so specially adapted to the functions of nutrition and mobilization of the sperm cells that the presence of a substance with marked pharmacological properties can scarcely be regarded as fortuitous'.

The first reference, however, to the existence of these compounds was made by Raphael Kurzrok, Charles C. Lieb and Sarah Ratner, from the Departments of

Biochemistry, Pharmacology and Obstetrics and Gynaecology, Columbia University in 1930. In a paper entitled 'The Action of Semen on the Human Uterus', Kurzrok had noted that when attempting artificial insemination by injecting 0.5ml of semen into the uterine cavity, it was promptly expelled (Kurzrok & Lieb, 1930). This did not occur when Ringer's solution was used. Using human uterine muscle strips they found that the response of the human uterus to semen is variable, causing either relaxation or contraction. These workers were primarily interested in the relationship to fertility of this uterine response.

A few years later, on 15th December, 1933, M.W. Goldblatt read a paper to the 159th meeting of the Biochemical Society in the Medical Lecture Theatre, St. Thomas's Hospital Medical School, in which he had observed the powerful contraction of the isolated guinea-pig uterus when an alcohol or acetone extract of human seminal fluid was applied to it (Goldblatt, 1933).

At about the same time, Von Euler of the Karolinska Institutet observed independently (1934, 1935) that 'extracts and secretions from the human prostate gland and seminal vesicles, as well as seminal fluid, greatly lower the blood pressure after injection into animals and even, in small amounts, stimulate the isolated intestine and the uterus (Von Euler, 1936).

As mentioned before he called this extract from the human seminal fluid, prostate and seminal vesicles, prostaglandin, and extracts from the seminal vesicles alone he called vesiglandin, as he felt it differed distinctly from prostaglandin (Von Euler, 1936).

It must not be forgotten that even prior to the work of Kurzrok & Lieb in 1930, biological actions of extracts from the accessory genital glands had been described several times before (Japelli & Scafa, 1906; Thaon, 1907; Camus & Gley, 1907; Götzl, 1910; Dubois & Boulet, 1911, 1919; Battez & Boulet, 1913) but these older demonstrations received no great attention, probably because the experimental data did not permit of definite conclusions as regards the nature and specificity of the active constituents.

Von Euler (1936) went on to describe a technique for prostaglandin extraction and purification by precipitating inert material with acid, alcohol or acetone and then extracting the active principle with ether from the acidified water solution. He found that the prostaglandin stimulated isolated strips of the human uterus, as well as animal uterus. By extraction with ether he excluded that this effect was due to histamine as Goldblatt had suggested in 1935. After extensively studying the biological properties of

prostaglandin obtained from human seminal fluid and sheep vesicular glands, Von Euler attributed a physiological role to these substances and felt that they probably were autonomic regulators for emptying the accessory genital glands i.e. when the smooth muscle stimulating principle had accumulated sufficiently it would act as a stimulus for emptying the glands.

Early chemical work in elucidating the structure of prostaglandins was carried out by Bergström (1949) who obtained a stable barium prostaglandin preparation. He confirmed Von Euler's findings that the biological activity was due to a new group of highly active lipid-soluble unsaturated hydroxy acids.

In 1959 Eliasson from the Department of Physiology, Karolinska Institutet, Stockholm, found that the prostaglandin present in seminal fluid in man was secreted exclusively from the seminal vesicles. This was shown by analysis of various constituents in the different fractions of split ejaculates (Eliasson, 1959).

He also found that prostaglandin may be of importance for the motility of the spermatazoa and may facilitate sperm migration in the female genital tract. Prostaglandin was found to produce, in most cases, an

increase in tone and activity of various smooth muscle organs. This,however, was not the case with the isolated human non-pregnant uterus, where it caused a decrease in activity and tone.

At the suggestion of Professor Von Euler in 1947 Professor Bergström started an investigation of the purification of a concentrate prepared by I.G. Farben from Icelandic sheep glands but only a small amount of material was available. The activity was shown to be associated with a fraction containing unsaturated hydroxy acids, which Bergström (1967) felt consisted mainly of a mixture of prostaglandins.

For technical reasons the project was laid aside until 1956 when the collection of frozen sheep glands was organised in the Northern Hemisphere. Thus it was not until the late 1950's that it was realised that prostaglandin was not a single substance but a mixture of several chemically related substances. This probably accounts for the variable results found before. The isolation in pure crystalline form from vacuum dried sheep prostate glands of the first 2 prostaglandins was described by Bergström & Sjövall (1960a, 1960b) in the

Department of Chemistry, Karolinska Institutet, Stockholm, Sweden, in 1960. These 2 prostaglandins are now called PGE_1 and $PGF_{2\alpha}$.

In 1962 their chemical structure was elucidated (Bergström, Ryhage, Samuelsson & Sjövall, 1962). Analysis of the first few milligrams by ultramicro-analysis and mass spectrometry proved that these substances were C_{20} compounds possessing a unique structure (See Figure 1, page 12). Several related prostaglandins have since been isolated from human seminal plasma and sheep vesicular glands and their chemical structure elucidated. PGE_2 and PGE_3 were subsequently isolated from the sheep glands. Mass spectrometry and nuclear-magnetic response yielded most of the complete structure (Samuelsson, 1963). They were identical with PGE_1, except that they contained respectively 1 and 2 additional cis double bonds (See Figure 2, page 12). The corresponding $PGF_{2\alpha}$ and $PGF_{3\alpha}$ were first isolated from sheep and bovine lung tissue (Samuelsson, 1964).

The structure of the 6 primary prostaglandins has been demonstrated in a number of different tissues. They occur in low concentrations, however, compared to the human seminal fluid which is the richest known source. Human seminal fluid contains 13 different

prostaglandins. These are the 5 initially recognised prostaglandins mentioned above: PGE_1, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ (Bergström & Samuelsson, 1962; Samuelsson, 1963) and the recently isolated additional 8 compounds: PGA_1, PGA_2, PGB, PGB_2, 19-hydroxy-PGA, 19-hydroxy-PGA_2, 19-hydroxy-PGB and 19-hydroxy-PGB_2 (Hamberg & Samuelsson, 1966).

The elucidation of the structure of the 6 primary prostaglandins led to the speculation that the essential fatty acids might be the natural precursors for the prostaglandins. That this was the case was proven by Dr. Van Dorp's group in the Unilever research laboratories in Holland, by Bergström's group in Sweden and by a group at the Upjohn Company in the U.S.A. This discovery in its turn led to the biosynthetic production of the primary prostaglandin compounds. Following this the total chemical synthesis by several methods was brought to practical use during the late 60's.

A new field of active analogues of prostaglandins is appearing and this should develop rapidly. At the time of the preparation of this thesis, however, only the primary prostaglandin $F_{2\alpha}$ was available to the author.

The early work on the physiological properties of prostaglandin was done with extracts of sheep vesicular glands or human seminal plasma as mentioned above on page 7. It was mainly limited to the cardiovascular

system and to the reactions of smooth muscles in the intestines and in the female reproductive tract.

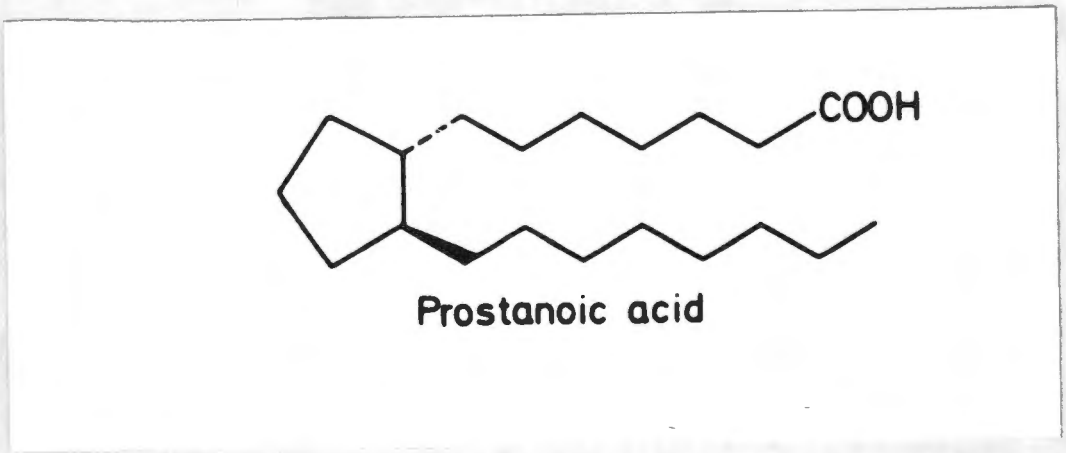
The physiological properties of the many prostaglandin compounds that have been isolated subsequently and the achievement of biosynthetic production and total chemical synthesis of the prostaglandins has led to the study of prostaglandins in many laboratories, so that the publications are exhaustive. As this thesis is concerned with the role of prostaglandins in reproduction a review of the wide variety of actions of these substances is outside its scope. A good review of the actions of prostaglandins has been prepared by Horton (1969). Even since that review newer and more varied physiological roles have been attributed to the prostaglandins and these were presented at an International Conference on Prostaglandins in Vienna in September, 1972 (Bergström, 1973).

1.3 SUMMARY ON NOMENCLATURE

The cyclopentane fatty acid, prostanoic acid, forms the carbon skeleton of most prostaglandins (See Figure 1).

FIGURE 1

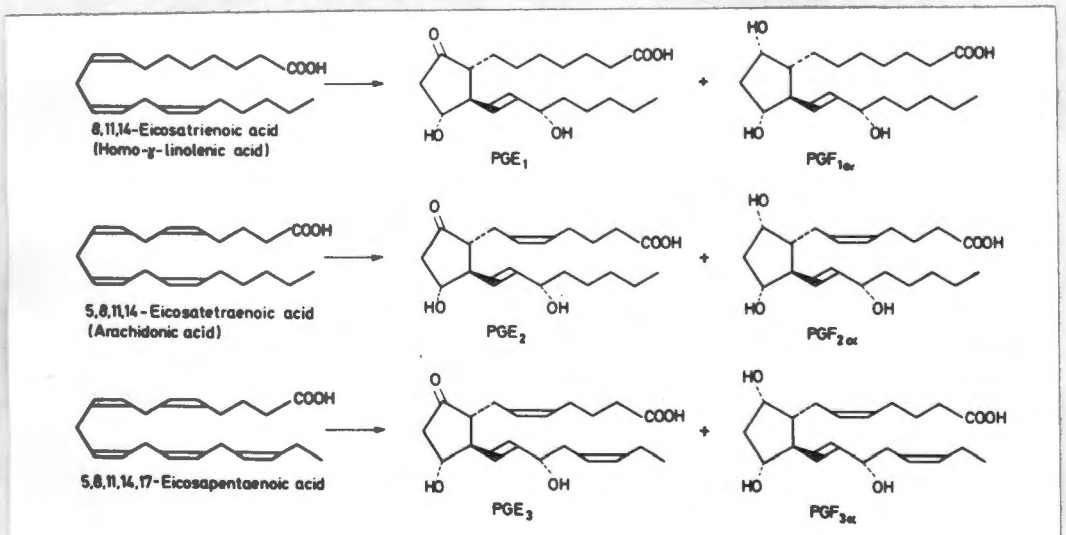
PROSTANOIC ACID



The group of 'primary prostaglandins' consists of 6 prostaglandins which are formed by conversion of 8, 11, 14-Eicosatrienoic acid (homo -ϑ- linolenic acid): PGE_1 and $PGF_{1\alpha}$; 5, 8, 11, 14-Eicosatetraenoic acid (arachidonic acid): PGE_2 and $PGF_{2\alpha}$; and 5, 8, 11, 14 17-Eicosapentaenoic acid: PGE_3 and $PGF_{3\alpha}$ (See Figure 2).

FIGURE 2

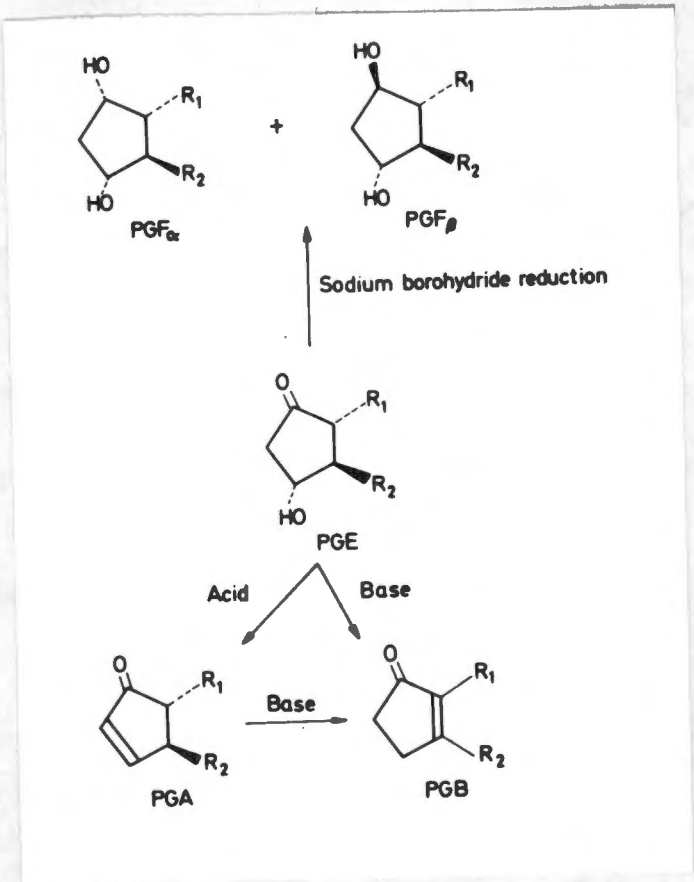
BIOCONVERSION TO 'PRIMARY PROSTAGLANDINS'



The chemical relations between PGE, PGF, PGA and PGB compounds are given in Figure 3.

FIGURE 3

CHEMICAL RELATIONS BETWEEN PGE, PGF, PGA AND PGB



The letters E and F in PGE and PGF refer to an early finding that PGE and PGF compounds could be partly separated by extraction with ether from phosphate buffer. The PGE compounds mainly appeared in the ether phase, whereas the PGF compounds mainly stayed in the phosphate (fosfat, in Swedish) buffer. The letters A and B in PGA and PGB refer to the formation of these derivatives from PGE compounds by acid and base treatment respectively (Hamberg, 1973).

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was used in this study. It is a C_{20} prostaglandin and its systematic name is 9, 11, 15L - Trihydroxyprosta - 5 cis, 13 trans - dienoic acid. It was supplied by the Upjohn Company in ampoules containing aqueous solutions of 5mg/ml $PGF_{2\alpha}$ equivalents as the THAM salt.

1.4 PROSTAGLANDINS IN PARTURITION

Effects of Prostaglandins in Seminal Plasma on the Human Uterus:

The 3 PGE compounds (PGE_1, PGE_2 and PGE_3) all decrease tonus, frequency and amplitude of the spontaneous motility of human non-pregnant myometrium in vitro (Bygdeman, 1967). The effect of the 2 PGF compounds ($PGF_{1\alpha}$ and $PGF_{2\alpha}$) differs and causes stimulation. Their effect is characterised by an increase in tonus, amplitude and frequency.

Eglington, Pickles and their colleagues, however, (Eglington et al, 1963; Pickles & Hall, 1963; Pickles et al, 1965) found that $PGF_{2\alpha}$ invariably increased the contractions of human non-pregnant myometrium, while PGE_2 gave a variety of effects, varying from mild stimulation to complete inhibition.

Pregnant myometrium reacted differently from non-pregnant myometrium to the prostaglandin compounds. Small doses of prostaglandin E_1 (0.01 - 0.03 µg/ml bath fluid) in some cases stimulated motility, the effect on tonus being most pronounced. An increase dose (0.03 - 0.1 µg/ml) gave the normal inhibition. The PGF compounds stimulated the motility in a similar way as with non-pregnant myometrium (Bygdeman, 1964). In 1968

Embrey & Morrison studying human pregnant myometrium in vitro found that while lower segment myometrium was relatively inactive, well marked effects were observed with upper segment myometrium (Embrey & Morrison, 1968). Not only did the F prostaglandins ($PGF_{1\alpha}$ and $PGF_{2\alpha}$) exhibit stimulatory effects but, for the first time, it was shown that, contrary to expectation, E group prostaglandins (PGE_1, PGE_2) also produced spasmogenic effects on pregnant myometrium.

Embrey (1969) then confirmed these results in a study on the intact uterus in pregnancy. Both the E and F prostaglandins stimulated myometrial contractility. In late pregnancy both PGE_2 and $PGF_{2\alpha}$ produced significant increases in the amplitude and frequency of contractions without, in the dosage used, causing appreciable hypertonus or undesirable side effects. The findings previously reported in vitro were thus corroborated. Embrey (1969) found the striking oxytocic effects of the E prostaglandin on the uterus in pregnancy of particular interest - because it differs from its reported inhibitory action in the non-pregnant state, emphasising that the effect of a pharmacological agent is influenced by the physiological state of the organ. The sensitivity of the human myometrium to the prostaglandins not only varies as to whether it is pregnant or not but also with the stage of the menstrual cycle.

The inhibitory effect of PGE is most pronounced around ovulation time and less during other phases of the menstrual cycle (Bygdeman, 1964).

Because of the action which prostaglandins seem to exert on the human myometrium, a great interest in the relationship of these compounds to labour was aroused.

Amniotic fluid is rich in prostaglandins (Karim, 1966). Prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ are only found in liquor during labour. There is an increased amount of PGE_2 in the liquor during labour as over term. Prostaglandins E_2 and $F_{2\alpha}$ are found in the maternal circulation only during labour (Karim & Devlin, 1967; Karim, 1968a). Gillespie et al (1972) investigated the possibility that prostaglandins cause the release of oxytocin from the maternal pituitary in a manner which corresponds closely to that found in spontaneous late first stage labour.

Brummer (1971) demonstrated that after exposure to the E prostaglandin, human pregnant myometrial strips in vitro show a greater contractile response to a given dose of oxytocin than before the exposure to prostaglandin. This phenomenon is termed enhancement. Gillespie (1972) confirmed this phenomenon in vivo and in addition demonstrated a 'potentiation' of effects if prostaglandin E or F is administered simultaneously with oxytocin.

Labour was successfully induced in 29 out of 35 women at or near term with a continuous infusion of $PGF_{2\alpha}$ by Karim et al (1969b).

Since then there have been many reports of the successful induction of labour with prostaglandins $F_{2\alpha}$, E_1 and E_2 (Karim et al, 1970; Beazley et al, 1970; Embrey, 1970). Vakhariya & Sherman (1972) felt that $PGF_{2\alpha}$ is as effective as oxytocin for the induction of labour in multiparous patients at term. Karim (1971) reported 96%, 67% and 56% success rates in 100 inductions each with PGE_2, $PGF_{2\alpha}$ and oxytocin respectively. Embrey (1969, 1970) found the effects of PGE_2 and $PGF_{2\alpha}$ to be qualitatively similar, but dose for dose the stimulating properties of PGE_2 were greater than those of $PGF_{2\alpha}$ in late and early pregnancy.

Beazley & Gillespie (1971) induced labour in 150 patients each with PGE_2 and oxytocin, with a success rate of 73% for both drugs. Roberts & Turnbull (1971) reported 4 cases of uterine hypertonus in 18 women with labour induced at term with PGE_2. Anderson et al (1971) also noticed mild hypertonus in 2 patients, 1 with $PGF_{2\alpha}$ and 1 with PGE_2 induction. Vakhariya & Sherman (1972) observed hypertonus in 7 cases. Besides hypertonus other side effects have been reported - Vakhariya & Sherman (1972) reported a generalised and a localised rash in 2 cases. Conflicting results have therefore been reported

both as regards success rates, which were not always clearly defined, and as regards side effects.

It has therefore not been established whether prostaglandins are more or less efficient, or safer than oxytocin for the induction of labour at term. The reasons for this are quite clear, namely:

1. A strictly supervised study has not been performed.
2. Comparable doses were not established prior to starting the studies.
3. Patients were not matched for factors known to affect the response to induction of labour.

As these factors have received inadequate scientific consideration it was considered pertinent to examine them all together in a carefully planned study. This was thought to be particularly important in South Africa which has no abortion law, as most studies on prostaglandins are now on first and second trimester terminations and the place of prostaglandins in induction of labour at or near term has remained unsettled.

This thesis was commenced in January, 1971, and completed in January, 1973.

PART 2

OBJECTIVES OF THE PRESENT STUDY

A strictly controlled investigation was therefore undertaken in order to clarify the efficacy of prostaglandin $F_{2\alpha}$ in labour induction in comparison to oxytocin, including a study of side effects, using statistically matched patients and comparable dosage schedules of the 2 drugs. Further, an attempt was made to determine a possible role for prostaglandin $F_{2\alpha}$ in spontaneous labour.

To this end the following studies were carried out:

1. A study to determine comparable dosage schedules of prostaglandin $F_{2\alpha}$ and oxytocin for labour induction so that a valid comparison could be made.
2. A study comparing the success of labour induction in matched patients receiving oxytocin or prostaglandin $F_{2\alpha}$ without amniotomy.
3. A study comparing the success of labour induction in matched patients receiving oxytocin or prostaglandin $F_{2\alpha}$ with amniotomy being performed at the time of induction.
4. To determine if the advantages claimed for prostaglandins in induction with an unripe cervix are real or spurious (Karim et al, 1970).
5. To assess the quality of the labour produced by the 2 drugs.
6. A study to determine the anti-diuretic effects of the 2 drugs in the induction of patients suffering from classical pre-eclampsia, the lack of an anti-diuretic effect being a supposed advantage of the prostaglandins (Roberts et al, 1970).

7. A study comparing the effects of a beta-adrenergic agent on labour induced alternatively with prostaglandin $F_{2\alpha}$ and oxytocin.

PART 3

PATIENTS AND METHODS

3.1 PATIENTS

The principal aims of this study required a detailed clinical history and examination and the collection of material from varying groups of women in order to match precisely the two treatment groups. To this end each patient was assessed personally.

The study comprised in-patients and out-patients of the Obstetric Department of Groote Schuur Hospital, Cape Town, who required induction of labour on obstetrical grounds.

The effect of ethnic differences on the response to induction of labour is unknown. The ethnic distribution of the patients in the study is as follows:

TABLE 1

THE ETHNIC DISTRIBUTION OF PATIENTS STUDIED

Race	No. of Patients
Asian	6
Bantu	9
Cape Coloured (Mulatto)	68

The number of patients who were studied in this thesis is such as to render it impractical to include individual case reports. However numerous factors are known to affect the response to induction of labour and these are considered below in Table 2.

TABLE 2

FACTORS AFFECTING THE RESPONSE TO INDUCTION

Criteria for Inducibility Studied
Age
Height
Pre-delivery weight
Parity
Drug ingestion
Urinary tract infection
Best estimate of gestational age
Station of presenting part
Cervical effacement
Cervical dilatation

AGE

The females in the study ranged in age from 15 to 30 years. Embrey & Anselmo (1962) found no significance attached to age in determining the latent period in labour induction.

HEIGHT

All patients in the study were of average height, i.e. ranging from 150 to 175 cm. Patients of short stature had a clinical and an X-ray pelvimetry, using A-P and lateral views, in order to exclude cephalo-pelvic disproportion. If this was found they were excluded from the trial.

PRE-DELIVERY WEIGHT

The patients ranged in weight from 45 to 100 kg.

The next Table (Table 3) shows the mean $\pm$ the standard deviation, for the factors age, height and pre-delivery weight of the patients in each group discussed in this thesis. There are no differences between the oxytocin and prostaglandin groups for these factors.

TABLE 3

AGE, HEIGHT AND PRE-DELIVERY WEIGHT OF THE PATIENTS

	Oxytocin			Prostaglandin		
	Age (Yrs)	Height (Cm)	Weight (Kg)	Age (Yrs)	Height (Cm)	Weight (Kg)
Number	43	43	43	40	40	40
Mean	21.9	155.8	70.1	21.7	157.2	65.9
S.D.	4.9	5.4	12.5	4.0	6.0	9.9

$P > 0.05$ in all factors as measured by Yates's correction of chi^2

PARITY

Only primigravidae were selected to avoid diluting the results with multipara, in whom there is a very low incidence of prolonged labour (O'Driscoll et al, 1969).

DRUG INGESTION

All sedative drugs were discontinued 12 hours prior to the induction of labour.

URINARY TRACT INFECTION

No patient had a urinary tract infection at the time of induction of labour.

BEST ESTIMATE OF GESTATIONAL AGE

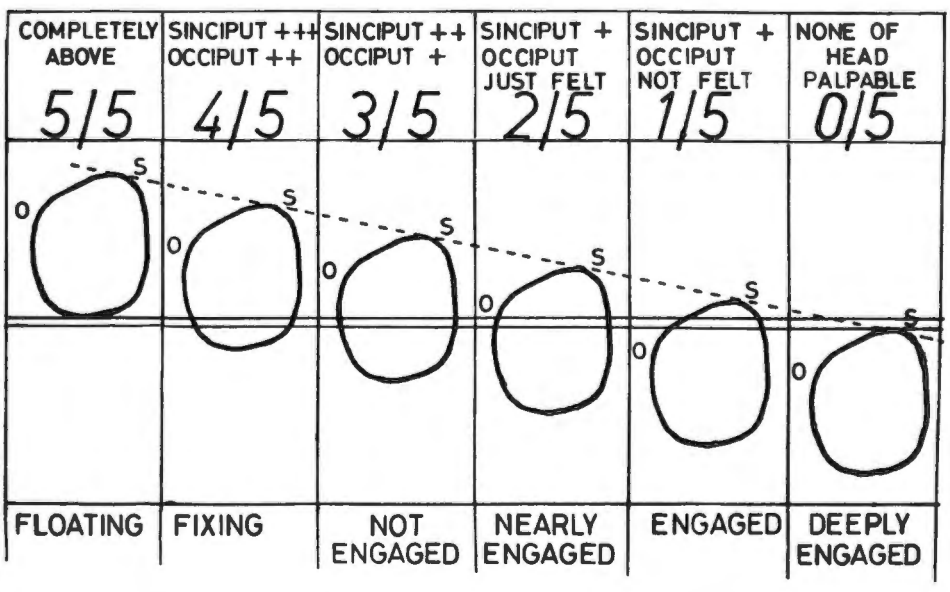
The gestational ages ranged from 36 to 43 weeks as confirmed post-natally by paediatric examination. The mean gestational age for both groups was 40 weeks.

STATION OF THE PRESENTING PART

Embrey & Anselmo (1962) feel that the degree of engagement of the presenting part or 'head station' is important to the successful induction of labour and is important in determining the length of the latent period in primigravidae. This was therefore very carefully determined by the author in every case at the time of induction of labour. Engagement of the fetal head was determined both by the reversed Lövsett's manoevre and by the technique of Fifths first described by Crichton (Philpott et al, 1972). He defined the level of the head in relation to the brim of the pelvis as the number of fifths still above the brim of the pelvis (See Figure 4 below).

FIGURE 4

THE 'FIFTHS' TECHNIQUE OF ASSESSING ENGAGEMENT OF THE FETAL HEAD



On vaginal examination the head was classified as being 1, 2 or 3 cm above or below the ischial spines. If the presenting part was level with the ischial spines a zero was recorded (See Table 4 below). There was no statistical difference between the two groups (P>0.05).

TABLE 4

THE HEAD STATION IN EACH GROUP (CLASSIFIED ACCORDING TO THE STATE OF THE CERVIX)

	Unripe		Ripe	
	Oxytocin	Prostaglandin	Oxytocin	Prostaglandin
- 3cm	16	17	9	5
- 2cm	10	3	3	7
- 1 and 0 cm	1	4	4	4

THE STATE OF THE CERVIX

Garrett (1960) feels that the state of the cervix is the only sign of practical importance in the prediction of the outcome of surgical induction of labour and Embrey & Anselmo (1962) showed the ripeness of the cervix to be the most influential clinical feature in labour induction using oxytocin. The author felt, however, that in addition to dilatation the length of the primigravid cervix is a major factor in considering the latent period after induction of labour in primigravidae. There is no guide on this point in the literature. The length of the primigravid cervix was regarded arbitrarily as 3 cm at the onset of labour. It was measured by placing the middle finger at the internal os and then marking off the length of the distal part of the cervix on this finger. This length was then measured with a rule and expressed as a percentage of 3 cm. This technique is illustrated in the diagram below:

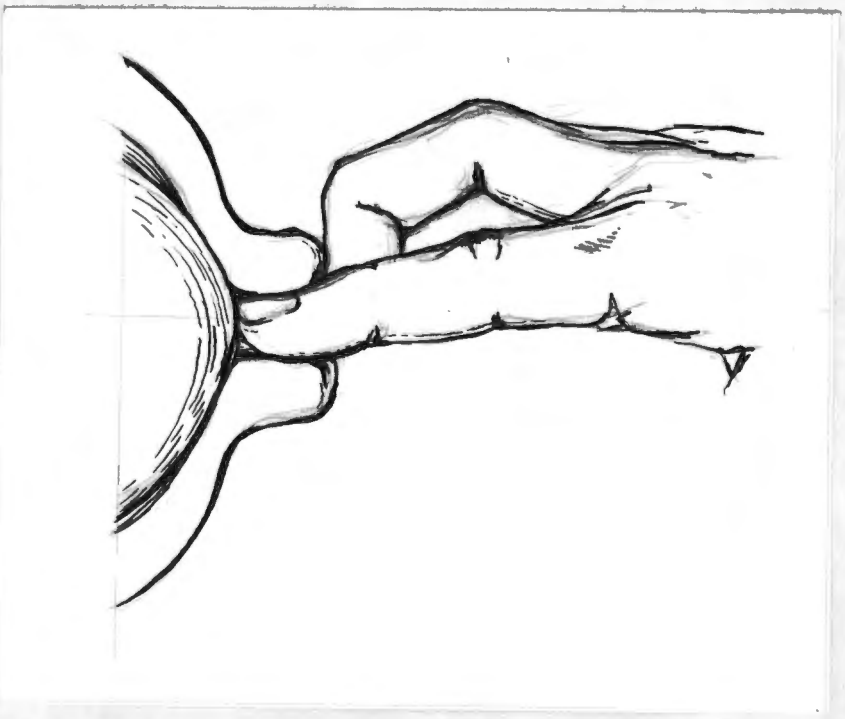


Table 5 below shows the degree of effacement in the oxytocin and prostaglandin groups, classified according to the state of the cervix. There is no statistical difference between the 2 groups (P> 0.05).

TABLE 5

CERVICAL EFFACEMENT IN EACH GROUP

(CLASSIFIED ACCORDING TO THE STATE OF THE CERVIX)

	Unripe		Ripe	
	Oxytocin	Prostaglandin	Oxytocin	Prostaglandin
0 -30%	20	15	2	4
40-50%	4	7	4	2
60-70%	3	2	5	2
80+ %	0	0	5	8

In assessing the dilatation of the cervix, no forceful attempt was made to introduce the finger into or through the cervical canal as it was felt that this might cause discomfort to the patient and might prejudice the onset or the progress of labour. All measurements were made against a standard plastic scale kept at the bedside (See photograph below).

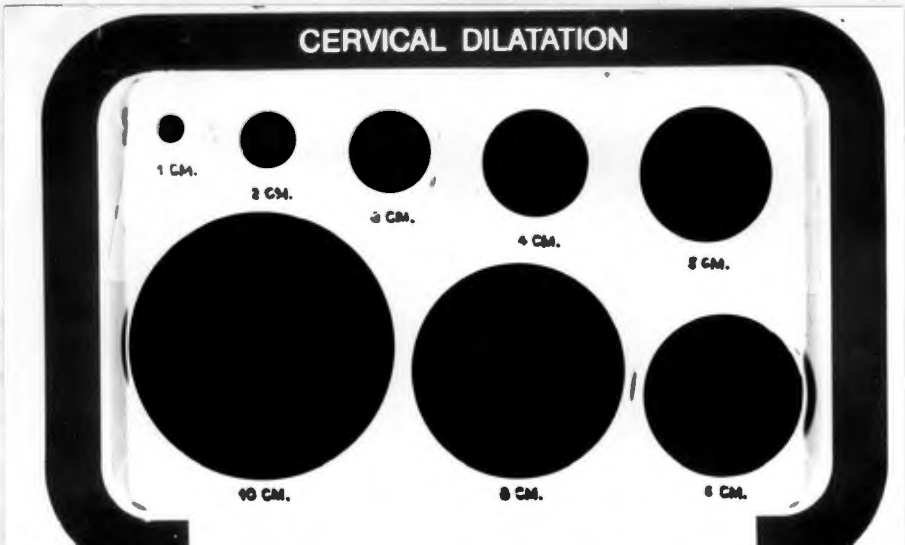


Table 6 shows the mean $\pm$ S.D. of the cervical dilatation of each group, classified according to the state of the cervix. There is no statistical difference between the 2 groups ($P > 0.05$).

TABLE 6

INITIAL DILATATION OF THE CERVIX IN OXYTOCIN AND PROSTAGLANDIN GROUPS

(CLASSIFIED ACCORDING TO THE STATE OF THE CERVIX)

	Unripe		Ripe	
	Oxytocin	Prostaglandin $F_{2\alpha}$	Oxytocin	Prostaglandin $F_{2\alpha}$
Number	27	24	16	16
Mean	0,93 cm	1,04 cm	2,08 cm	2,50 cm
S.D.	0,68	0,58	0,76	0,67

Friedman (1967) has shown that the error with digital examination, as opposed to a cervimeter, is insignificant, and that frequent digital examination is a much more expedient, albeit less critical, means of establishing the same end.

Table 7 (a) below records the consistency in each group. The consistency of the cervix was recorded as firm, medium or soft. The position of the cervix was classified as being posterior, mid-line or anterior and is shown in Table 7 (b) below. There is no statistical difference ($P>0.05$) between the oxytocin and prostaglandin groups for the factors consistency and position. Variations in interpretation of the cervical state were avoided by having 1 person assess the cervix (Anderson, 1965) and all the cervical examinations were personally carried out by the author.

TABLE 7 (a)

CONSISTENCY OF THE CERVIX IN EACH GROUP
CLASSIFIED ACCORDING TO THE STATE OF THE CERVIX

	Unripe		Ripe	
	Oxytocin	Prostaglandin $F_{2\alpha}$	Oxytocin	Prostaglandin $F_{2\alpha}$
Firm	4	3	0	0
Medium	6	5	1	4
Soft	17	16	15	12

TABLE 7 (b)

CERVICAL POSITION IN EACH GROUP
CLASSIFIED ACCORDING TO THE STATE OF THE CERVIX

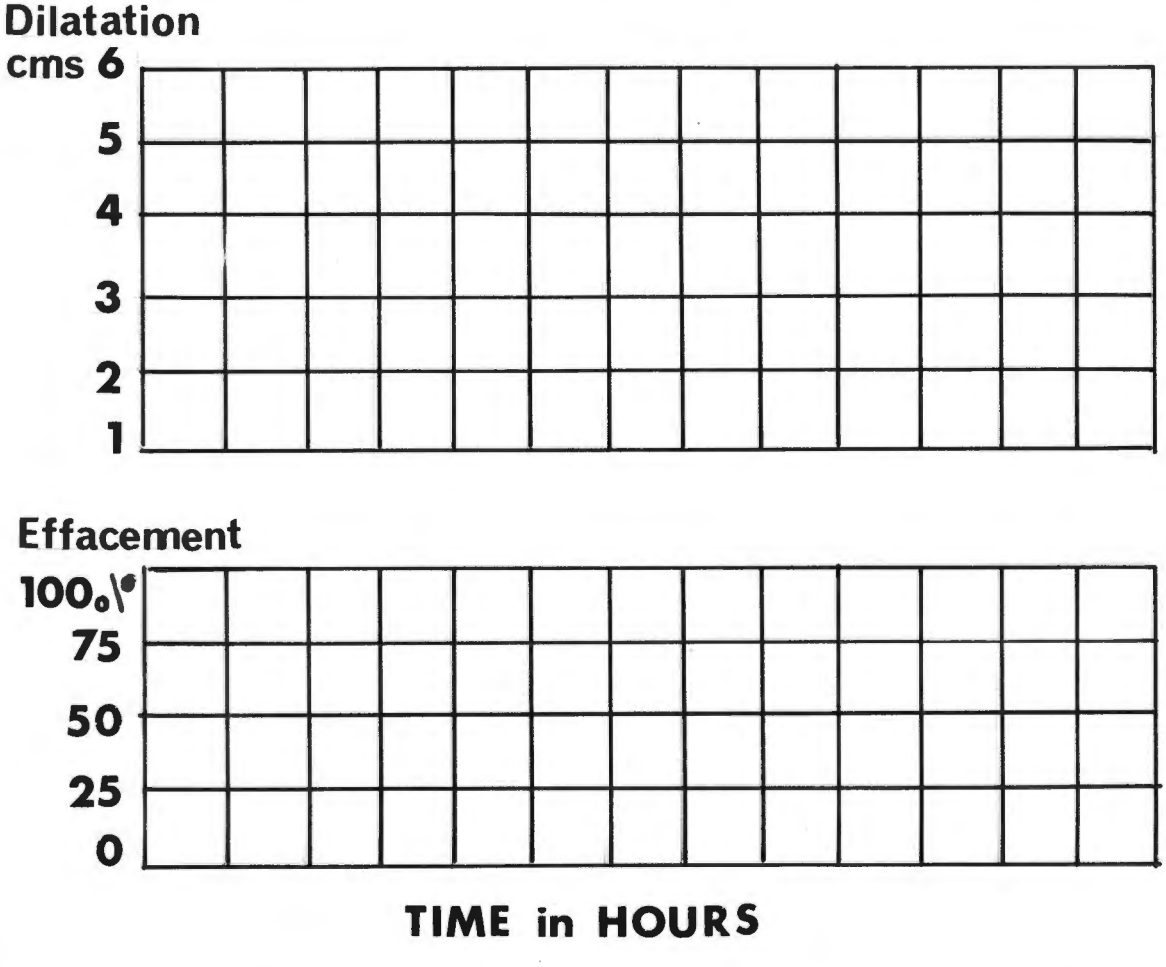
	Unripe		Ripe	
	Oxytocin	Prostaglandin $F_{2\alpha}$	Oxytocin	Prostaglandin $F_{2\alpha}$
Posterior	16	12	4	3
Mid-line	10	10	8	11
Anterior	1	2	4	2

The cervix was assessed prior to induction and then every 2 hours thereafter. Strict asepsis was observed during every vaginal examination. Changes in dilatation and effacement were recorded against a time scale and 'cervicograms' and 'effacement-grams' are shown below. These were kept on all 83 patients studied in this thesis.

CERVICOGRAM/EFFACEMENTGRAM

NAME of PATIENT _____

FOLDER NO _____ DATE _____



UTERINE IRRITABILITY

Uterine irritability was assessed clinically by means of the contractile response to palpation. In addition the number of painless contractions over a ten minute period (as recorded on the cardiotocograph) was counted for each case. No difference was found between the two groups.

PAST MEDICAL AND SURGICAL HISTORY

Patients with a history of cardio-vascular disease or on maintenance drug therapy prior to their pregnancy were excluded from the study. Further, any patient who had had any surgical procedure which might conceivably have influenced the course or outcome of labour was excluded.

3.2 METHODS

3.2.1 GENERAL

All the patients studied had the same history taken and the same examinations and investigations performed at each visit. Accordingly a set protocol or trial form designed by the Upjohn Company, Kalamazoo, Michigan was used. During the study, factors were encountered which necessitated revision of the form. The alterations are cross-hatched in Appendix A. These are mainly as a result of using primigravidae only. The cervical changes are analysed in detail later.

After completion of the study all data were transferred on to Univac 1106 computer punch cards for subsequent analysis and statistical evaluation through a Univac 1106 computer. The punch card code is seen in Appendix B.

3.2.2 CONSENT

Provided all the criteria demanded by the study had been satisfied the patient was interviewed and the project fully explained to her. Great care was taken to ensure that the patient understood that the proposed research entailed investigations and procedures which were of a non-essential nature and were being done for research purposes and carried slight, but definite risks to both the mother and the fetus, over and above the normal risk of labour. If, having had the proposed study explained, any patient showed signs of hesitancy or fear, she was excluded from the group. If there were any objections from the husband, the patient was excluded. In addition, there must have been no history of involuntary infertility of more than 1 year's duration. If the husband was agreeable that his wife participate in the research project, written consent was obtained.

3.2.3 ANTENATAL CARE

All the patients had attended antenatal clinics and were managed at these attendances according to the rules of the Department of Obstetrics and Gynaecology of the University of Cape Town. Each patient was seen at 2 weekly intervals up to the 36th week of pregnancy and

at weekly intervals thereafter. If any pregnancy complication was noted the patients were admitted into the wards. At each visit the patients were weighed, blood pressure recordings made, the height of the fundus palpated and the fetal heart auscultated. Urine analysis for the presence of proteinuria and glycosuria was undertaken at each visit. All information was recorded on the patient's antenatal notes.

3.2.4. INDICATIONS FOR INDUCTION OF LABOUR

Only patients requiring induction on obstetric grounds were selected. The indications are listed below:

TABLE 8

INDICATIONS FOR THE INDUCTION OF LABOUR

Indication	Drug Used	
	$PGF_{2\alpha}$	Oxytocin
Hypertension and weight gain	3	3
Hypertension and proteinuria	4	4
Hypertension alone	16	18
Postmaturity (>42)	13	14
Placental insufficiency	1	2
Diabetes	2	2
Term with Clomiphene induced pregnancy	1	-
Total	40	43

The ultimate number of patients completely studied was 83, divided into 2 major sub-groups. The first group comprised 43 patients in whom amniotomy was not performed at the time of induction of labour. The second group of 40 patients had the membranes ruptured at the time of induction of labour.

3.2.5 PRE-INDUCTION MANAGEMENT

All patients requiring induction of labour were initially admitted into the antenatal ward. During a personal assessment by the author a history was taken and the patient examined to determine the clinical condition present. The data obtained were recorded on the protocol form (See Appendix A). When performing abdominal examination the traditional relationship of the uterine fundus to abdominal landmarks at different gestational levels throughout pregnancy was used (The Queen Charlotte's Textbook of Obstetrics, 1970). When patients were uncertain of the date of their last normal menstrual period a single X-ray film of the abdomen was taken on one occasion during the last 10 weeks of pregnancy. As it would appear from the literature (Russell, 1969) that the time that this investigation yields most information is after the 36th week of pregnancy an attempt was made to X-ray the patients after this stage of their pregnancies.

Special attention was given to the assessment of the cervix, as described above on page 30.

Antenatal management in the wards was otherwise as is routine for the Department of Obstetrics and Gynaecology of the University of Cape Town, except where the patient's clinical condition is indicated. All drug therapy was discontinued and buccal oxytocics were forbidden.

SPECIAL INVESTIGATIONS

Maternal blood was collected from the antecubital vein immediately before, during and 12 hours after labour. The blood urea was measured and a haematological analysis made by standard methods in the Departments of Chemical Pathology and Haematology of the University of Cape Town.

METHOD OF UREA ESTIMATION

Blood urea was analysed using a Technicon Auto-Analyzer. The method employed was the diacetyl monoxime method using thiosemicarbazide to enhance the colour formation (Technicon Method N-1b, Technicon Methods Manual).

METHOD OF HAEMATOLOGICAL ANALYSIS

Haemoglobin, Red Cell Count, Mean Red Cell Volume, Mean Cell Haemoglobin, Haematocrit, Mean Cell Haemoglobin Concentration and Total White Cell Count were performed using a Coulter Counter, Model S.

Platelet counts were performed manually and using a Coulter Counter Model Fn.

3.2.6 TECHNIQUE OF INDUCTION OF LABOUR

On the morning of induction the patient was transferred into the labour ward. The patients were starved and an intravenous infusion was commenced, using a Baxter R41 infusion set (10 drops/ml) into a large arm vein. The drip rate was regulated by an Ivac constant infusion pump.

As it had been claimed that prostaglandins are more effective in labour induction when the cervix is unripe (Karim et al, 1970), it was initially decided to test these cases without rupturing the membranes at the onset of the infusion, as it may be difficult to rupture membranes with an unripe cervix. This was followed in the first 43 patients. The technique of rupturing the membranes carried out in the remaining 40 patients in this study was as described below:

The patient was placed in the dorsal position and following an aseptic technique which involved the surgeon 'scrubbing up' and the patient being swabbed and draped with sterile towels, a vaginal examination was performed. The index finger was inserted through the cervix and the membranes swept to as high a level as possible. A forewater rupture was performed using Kocher's forceps and as much liquor as possible was allowed to drain. At the completion of this procedure the fetal heart was closely auscultated. Either prostaglandin $F_{2\alpha}$ or oxytocin was then added to the infusion bottle, depending on whether the patient's case record number ended in an odd or even digit. These agents were administered on a titration basis according to the schedules outlined on page 49.

OBSERVATIONS DURING LABOUR

All patients were attended by a 'special' nurse and half-hourly recordings of the maternal pulse rate and blood pressure were made.

Uterine contractions and fetal heart rate recordings were monitored throughout labour with a Hewlett Packard cardiotocograph 8020A. Baseline recordings were obtained for at least 15 minutes before the start of the

infusion. This was calculated as seconds/10 minutes of contractions and no statistical difference was found between the 2 groups and in neither were any patients in labour. The uterine activity could not be quantitated because external tocography of the uterus was used, to avoid any possibility of mechanical stimulation of the uterus (Embrey, 1969).

The times of alteration in the infusion rate were recorded, ensuring knowlege of the total quantity of each agent used.

The presence of any maternal cardiovascular or gastro-intestinal side effects was noted. Strict fluid balance charts were kept, and the patients were catheterised at the endpoint of the trial to ensure an accurate estimation of their urinary output.

Fetal well being was assessed by Apgar scores taken at 1 and 5 minutes.

3.2.7 CRITERIA OF A SUCCESSFUL INDUCTION

Induction of labour was considered successful when 5cm dilatation of the cervix had been achieved, or delivery had occurred within 12 hours of the start of the infusion. Five cm was selected arbitrarily as the endpoint as a primigravid patient is unquestionably in established labour at this dilatation and labour can therefore be regarded as successfully induced.

For further comparison of the 2 drugs to be made, certain fixed points in labour were selected by which this could be done. The first point was where initial contractions (I.C.) occurred (Scher et al, 1972). This was the first appearance of stimulated uterine activity on the cardiotocograph paper. The next point was where regular contractions became painful to the patient. Anderson (1965) took this point of painful contractions as the onset of labour. This was known as the point of adequate contractions (A.C.). The endpoint of the trial was the next parameter used for comparison and this was the point at which the cervix reached 5cm dilatation.

3.2.8 CALCULATION OF TITRATION SCHEDULES FOR PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN

It is fruitless to argue which is the stronger of 2 drugs. The clinician wants safe delivery and the effects of equivalent drugs must therefore be those which provide

this. It was felt that unless comparable dosage schedules of the 2 drugs were used no conclusion would be able to be drawn about their relative effectiveness. Dewhurst (1972) feels this comparability to be a major point. The author therefore felt it would be important to choose a good model using in-patient control to establish comparable drug dosages. No comparable dosage schedules for prostaglandin $F_{2\alpha}$ and oxytocin were available in the medical literature and a study was undertaken to derive these. This study is described below.

Patients

Six primigravid patients who required induction of labour on obstetric grounds were selected. All gave their informed consent once the procedure had been described to them in detail. All the patients were at term and only those who were certain of the date of their last menstrual period were selected.

Abdominal palpation recorded a cephalic presentation in all the cases. On vaginal examination the cervices were effaced and less than 2cm dilated.

Method

An anteriorly situated placenta was excluded clinically, and by ultrasound where uncertainty existed, and the lie and position of the fetus determined. The

abdominal wall was infiltrated with a local anaesthetic agent (1% Lignocaine Hydrochloride - Propan Pharmaceuticals). A surgically aseptic technique was observed throughout. The site for puncture was selected as the area between the fetal chin and thorax. A Tuohy needle was introduced into the amniotic cavity and the trochar was withdrawn. An epidural cannula ('PORTEX' with needle guard Ref. 100/380/010 Length 90cm) was inserted into the amniotic cavity. It was then filled with normal saline into which ½ gm of Ampicillin ('Penbritin', Beecham) had been instilled. The catheter was then attached to a Hewlett Packard pressure transducer, number 1280B, used in conjunction with a Hewlett Packard transducer, number 1513713, connected to a Hewlett Packard cardiotocograph 8020A.

Maternal and fetal heart rates were recorded continuously phonocardiographically as previously described on page 42.

Oxytocin was then administered intravenously at a rate sufficient to produce uterine contractions compatible with early established labour i.e. contractions causing a rise of intra-uterine pressure of about 50mm mercury above resting pressure every 2 to 3 minutes, with a uterine activity of 150 Alexandria units (El-Sahwi et al, 1967). The oxytocin infusion was stopped once this stage had been reached.

PHOTOGRAPH SHOWING TECHNIQUE
OF DIRECT INTRA-AMNIOTIC PRESSURE RECORDING

When the uterine activity had returned to the original level the first drug was discontinued and prostaglandin $F_{2\alpha}$ was substituted. The whole procedure was then repeated. At the conclusion of the experiment the membranes were ruptured and labour was allowed to continue. All patients were delivered vaginally and all neonates were in good biological condition.

Results

Table 9 shows the respective dosages of oxytocin and prostaglandin $F_{2\alpha}$ required to produce a similar amount of uterine activity in each patient.

TABLE 9

DETAILS OF DRUG DOSAGES AND UTERINE ACTIVITIES IN EACH CASE

	Oxytocin		Prostaglandin $F_{2\alpha}$	
Case	Uterine activity	*Dose (m-u/min)	Uterine activity	*Dose (µg/min)
1	200	4	224	24
2	227	4	251	8
3	251	8	230	16
4	196	4	184	16
5	234	4	220	16
6	250	4	260	8
Mean	226	4 2/3	228	14 2/3

*Alexandria Units (El-Sahwi et al, 1967)

It can be seen that the ratio of prostaglandin $F_{2\alpha}$ to oxytocin is 3.14:1 when comparing potency. There were no maternal side effects. As a result of this study the following titration schedules were calculated:

OXYTOCIN DOSAGE SCHEME

Oxytocin Dose	Drip Rate	
	15 drops/min	30 drops/min
4 iu in 1 L 5% D/W	4	8
16 iu in 1 L 5% D/W	16	32
64 iu in 1 L 5% D/W	64	128 m-u/min

20 minute increments

PROSTAGLANDIN $F_{2\alpha}$ DOSAGE SCHEME

Prostaglandin $F_{2\alpha}$	Rate
1 amp (5mg) in 500 ml 5% D/W	5 drops/min
	10 drops/min
	20 drops/min
	40 drops/min

1 drop = 1 μg

30 minute increments

The oxytocin infusion was started at 15 drops/minute, the rate being doubled every 20 minutes until the contractions were optimal, as recorded on the cardiotocograph.

It can be seen that if the maximum dose of each drug is attained the ratio of oxytocin to prostaglandin is 3.2:1. The prostaglandin schedule takes longer to reach this maximum dose because of the danger of hypertonus.

HYPERTONUS ENCOUNTERED WITH THE PROSTAGLANDIN $F_{2\alpha}$ INFUSION SCHEME

Initially only a 20 minute interval was allowed between increasing dosage of the drug, but deflection of the uterine pressure recordings from the base line occurred, unrelated to interfering factors such as maternal or fetal movement. This indicated hypertonus. Intra-uterine pressure was then recorded directly intra-amniotically by the method described on page 46 in 6 patients who were not included in the trial. From Figure 5 the hypertonus which occurs on increasing the prostaglandin at 20 minute intervals can be seen. Figure 6 shows the lack of hypertonus when the interval between doses is increased to 30 minutes, even though it can be seen that the initial activity was greater in Figure 5.

FIGURE 5

TWENTY MINUTE INCREMENTS

OF PROSTAGLANDIN $F_{2\alpha}$

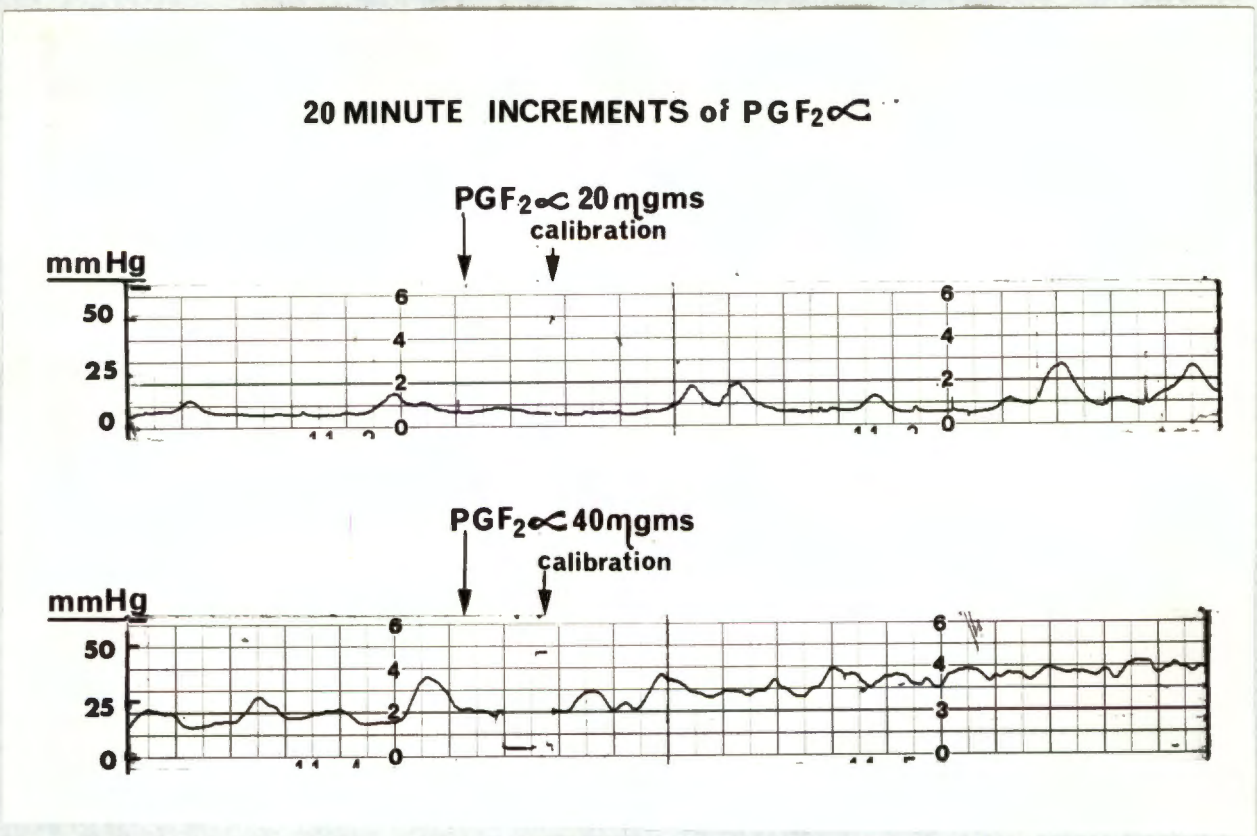
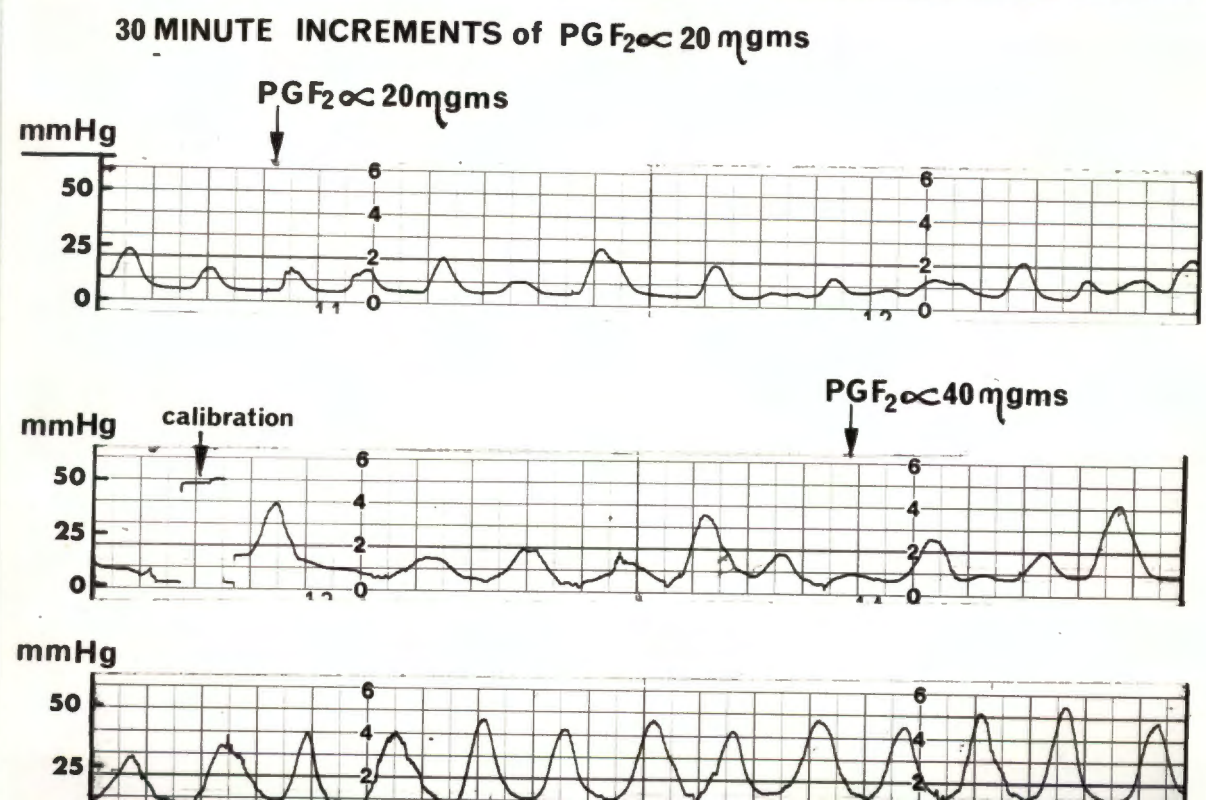


FIGURE 6

THIRTY MINUTE INCREMENTS

OF PROSTAGLANDIN $F_{2\alpha}$



Once these comparable dosage schemes for the two drugs had been calculated, and the initial difficulty which was encountered with the hypertonus using prostaglandin $F_{2\alpha}$ had been overcome, the schemes were used throughout this thesis.

3.2.9 STATISTICAL ANALYSIS (APPENDIX B)

All data were analysed through a Univac computer with the assistance of a computer programmer and statistician (See Acknowledgments). The statistical tests applied were basically the student t distribution for continuous measurements (eg. weight, height, blood pressure) and the chi^2 distribution test for clinical features (eg. diarrhoea, venous erythema, vomiting). Yates's correction for small sample size was applied. Where expected frequencies were less than 5, the exact test for fourfold tables was used.

RESULTS

In all, 43 oxytocin inductions are compared with 40 patients where prostaglandin $F_{2\alpha}$ was used. Rupture of the membranes was performed at the start of the infusion in half the cases. The author would again like to emphasise that a single person did all the cervical assessments to avoid variation in interpretation and the cases were 'specialled' by 1 trained research assistant during the entire trial period.

PART 4

RESULTS

4.1 OVERALL SUCCESS RATE FOR EACH GROUP

By the criteria of success described on page 44 30 out of 43 oxytocin inductions, or 69%, and 33 out of 40 prostaglandin $F_{2\alpha}$ inductions, or 82%, succeeded. (See Table 12 below).

TABLE 12

OVERALL INDUCTION SUCCESS RATES

FOR THE 2 DRUGS TESTED

Drug Used	No. of Cases	Success No.	Success %
Oxytocin	43	30	69
Prostaglandin $F_{2\alpha}$	40	33	82

Although the prostaglandin group had a numerically better success rate this is not at a statistical level.

4.2 INFLUENCE OF THE STATE OF THE CERVIX ON THE OUTCOME OF THE INDUCTION BY THE 2 AGENTS

It can be seen from the table below that a ripe cervix has a favourable response on labour outcome whether prostaglandin $F_{2\alpha}$ or oxytocin is used for the induction. This work supports the findings of other workers (Embrey, 1969; Garrett, 1960).

TABLE 13

SUCCESS RATE OF LABOUR INDUCTION

RELATED TO THE STATE OF THE CERVIX

Drug Used	State of Cervix	No. of Cases	Success
Oxytocin	Ripe	15	12
	Unripe	28	18
Prostaglandin $F_{2\alpha}$	Ripe	16	15
	Unripe	24	18

4.3 THE INFLUENCE OF RUPTURE OF THE MEMBRANES ON LABOUR INDUCED BY PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN

As the trial had been carefully controlled and the cases had been compared for the factors affecting inducibility the remaining variable was rupture of the membranes.

The author ruptured the membranes at the time of the onset of the infusion using a standard technique. This involved sweeping the membranes off the lower uterine segment and then rupturing the forewaters with a Kocher's forceps. Table 14 below shows the effect of rupture of themembranes when prostaglandin $F_{2\alpha}$ was used as the oxytocic agent.

TABLE 14

THE EFFECT OF AMNIOTOMY

ON PROSTAGLANDIN $F_{2\alpha}$ INDUCED LABOUR

	Success	Failure	Total
Prostaglandin $F_{2\alpha}$			
Without amniotomy	14	6	20
With amniotomy	19	1	20

The failure rate when amniotomy is performed is statistically significantly reduced ($p < 0.05$).

From Table 15 the effect of amniotomy on labour induced with oxytocin can be seen.

TABLE 15

THE EFFECT OF AMNIOTOMY

ON OXYTOCIN INDUCED LABOUR

	Success	Failure	Total
Oxytocin			
Without amniotomy	13	10	23
With amniotomy	17	3	20

Although the failure rate following induction with oxytocin is numerically decreased when amniotomy is carried out, this difference is not statistically significant. Subsequent to compiling this thesis, however, we have completed further investigations and the difference has reached statistical significance ($p < 0.05$).

Table 16 relates the effect of amniotomy to the state of the cervix with the use of prostaglandin $F_{2\alpha}$ and oxytocin in induction of labour.

TABLE 16

THE EFFECT OF AMNIOTOMY

RELATED TO THE STATE OF THE CERVIX

Drug	State of Cervix	No. of Cases	Success
Oxytocin	Ripe	7	4
	Unripe	16	9
Prostaglandin $F_{2\alpha}$	Ripe	8	7
	Unripe	12	7
*Oxytocin	Ripe	8	8
	Unripe	12	9
*Prostaglandin $F_{2\alpha}$	Ripe	8	8
	Unripe	12	11

* Amniotomy at Time of Induction

It can be seen that the success rate for prostaglandin $F_{2\alpha}$ is much greater with an unripe cervix when

amniotomy is performed. Using the exact method of fourfold tables (Armitage, 1971) this is significant at the 8% level.

These results indicate that if the cervix is unripe the best success rate is obtained if prostaglandin $F_{2\alpha}$ is used as the oxytocic agent and amniotomy is performed at the time of induction but that this is an effect of the rupture of the membranes.

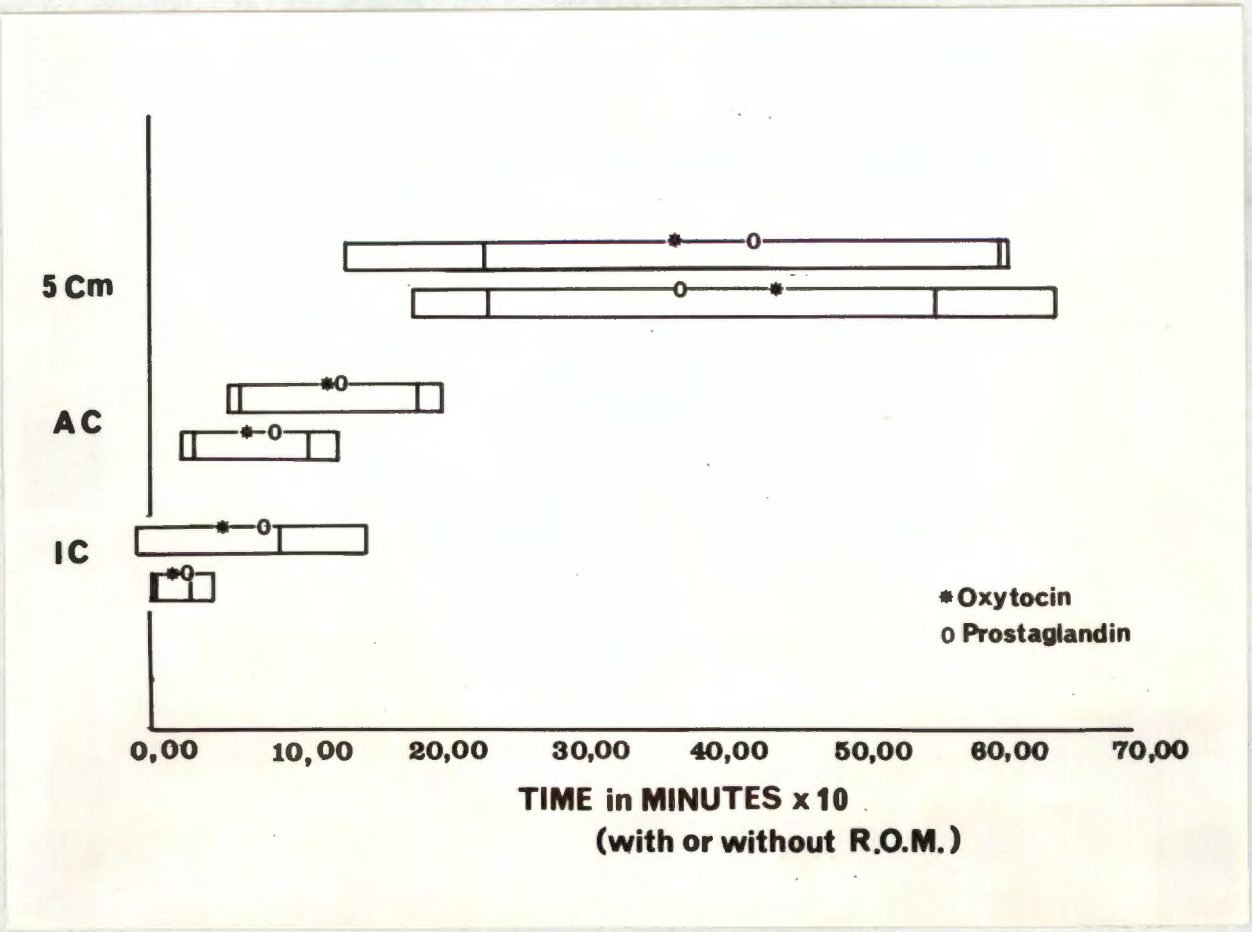
4.4. THE INFLUENCE OF RUPTURE OF THE MEMBRANES ON VARIOUS PARAMETERS OF LABOUR

The parameters which were previously selected to compare the success rates of induction of labour with the 2 drugs were studied to determine if either agent had any advantage at these stages. Figure 7 below shows the mean time $\pm$ the standard deviation taken by the 2 drugs to reach these stages. Time is recorded along the horizontal axis and the points I.C., A.C. and 5cm dilatation along the vertical axis. There was no statistically significant difference for either drug at these points. The lower block diagrams at each stage represent those cases where rupture of the membranes was carried out at the time of induction of labour. The marked shift to the left is seen when amniotomy has been performed and this is statistically significant ($p < 0.05$) for the points I.C. and A.C. This demonstrates that elective artificial rupture of the membranes statistically significantly speeds up the rate of labour.

FIGURE 7

COMPARISON OF TIMES ($\pm$ S.D.)

TAKEN BY PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN



4.5 THE QUALITY OF THE LABOUR PRODUCED BY PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN

The quality of labour activity using prostaglandin $F_{2\alpha}$ and oxytocin was compared using the formula of Effer et al (1969), shown below.

$$I.U.A. = \frac{100\ S.D.}{\bar{x}}$$

I.U.A. = Index of Uterine Arrhythmia

S.D. = Standard Deviation

$\bar{x}$ = Mean

Twenty intervals of time elapsing from peak to peak of consecutive contractions were analysed. The co-efficients of variation of these 20 intervals were calculated. This co-efficient is an index of uterine arrhythmia, being higher when the rhythm is more irregular. The different degrees of rhythm are categorised as follows:

Category of Rhythm	Range of I.U.A.
Very regular	0 - 15
Regular	16 - 25
Irregular	26 - 35
Very irregular	36 +

Effer et al (1969) feel that one of the clinical applications of the index of uterine arrhythmia is the evaluation of the response to drugs which modify uterine contractions. Table 17 below shows the pattern description for the 2 groups.

TABLE 17

THE QUALITY OF LABOUR

PRODUCED BY THE 2 DRUGS

Drug Used	Pattern Description		
	Regular	Irregular	Very Irregular
Oxytocin	20	13	8
Prostaglandin $F_{2\alpha}$	20	13	8

There is clearly no difference in the quality of the labour produced by prostaglandin $F_{2\alpha}$ and oxytocin. It has also been found that rupture of the membranes may cause hypertonus when prostaglandin is used to stimulate labour (Roberts & Turnbull, 1971). The effect of amniotomy on the quality of labour produced by prostaglandin $F_{2\alpha}$ and oxytocin is shown in Table 18 below:

TABLE 18

THE EFFECT OF AMNIOTOMY

ON THE QUALITY OF LABOUR

PRODUCED BY OXYTOCIN AND PROSTAGLANDIN $F_{2\alpha}$

Drug Used	Pattern Description		
	Regular	Irregular	Very Irregular
Oxytocin			
Without R.O.M.*	8	7	6
With R.O.M.	12	6	2
Prostaglandin $F_{2\alpha}$			
Without R.O.M.	6	9	5
With R.O.M.	13	4	3

* R.O.M. = Rupture of Membranes

It can be seen that rupturing the membranes does not produce irregularity of uterine activity compared to cases where they are left intact.

4.6 MATERNAL SIDE EFFECTS STUDIED

The side effects studied are listed below:

1. Changes in urea and haematological changes which included the total white cell count and a differential count.
2. Changes in blood pressure.
3. Changes in temperature.
4. Instances of vomiting.
5. Instances of diarrhoea.
6. 'Phlebitis'.
7. Urinary output.

4.6.1 CHANGES IN THE BLOOD UREA

The mean and standard deviation of the blood urea levels in the 2 groups with and without rupture of the membranes is shown in the tables below. Table 19 shows the group where the membranes were electively ruptured at induction. There was no difference between the 2 groups before delivery. There was, however, a significant difference after delivery. Where prostaglandin $F_{2\alpha}$ was used for induction the blood urea value rises after delivery. Where oxytocin was used the value falls slightly.

TABLE 19

BLOOD UREA VALUES IN THE 2 GROUPS

(AMNIOTOMY PERFORMED)

	Prostaglandin $F_{2\alpha}$		Oxytocin	
	Before Delivery mg %	After Delivery mg %	Before Delivery mg %	After Delivery mg %
MEAN	15.7	19.2	17.8	14.7
S.D.	4.9	6.2	8.5	5.8

Where the membranes were not ruptured at the time of induction there was no significant difference in the prostaglandin and oxytocin groups, although the trend was similar. This is shown in Table 20 below:

TABLE 20

BLOOD UREA VALUES IN THE 2 GROUPS

(AMNIOTOMY NOT PERFORMED)

	Prostaglandin $F_{2\alpha}$		Oxytocin	
	Before Delivery mg %	After Delivery mg %	Before Delivery mg %	After Delivery mg %
MEAN	20.7	17.9	16.5	19.3
S.D.	11.7	7.8	6.9	9.8

Following rupture of the membranes the statistically significant rise in the blood urea in the prostaglandin group ($p < 0.05$) as opposed to the cases where oxytocin was used, suggests that prostaglandin $F_{2\alpha}$ does not cause water retention.

4.6.2 THE INCIDENCE OF DIARRHOEA

The incidence of diarrhoea in the 2 groups is shown below:

TABLE 21

THE INCIDENCE OF DIARRHOEA IN THE 2 GROUPS

	No. of Cases with Diarrhoea	Total No. of Cases
Oxytocin	11	43
Prostaglandin $F_{2\alpha}$	16	40

There was no significant difference between the effects of the 2 drugs on the amount of diarrhoea produced.

4.6.3 THE INCIDENCE OF VOMITING

The number of patients who vomited in each group is shown in Table 22 below:

TABLE 22

THE INCIDENCE OF VOMITING IN THE 2 GROUPS

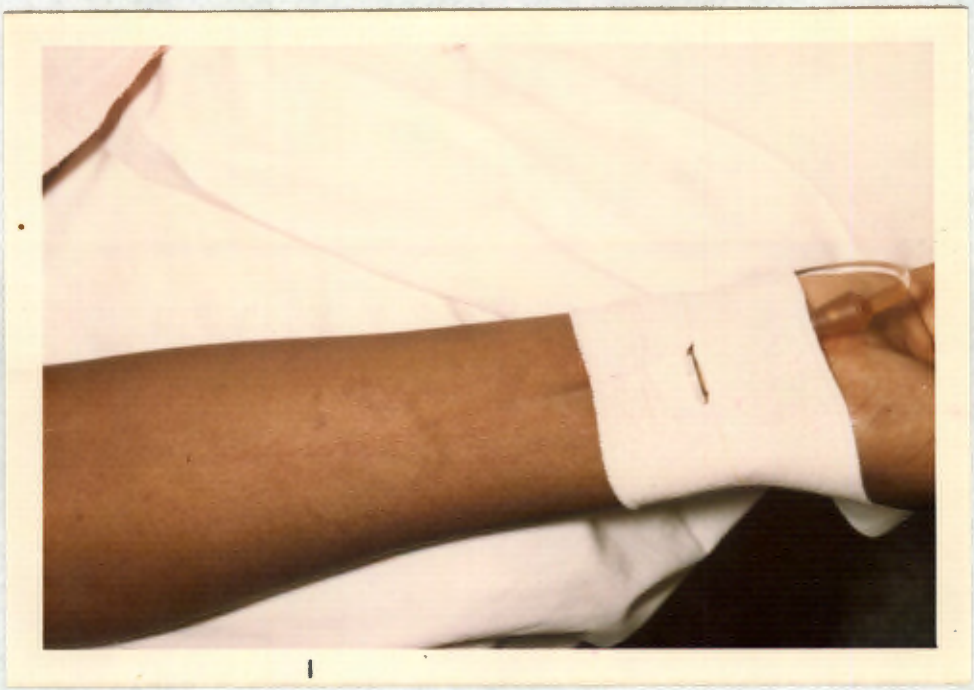
	Prostaglandin $F_{2\alpha}$	Oxytocin
Vomited	14	10
Total No.	40	43

There was no significant difference between the effects of the 2 drugs on the incidence of vomiting.

4.6.4 THE INCIDENCE OF 'PHLEBITIS'

The colour plate below shows the appearance of the transient red line in the skin along the area draining the infusion site in a patient receiving prostaglandin $F_{2\alpha}$.

PLATE SHOWING THE RED LINE DRAINING THE INFUSION SITE CAUSED BY PROSTAGLANDIN $F_{2\alpha}$



The incidence of 'phlebitis' which occurred in the 2 groups is shown in Table 23 below:

TABLE 23

THE INCIDENCE OF 'PHLEBITIS' IN THE 2 GROUPS

	Prostaglandin $F_{2\alpha}$		Oxytocin	
	No.	%	No.	%
Total No. of Cases	40	100	43	100
'Phlebitis'	14	35	1	2.3

The difference in the incidence of 'phlebitis' in the 2 groups is statistically significant ($p < 0.001$).

4.6.5 HAEMATOLOGICAL EFFECTS

(a) Haemoglobin

Table 24 below shows the mean $\pm$ standard deviation for the haemoglobin levels before and after delivery in the 2 groups. There were no significant differences between the 2 groups.

TABLE 24

PRE- AND POST-DELIVERY HAEMOGLOBIN LEVELS IN THE 2 GROUPS

Haemoglobin	Prostaglandin $F_{2\alpha}$		Oxytocin	
	Before Delivery g%	After Delivery g%	Before Delivery g%	After Delivery g%
MEAN	12.98	13.00	13.06	13.02
S.D.	1.19	1.31	1.07	1.35

(b) Total White Cell Count, Differential Count and Platelet Count

Table 25 below shows the mean $\pm$ standard deviation of the total white blood cell count, differential count and platelet count in the 2 groups before and after delivery. No statistical differences were shown.

TABLE 25

TOTAL WHITE CELL COUNT, DIFFERENTIAL COUNT AND PLATELET COUNT IN THE TWO GROUPS

	Prostaglandin $F_{2\alpha}$		Oxytocin	
	Before delivery	After delivery	Before delivery	After delivery
White Cell Count/100	113.1 ± 50.5	154.0 ± 57.8	97.4 ± 25.0	160.1 ± 44.7
Neutrophils	70.82 ± 9.02	78.63 ± 8.44	70.16 ± 8.83	80.31 ± 8.25
Lymphocytes	21.12 ± 7.92	14.67 ± 7.98	23.16 ± 9.91	14.00 ± 5.94
Monocytes	6.36 ± 4.53	5.30 ± 3.74	5.70 ± 2.75	5.36 ± 3.30
Platelets/1000	180.41 ± 56.81	185.30 ± 53.52	184.43 ± 62.20	192.71 ± 54.50

4.6.7 PULSE RATE, RESPIRATION AND BLOOD PRESSURE

No difference was found in maternal pulse rate, blood pressure and respiration between the oxytocin and prostaglandin $F_{2\alpha}$ treated groups. The results for these factors are shown in Table 26 below:

TABLE 26

PULSE RATE, RESPIRATORY RATE AND BLOOD PRESSURE RANGES IN THE TWO GROUPS

	Oxytocin			Prostaglandin $F_{2\alpha}$		
	No.	Mean	S.D.	No.	Mean	S.D.
Pulse Rate (beats/minute)						
Pre-treatment	43	94	13	40	95	15
Minimum of range	43	79	12	40	79	10
Maximum of range	43	99	13	40	103	15
After treatment	35	91	13	35	90	15
Respiration (rate/minute)						
Pre-treatment	43	20	2	40	20	3
Minimum of range	39	19	2	37	19	2
Maximum of range	38	25	5	37	24	3
Systolic Blood Pressure (mmHg)						
Pre-treatment	43	128	14	40	128	15
Minimum of range	43	113	13	40	116	12
Maximum of range	43	139	13	40	140	14
After delivery	36	129	17	36	133	19
Diastolic Blood Pressure (mmHg)						
Pre-treatment	43	84	12	40	85	14
Minimum of range	43	73	11	40	76	8
Maximum of range	43	95	10	40	97	11
After delivery	35	81	12	35	84	14

4.7 FETAL SIDE EFFECTS

Fetal heart rate patterns were recorded by external cardiotocography. Fetal scalp sampling was not performed as the membranes were intact in the first phase of the trial. Further, it was felt that the passage of an amnioscope might interfere with the rate of cervical dilatation. Table 27 below gives the description of the fetal heart rate patterns which were obtained:

TABLE 27

FETAL HEART RATE PATTERNS OBTAINED WITH THE 2 DRUGS

	Benign Change	Abnormal Change	No Change
Oxytocin	10	0	33
Prostaglandin $F_{2\alpha}$	7	0	33

Abnormal Change = Late deceleration in relationship to contractions or loss of beat to beat variation.

Benign Change = Any other alteration of the fetal heart rate pattern.

All infants in this study were born in good biological condition and the mean fetal Apgars recorded at 1 minute and 3 minutes were satisfactory and the mean fetal and placental weights of both groups were the same.

4.8 COMMENTS ON RESULTS OBTAINED ABOVE

A very carefully controlled physiological study has been performed. Eighty-three patients are reported. This number is smaller than many huge computer studies on labour but it is felt to be more meaningful. The patients were carefully selected and matched for the factors affecting inducibility. Each patient was 'specialled' by a trained research midwife ensuring accuracy of all data recorded. All cervical changes were personally assessed by the author every 2 hours throughout this thesis.

Comparable dosage schedules of prostaglandin $F_{2\alpha}$ and oxytocin were determined before starting the trial for the reasons outlined on page 45. Embrey (1969) commented on comparable effects of prostaglandins and oxytocin on uterine activity at term. He found, however, that infusions of prostaglandins in the range of 4 to 8 μg per minute were roughly comparable with the response to the infusion of 5 m-u of oxytocin per minute. He commented, however, on an important qualitative difference in that at this level of comparability the initial action with the prostaglandins was slow (15 to 20 minutes) compared with the latent period for oxytocin which acted almost immediately. The oxytocin regimen which we used was similar to that described by Turnbull & Anderson (1968).

No statistical difference was found in the success rates for induction of labour between the 2 drugs, no matter whether the cervix was classified as unripe or ripe. The prostaglandins were, however, better numerically. The only advantage with prostaglandin $F_{2\alpha}$ over oxytocin is where the membranes are ruptured and the cervix unripe. We selected various parameters in labour by which to judge the success of the 2 induction techniques. Embrey & Anselmo (1962) felt that the latent period from the start of the induction to the onset of labour was a useful yardstick by which to compare success in induction. We called this point I.C. (Initial Contractions). The author felt, however, that this alone is inadequate, as it does not necessarily imply that induction has occurred, and that a point indicating established labour was necessary. Once pain was experienced by the patient at the time of uterine contractions the uterine pressure, recorded directly intra-amniotically, was found to average 35mm of mercury (Scher & Baillie, unpublished observations). This pressure is within the range of peak pressures described in standard text books (Turnbull, 1957; Chassar Moir & Myerscough, 1971) for early first stage of labour and it indicates a satisfactory response to induction. This was the point referred to as A.C. (Adequate Contractions).

The endpoint of the trial - 5cm - was selected because this is already beyond Friedman's phase of maximum slope (Friedman, 1967) and at this stage the patient is unquestionably in labour. Cervical dilatation did not occur until effacement was complete.

Rupturing the membranes at the time of induction statistically significantly increased the induction success rate when prostaglandin $F_{2\alpha}$ was used. When oxytocin was the agent used the improvement was a numerical one only. Amniotomy did accelerate labour using the parameters of assessment discussed above. There is a paucity of physiological prospective studies of the effect of rupturing the membranes on the course of labour in the world literature and the published articles deal mainly with the problem of infection (Calkins, 1934; King, 1940; Keetel et al, 1940; Tennant & Block, 1954). The findings in this thesis of a beneficial effect from amniotomy on the course of labour is in disagreement with the findings of Friedman (1967) who found that amniotomy caused arrest of cervical dilatation in 82% of 61 amniotomies performed in the stage of rapid dilatation of the cervix. Friedman states 'this clearly serves to illustrate the general inefficiency of this ostensibly stimulatory device'. Friedman states that the status of the membranes does not seem to influence the course of labour and in fact found that more rapid dilatation in the active phase in multiparous labour does seem to occur when therapeutic amniotomy is not done. He does state,

however, that this does require further examination. In nulliparous patients, whom we have studied in this thesis, he found significant lengthening of the latent phase when the membranes ruptured during the latent phase. He concluded that it must be asserted that amniotomy in the latent phase is detrimental to the course of labour in that the latent phase in such cases tends to be significantly prolonged. Friedman felt, however, that a definitive controlled study of artificial amniotomy (for the purpose of induction) is needed to test this effect on the duration of the latent phase in labour. A possible reason for the conflicting results which Friedman obtained may be that they come from a large computer study involving every case entering the ward. Amongst these undoubtedly would be many cases with early rupture of the membranes associated with abnormal positions and dysfunctional uterine activity. There would be some cases conforming to findings in this thesis. But if one puts them all together and averages them all out no effect on labour may be found. This is a fault of all major computer studies as opposed to a smaller physiological study. Donald (1969) feels that there are many advantages of intact membranes during labour and that active retention of the fetus as a result of tonic uterine contractions cannot occur and that fetal asphyxia is less likely with intact membranes. We did not find that

rupture of the membranes led to hypertonus nor an incidence of fetal distress. No patient induced either with prostaglandin $F_{2\alpha}$ or oxytocin developed a genital infection. This is in agreement with other reported series (Calkins, 1934; King, 1940; Keetel et al, 1940; Tennant & Block, 1954). Aseptic techniques were adhered to throughout the study.

The quality of the labour produced by the 2 drugs was identical. This also applied after elective amniotomy. This is contrary to the findings of Roth-Brandel & Adams (1970) who found that prostaglandin produced an abnormal quality of labour which they felt might even prevent it from being used for the induction of labour.

A high incidence of diarrhoea and vomiting has been ascribed to the prostaglandins. As regards the incidence of diarrhoea the author discovered that 37 of the patients in the prostaglandin group and 36 of the oxytocin series had an enema on the night prior to induction. This is routine practice in some midwifery units and should be borne in mind when assessing side effects. Further, it must be remembered that these early results came from initial toxicity studies using infusion rates higher than necessary for the induction of labour at term (Beazley, 1971). The only side effect

which we found to be statistically significant was the incidence of 'phlebitis' at the site of injection of prostaglandin $F_{2\alpha}$. This was transient and did not cause the patient any discomfort. The finding that induction of labour at term by prostaglandins has few complications is entirely in agreement with that of Beazley (1971).

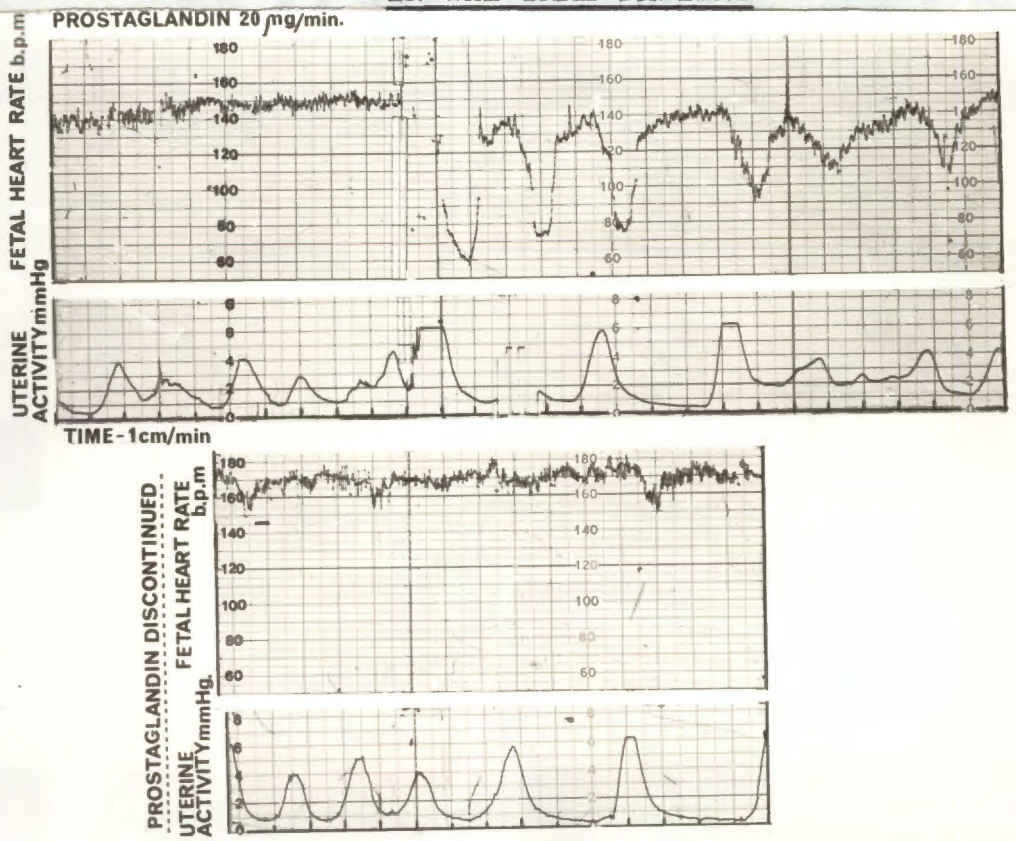
No abnormalities of the fetal heart rate pattern were detected, except in 1 patient whose cardiotocograph tracing is shown below in Figures 8 and 9. This case was encountered during the preliminary series on comparable dosages of prostaglandins. The patient developed late decelerations (Type 2 dips - Caldeyro-Barcia et al, 1966) in the fetal heart rate pattern during a prostaglandin infusion. On stopping the infusion the pattern became normal. On commencing an infusion of oxytocin in the same patient, however, the abnormal pattern recurred, and it once again disappeared on discontinuing the infusion. This reinforces the concept that it is the feto-placental reserve which is important in determining the response of the fetus to labour (Scher & Baillie, in press).

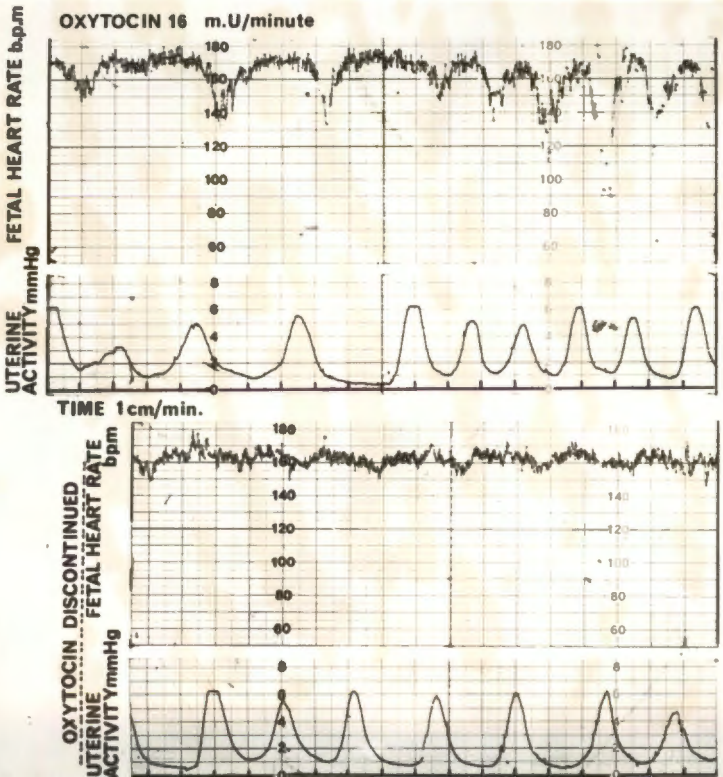
FIGURES 8 AND 9

TYPE 2 DIPS

FOLLOWING INTRAVENOUS PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN

IN THE SAME PATIENT





The work of Roberts et al (1970) suggests that prostaglandins as compared to oxytocin have no anti-diuretic effect, a disadvantage of oxytocin. Corroboratory evidence for this has been shown above by the finding that the blood urea was significantly higher in the prostaglandin treated patients compared to the oxytocin group, which suggests that the latter may have retained fluid. Like Roberts & Turnbull (1970) the author felt that this aspect needed further careful investigation, especially as the state of hydration of the patient prior to induction is critical. These cases include patients suffering from pre-eclampsia and those with cardiac and renal disease. A fluid balance study on patients with classical pre-eclampsia was therefore devised.

PART 5

A COMPARISON BETWEEN THE EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN DURING INDUCTION OF LABOUR IN PATIENTS SUFFERING FROM CLASSICAL PRE-ECLAMPSIA

5.1 INTRODUCTION

Oxytocin is anti-diuretic (Gupta & Cohen, 1972) and prostaglandins therefore may well be specifically indicated for induction of labour in cases where fluid retention is a problem. Although this has been suggested (Roberts et al, 1970; Roberts, 1970; Scher et al, 1972), an adequate comparison is not available. No scientific conclusion could be drawn from the results of our fluid balance measurement in the first attempt at assessment described above. Therefore a study was designed to test this effect by comparing water retention in cases of classical pre-eclampsia being induced with prostaglandin $F_{2\alpha}$ and oxytocin.

5.2. MATERIAL

The principle aims of the study involved careful selection of primigravid patients suffering from classical pre-eclampsia. Rigid criteria were established for selection:

(a) Blood pressure of more than 140/90 mm of mercury on at least 2 occasions.

(b) Proteinuria in a midstream urine specimen of an amount appropriate to the hypertension.

(c) Occurrence of features (a) and (b) above after the 28th week of pregnancy with escalating signs and symptoms.

(d) No past history of renal disease or hypertension.

Seventeen patients suffering from classical pre-eclampsia and requiring induction of labour were studied.

5.3 METHODS

5.3.1 OBSERVATIONS PRIOR TO INDUCTION

All patients were hospitalised for at least 3 days prior to induction of labour. All had the same history, examination and investigations performed. Accordingly, it was possible to establish a certain protocol or trial form. This trial form lists the serial blood and urinary investigations for each patient (See Appendix C). In the ward strict intake and output measurements were made and recorded. The patients were weighed daily and in addition to a full blood count the following renal function tests were performed:

(a) Midstream urine specimens were examined for protein, sugar, white and red blood cells and casts. In addition, an attempt was made to culture organisms from the specimens.

(b) Two creatinine clearance tests were performed.

(c) Daily serum and urinary osmolalities were measured, as well as daily serum and urinary electrolytes.

(d) Estimates were made of the blood levels of urea, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total bilirubin, serum albumin and the total serum proteins.

5.3.2 OBSERVATIONS AT INDUCTION

After being transferred to the labour ward the patient was weighed. All the inductions were personally done by the author. The membranes were ruptured by the method described on page 42 and the volume of liquor measured by draining it into a bedpan. Comparable doses of either prostaglandin $F_{2\alpha}$ and oxytocin were infused according to the schemes described above on page 49. An in-dwelling Foley's catheter was inserted. The last 6 patients in the trial received continuous lumbar epidural analgesia as it was felt that the degree of pain experienced by the patient may affect urinary output by promoting the stress release of anti-diuretic hormone from the posterior pituitary gland (Turnbull, personal communication).

5.3.3 OBSERVATIONS DURING LABOUR

The patients were 'specialled' by the research midwife. Their vital signs were monitored. Uterine contractions and the fetal heart were recorded continuously by means of an external cardiotocograph. Every 30 minutes the urinary volume was recorded and the osmolality was measured by the freezing point depression method on a Knauer Halbmikro-osmometer.

Venous blood was sampled from the anterior cubital vein every 3 hours and the serum osmolality measured by the method described above. The creatinine clearance was measured every 3 hours. These measurements and recordings were kept for at least 6 hours of labour.

5.3.4 OBSERVATIONS AFTER DELIVERY

Blood and urine samples were collected from the patients 12 hours after delivery for osmolality and electrolyte estimations.

5.3.5 RESULTS

All patients were delivered within 18 hours and all neonates were in good biological condition.

The mean total doses of oxytocin and prostaglandin $F_{2\alpha}$ administered conformed to the equivalent dosage schedules.

The fluid balance (ml/hour) results in the prostaglandin $F_{2\alpha}$ and oxytocin groups are listed below in Table 28.

TABLE 28

EFFECT OF OXYTOCIN AND PROSTAGLANDIN $F_{2\alpha}$ ON WATER BALANCE DURING INDUCED LABOUR (ml/hour)

	Case No.	Intake	Output	Balance
Oxytocin	1	97	21	+ 76
	2	98	22	+ 76
	3	55	56	- 1
	4	134	54	+ 80
	5	154	24	+130
	6	70	13	+ 57
	7	138	59	+ 79
	8	90	19	+ 71
	Mean	100.5	33.5	+ 71
Prostaglandin $F_{2\alpha}$	9	26	30	- 4
	10	21	24	- 3
	11	-	-	-
	12	84	25	+ 59
	13	27	42	- 15
	14	44	20	+ 24
	15	43	28	+ 15
	16	171	26	+145
	17	75	41	+ 34
	Mean	61	29	+ 32
		P<0.05	NS	NS

The intake of the oxytocin group was on an average 39.5 ml/hour more than that of the prostaglandin group. This was the only significant difference established in the entire study. There was no difference between the urinary output of the 2 groups. The osmolality of the urine passed (milli-osmoles/litre) is listed below in Table 29. There was no difference between the 2 groups. There was no difference between the osmolar clearances before and at induction. The mean osmolar clearance for oxytocin was 1.313 ± 0.56 osmoles/minute and the mean osmolar clearance for prostaglandin was 1.307 ± 0.28 osmoles/minute. Plasma electrolytes showed no variation at all.

TABLE 29

EFFECT OF OXYTOCIN AND PROSTAGLANDIN $F_{2\alpha}$ ON URINARY OSMOLALITY (milli-osmoles/litre)

Case No.	Pre-induction	Post-induction (hours) 1	2	3	4	5	6
1	865	783	775	825	758	710	788
2	800	775	810	740	705		
3	300	370	425	510	562		
4	311	275	287	306	324	334	362
5	731	701	770	671	549	497	453
6	363	396	408	435	496		
7	665	628	383	501	678	279	422
8	731	686	657	671	667	704	830
Mean	596±232	577±199	564±210	582±173	592±140	505±201	571±220
9	684	682	635	563			
10	823	853	848	830	868	743	
11	619	635	688	616	614	624	645
12	671	717	715	773	677	477	
13	624	494	320	384	515	696	781
14	524	617	631	493	595		
15	541	800	788	762	781	724	
16	695	750	780	805	820	878	823
17	538	530	578	639	765	643	596
Mean	635± 96	675±119	665±155	652±153	708±129	701±141	718± 95

5.3.6 COMMENT

The quality of the urine passed by all cases was the same. The fluid load was greater in the oxytocin group yet these patients passed the same amount of urine as the patients who received prostaglandins. The design of the experiment may well have been to give the same fluid load to both groups but as the primary object was to induce labour it was felt that this method was more applicable clinically. Although this is the first study comparing the effects of prostaglandin and oxytocin on fluid balance in classical pre-eclamptics it does support the work of Roberts et al (1970) which shows that oxytocin is anti-diuretic compared to prostaglandin $F_{2\alpha}$. A greater amount of water was retained when oxytocin was used to induce labour than when prostaglandin $F_{2\alpha}$ was used.

Again, the finding in the first section of this thesis that when prostaglandin $F_{2\alpha}$ was used for induction of labour the blood urea rose after delivery compared with oxytocin inductions where it fell slightly (See page 64) suggests that prostaglandin $F_{2\alpha}$ does not cause fluid retention.

PART 6

THE ROLE OF PROSTAGLANDINS IN SPONTANEOUS LABOUR

6.1 INTRODUCTION

Karim (1966) and Karim & Devlin (1967) have shown that prostaglandin $F_{2\alpha}$ is present in human amniotic fluid obtained during labour and that prostaglandin $F_{2\alpha}$ appears in the maternal venous blood in variable amounts during labour (Karim, 1968a). This work has prompted the suggestion that prostaglandin $F_{2\alpha}$ may play a part in parturition. Further evidence for this role is suggested by the successful use of prostaglandin $F_{2\alpha}$ to induce labour (Karim, 1968a; Karim et al, 1968; Karim et al, 1969b; Scher et al, 1972).

Spontaneous uterine activity and the uterine activity developed with appropriate doses of oxytocin are identical to usual parameters of measurement (Karim et al, 1969b). As it has been shown that the uterine activity obtained with oxytocin and prostaglandin $F_{2\alpha}$ is identical it provides further evidence that prostaglandin $F_{2\alpha}$ may have a physiological role in labour.

Liggins et al (1972) have discussed a possible physiological role of prostaglandin $F_{2\alpha}$ in the mechanism of the onset of labour in sheep. Karim (1972) has discussed evidence supporting a role for prostaglandins in spontaneous labour and abortion. The author decided to test for further evidence of the role of prostaglandin

$F_{2\alpha}$ in parturition. It was felt that it may be implicated in the acceleratory phase of labour, as it had been noted that beta-adrenergic agents are not successful in stopping premature labour once the stage of rapid cervical dilatation has been reached (Baillie et al, in press). The cause of the augmented uterine activity is uncertain, but it is known that prostaglandins augment uterine activity (Gillespie, 1972), and that it is possibly due to stimulation of oxytocin secretion by the maternal pituitary (Gillespie et al, 1972). Karim (1968a) has also demonstrated that prostaglandin $F_{2\alpha}$ appears in the blood during labour in close relation to uterine contractions.

As a result, the author decided to test the effect of Orciprenaline, a beta-adrenergic agent, on prostaglandin $F_{2\alpha}$ and oxytocin induced uterine activity in vivo at term in the same patient, to assess whether the effect of beta-adrenergics was consistent with the hypothesis that prostaglandins are implicated in the stage of rapid dilatation of the human cervix. Attention was thus directed towards an area where ready application to clinical medicine might be available, as most cases of premature labour are admitted in the acceleratory phase of labour, and hence are resistant to beta-adrenergic treatment (Baillie, personal communication).

6.2 MATERIALS AND METHODS

Ten patients with clinically normal cardiovascular systems in whom labour was being induced at term for epidemiological reasons were studied.

An amniocentesis was performed and a cannula (90cm Portex Epidural Cannula, ref. 100/380/010) was passed into the amniotic cavity, the intra-uterine pressure being recorded by means of a Hewlett Packard pressure transducer, number 1280B, used in conjunction with a Hewlett Packard transducer adaptor 1513713, connected to a Hewlett Packard cardiotocograph 8020A. Fifty mg of Pethidine was administered intravenously and labour was randomly induced with oxytocin or prostaglandin $F_{2\alpha}$, using a constant rate infusion pump. Comparable dosage schedules of the 2 drugs were used as discussed earlier on page 74.

When the uterine activity was compatible with early established labour i.e. at least 150 Alexandria units (El-Sahwi et al, 1967), 0.25 mg of Orciprenaline was administered intravenously. The effect on uterine activity, maternal pulse rate (recorded continuously phonocardiographically) and maternal blood pressure (auscultated repeatedly) was noted. When the uterine activity returned to the original level, the first drug was discontinued and the other substituted. The whole procedure was then repeated.

At the conclusion of the experiment the membranes were ruptured and labour was allowed to continue. In only 1 case (number 4) was the cervix more than 4cm dilated. All cases were delivered vaginally within 18 hours and all neonates were in good biological condition.

The effect of Orciprenaline on uterine activity, maternal pulse rate and maternal blood pressure in oxytocin and prostaglandin $F_{2\alpha}$ induced labour was then compared.

6.3 RESULTS

The effect of Orciprenaline on the pulse rate, blood pressure and uterine activity after stimulation with oxytocin and prostaglandin $F_{2\alpha}$ respectively is seen in the tables below:

TABLE 30

EFFECT OF ORCIPRENALINE ON PULSE RATE AND BLOOD PRESSURE AFTER OXYTOCIN

	Pulse Rate (per min)			Blood Pressure (mmHg)		
Case	Initial	Highest	Time to Stability (min)	Initial	Lowest	Time to Stability (min)
1	80	130	8,8	140/105	150/180	4,0
2	80	130	77,0	130/ 80	130/ 40	6,0
3	115	160	44,0	165/100	120/ 40	12,0
4			Delivered			
5	90	150	43,0	145/ 95	135/ 55	7,0
6	85	145	40,0	150/ 90	130/ 55	8,0
7	70	115	15,0	120/ 90	120/ 40	8,0
8	90	155	16,5	135/ 85	125/ 70	4,0
9	75	125	19,0	105/ 85	65/ 0	16,0
10	80	135	8,0	130/ 80	70/ 50	10,0
Mean ±SD	85±13	137±14	30,1±22,7	136±17 / 90± 9	115±29 / 48±23	8,3±3,9

TABLE 31

EFFECT OF ORCIPRENALINE ON UTERINE ACTIVITY*
AFTER OXYTOCIN

Case	Uterine Activity* BL = Baseline tension			Time to Stability (min)
	Initial	Lowest	Stable	
1	227 BL 5	16 BL 3	221 BL 5	18,0
2	251 BL 10	28 BL 8	231 BL 6	94,0
3	112 BL 12	32 BL 8	147 BL 8	42,0
4		Delivered		
5	196 BL 9	25 BL 6	200 BL 6	51,0
6	206 BL 8	20 BL 5	198 BL 5	48,0
7	230 BL 9	0 BL 7	205 BL 9	31,0
8	220 BL 21	75 BL 7	213 BL 9	18,5
9	234 BL 5	0 BL 2	258 BL 3	48,3
10	168 BL 3	0 BL 0	168 BL 3	64,0
Mean ±SD	205±42 BL9± 5	22±24 BL5± 3	205±33 BL6± 2	46,1 ±23,6

* Alexandria units

TABLE 32

EFFECT OF ORCIPRENALINE ON PULSE RATE AND BLOOD PRESSURE AFTER PROSTAGLANDIN $F_{2\alpha}$

	Pulse Rate (Per min)			Blood Pressure (mmHg)		
Case	Initial	Highest	Time to Stability (min)	Initial	Lowest	Time to Stability
1	85	125	22,0	125/80	140/70	4,5
2	70	95	13,3	145/80	140/65	4,8
3	87	135	33,0	150/110	180/70	5,3
4	65	125	47,0	140/90	110/40	10,0
5	75	120	29,0	140/90	140/60	6,0
6	70	125	32,0	130/85	135/55	7,0
7	85	137	25,5	140,80	130/80	6,0
8	90	140	14,5	130/85	120/60	2,3
9	78	128	10,0	140/90	115/80	7,5
10	70	150	14,3	120/90	0/0	6,8
Mean ±SD	78±9	128±15	24,1±11,6	136± 9 88± 9	121±47 58±24	6,0±2,1

TABLE 33

EFFECT OF ORCIPRENALINE ON UTERINE ACTIVITY* AFTER PROSTAGLANDIN $F_{2\alpha}$

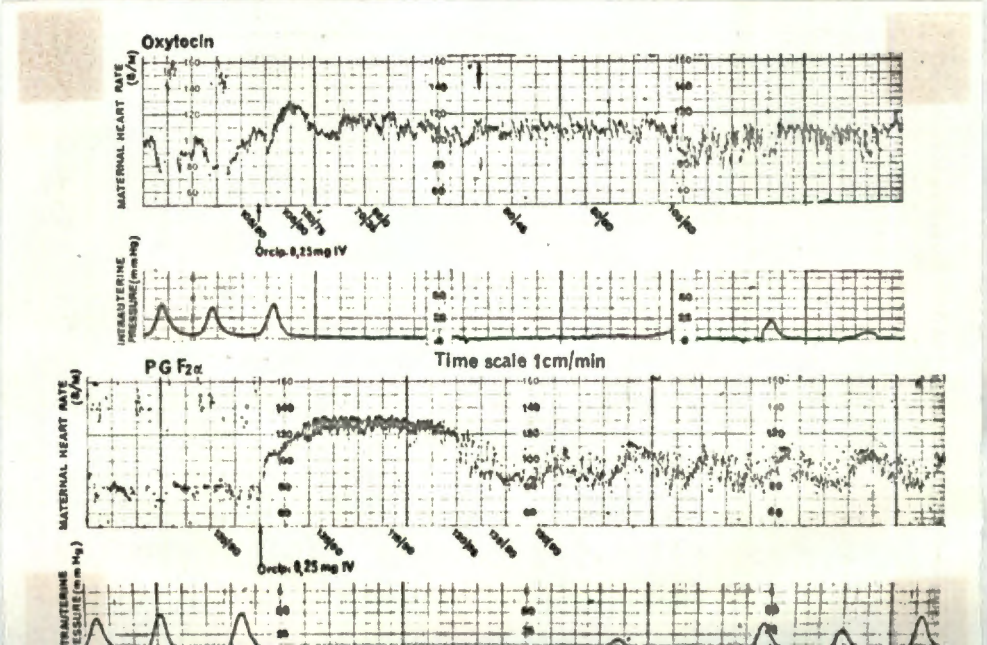
Case	Uterine Activity* BL = Baseline tension			Time to Stability (min)
	Initial	Lowest	Stable	
1	251 BL 12	0 BL 15	267 BL 12	16.0
2	177 BL 20	42 BL 15	262 BL 18	18,0
3	159 BL 18	12 BL 12	146 BL 15	16,5
4	184 BL 8	0 BL 3	264 BL 3	44,0
5	192 BL 17	13 BL 9	235 BL 12	23,0
6	200 BL 20	10 BL 10	240 BL 15	28,0
7	470 BL 18	43 BL 20	417 BL 18	29,0
8	189 BL 20	151 BL 12	281 BL 19	14,5
9	347 BL 3	0 BL 3	225 BL 7	20,0
10	209 BL 5	0 BL 3	296 BL 7	25,5
Mean ± SD	238±98 BL14± 7	27±47 BL9± 6	263±68 BL13± 5	23,5 ±8,8

* Alexandria units

There was no difference in the effect of Orciprenaline on the cardiovascular variables, pulse rate and blood pressure, when labour was induced with prostaglandin $F_{2\alpha}$ and oxytocin. Maternal tachycardia and an increase in blood pressure were noted in all. From the initial pulse rate and blood pressure recordings in Table 32, it appears that there is no alpha-adrenergic effect of the prostaglandin at the dosage used. Tables 31 and 33, however, show a clear difference in effect on uterine activity. Uterine activity was abolished for significantly longer periods when the contractions were induced using oxytocin, in spite of an initially higher level of uterine activity in the prostaglandin series (288 Alexandria units as opposed to 205 Alexandria units for oxytocin). This applied to every case. Figure 10 shows this effect in 1 patient.

FIGURE 10

EFFECT OF ORCIPRENALINE ON UTERINE ACTIVITY AND MATERNAL HEART RATE FOLLOWING PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN



6.4 COMMENT

The finding that Orciprenaline was not as effective in stopping uterine activity in cases induced with prostaglandin $F_{2\alpha}$, as opposed to oxytocin, is further evidence for a role of endogenous prostaglandins in spontaneous labour and prostaglandin $F_{2\alpha}$ may be implicated in the acceleratory phase of labour. This supports the evidence mentioned in the Introduction, on page 92, which is already available for the role of prostaglandins in spontaneous labour and abortion. Prostaglandin E and prostaglandin $F_{2\alpha}$ are present in human amniotic fluid samples obtained during labour or spontaneous abortion only (Karim, 1966; Karim & Devlin, 1967; Karim & Hillier, 1970).

In addition, the same prostaglandins are present in the maternal circulation in high concentrations during labour and spontaneous abortion (Karim, 1968 a,b, 1970a; Karim & Hillier, 1970). Labour and abortion can both be induced with prostaglandins (Karim et al, 1969b; Beazley et al, 1970; Embrey, 1970; Karim et al, 1970; Karim & Filshie, 1970 a,b; Beazley & Gillespie, 1971; Embrey & Hillier, 1971).

PART 7

DISCUSSION

7.1 THE PROSTAGLANDIN USED

The discovery of the biosynthetic production of the primary prostaglandin compounds and their total chemical synthesis enabled these substances to be studied extensively in many laboratories. This led to an exhaustive literature on the functional significance of the prostaglandins in most of the body systems. For information on these systems the reader is referred to the many articles and monographs available (Vogt, 1958; Eliasson, 1959; Horton, 1965, 1968, 1969; Bergström, 1966, 1967, 1973; Pickles, 1967; Von Euler & Eliasson, 1968; Bergström & Samuelsson, 1968; Bergström et al, 1968).

The effects of prostaglandins of the E and F series on the non-pregnant human uterus have been studied in vitro (Bygdeman, 1967; Eglington et al, 1963; Pickles & Hall, 1963; Pickles et al, 1965) and on human pregnant myometrium both in vitro (Embrey & Morrison, 1968) and in vivo (Embrey, 1969). It was shown by Embrey (1969) that both the E prostaglandins and those of the F series stimulate myometrial activity of the pregnant uterus, although the E prostaglandins have an inhibitory action in the non-pregnant state which, he felt, emphasised that the effect of a pharmacological agent is influenced by the physiological state of the organ.

Prostaglandin $F_{2\alpha}$ was used in this study as it was the only prostaglandin available to the author at the commencement of his research.

Along with PGE_2 the F prostaglandins probably have a physiological role in labour (Karim, 1966; Karim & Devlin, 1967; Karim, 1968b; Embrey, 1969). Equally, at this time it was the only prostaglandin that could be assayed satisfactorily (Hillier, personal communication).

7.2 DESIGN OF STUDY

A great deal of care was taken in the design of this study in order that real comparisons could be made and scientific conclusions drawn. The cases were carefully selected with particular attention to the factors affecting the response to the induction of labour. For this reason only primigravidae were studied. When comparisons were made there was no statistical difference between the 2 groups of patients for these factors. Beazley & Gillespie (1971) felt that meaningful conclusions could not be drawn without using matched cases.

The patients were 'specialled' during labour by a single trained research midwife, and all cervical assessments were personally carried out by the author. This individualisation of cases minimises observer error which must be a fault of larger computer series.

Prior to comparing the effects of prostaglandin $F_{2\alpha}$ and oxytocin, comparable dosage schedules of the 2 drugs were derived. The failure to do this is a fault of other similar studies (Dewhurst, 1972), and may account for the widely varying results obtained.

The equivalent dosages were derived using in-patient control under the conditions where the drugs are used i.e. induction of labour at or near term. These stringent demands should be met when drug dosages are derived. Common errors are:

(a) Not using in-patient control, as the effects of oxytocics vary widely from patient to patient.

(b) Not using an in vivo situation comparable to clinical usage, as it is fruitless to compare an in vitro with an in vivo situation because of the differing physiological states, or even one clinical situation to another which is apparently closely analagous. Even more fallacious is the attempt to relate to clinical work findings derived from either in vitro human studies or any animal studies, whether in vitro or in vivo. This lack of correlation is well established and reviewed (Pauerstein & Zauder, 1970; Pulkinen, 1970).

Standard fluid balance recordings were kept during the study. It became apparent, however, on analysing the results that no conclusions could be drawn. As a result a further more careful study was designed. Again, the testing of comparable doses of drugs in conditions associated with fluid retention has not been performed

previously. Roberts et al (1970), although doing a good fluid balance study, did it on 6 normal patients in mid-pregnancy who are different from pre-eclamptics (Hytten & Leitch, 1971).

The original protocol form for this study has been re-designed to ensure that patients receive an equal amount of fluid before and during the trial.

7.3 DOSAGE SCHEDULES OF PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN

Since it has been realised that the prostaglandins may also be oxytocic numerous papers have appeared comparing their efficacy with that of oxytocin (Anderson et al, 1971; Beazley & Gillespie, 1971; Craft et al, 1971; Vakhariya & Sherman, 1972).

From these trials no conclusions can be drawn about the relative effectiveness of these 2 drugs as comparable doses of oxytocin and prostaglandin $F_{2\alpha}$ were not used (Scher & Baillie, in press). Dewhurst (1972) feels this is a major criticism of such studies.

The result of the present investigation would thus appear to be of value in that a scientific attempt was made to enable 2 drugs to be compared.

It is fruitless to argue which is the stronger of 2 drugs. The clinician wants safe delivery and the effects of equivalent drugs must be those which provide this. Further, as mentioned above on page 106, one cannot correlate animal work to human work (Pauerstein & Zauder, 1970), or even in vitro human work to the clinical situation. Thus the author felt it would be important to choose a good model using in-patient control to establish drug dosages. Both drugs were tested in each patient.

The ratio of prostaglandin $F_{2\alpha}$ to oxytocin is 3.14:1 when comparing potency and this was used in devising the comparable dosage schedules described on page 49. These 2 drugs are dissimilar and have different molecular weights but it nevertheless provides a means for comparing them clinically.

7.4 SUCCESS OF PROSTAGLANDIN $F_{2\alpha}$ IN INDUCING LABOUR AT TERM AS COMPARED WITH OXYTOCIN

The results of the present study show that using comparable dosage schedules, prostaglandin $F_{2\alpha}$ is numerically better in its ability to induce labour at term than oxytocin, but this is not at a statistically significant level (82% versus 65%). This is in agreement with the work of Vakhariya & Sherman (1972), although their study involved multigravid patients. They achieved a 96% success rate with oxytocin and 94% with prostaglandin $F_{2\alpha}$. Beazley & Gillespie (1971) induced labour in 150 patients each with prostaglandin E_2 and oxytocin. Seventy-three per cent of patients in each group were delivered, or achieved 5cm dilatation of the cervix within 12 hours of the start of the infusion. The patients were not matched for factors known to affect labour, however, and amniotomy was not performed at induction.

Primigravidae treated with prostaglandin E_2 were successfully induced in 67% of cases and those treated with oxytocin had a 69% success rate. Karim (1971), however, reported 67% and 56% success rates in 100 inductions each with prostaglandin $F_{2\alpha}$ and oxytocin respectively. However, comparable doses of the 2 drugs were not used. No details of how the patients were matched were given and a very low maximum dosage of oxytocin is described. This obviously biases success in induction of labour towards prostaglandins rather than oxytocin. Embrey (1970) successfully induced labour in 23 out of 25 patients at, or near term using prostaglandin E_1 or E_2. The success rate for the prostaglandin $F_{2\alpha}$ patients with a ripe cervix in this thesis was 94% and for the oxytocin group with a ripe cervix 80%. With an unripe cervix prostaglandin $F_{2\alpha}$ was successful in 75% of cases and oxytocin in 64% of cases. Anderson et al (1971) only achieved a 23% success rate using prostaglandins E_2 and $F_{2\alpha}$ in term induction in multipara with Bishop scores of 6 or less. Their titration schedules were of a very low order, however, and they subsequently improved their success rate by increasing maximum dosages. Based on the results of this study the author is convinced that prostaglandin $F_{2\alpha}$ is as effective as oxytocin for the induction of primigravidae at term, particularly as comparable dosage schedules of the 2 drugs were used

which was a failure in most other studies (Dewhurst, 1972). This is to be expected. Differences in the incidence of side effects are therefore of crucial importance in deciding which drug is superior.

The dosage schedules devised are not only comparable but simple to use, easy to follow, and could easily be used by midwives. Thus they have practical significance. Conflicting success rates in some studies comparing the use of prostaglandins and oxytocin in induction of labour may be due to using rather a low dose of 1 drug compared to the other.

7.5 ASSESSMENT OF THE CERVIX

As mentioned under methodology, all patients were assessed by the author for the factors known to affect the response to induction. Much emphasis was placed on the state of the cervix, as Embrey & Anselmo (1962) had shown that the ripeness of the cervix is the most influential clinical feature in labour induction using oxytocin. Turnbull & Anderson (1967) concluded that ripeness of the cervix is a major clinical factor affecting the outcome of amniotomy in labour induction. Further, Garrett (1960) felt that the state of the cervix is the only sign of practical importance in the prediction of the outcome of surgical induction. The author classified the cervix as ripe or unripe after Embrey's classification

of the primigravid cervix (1962) which is as follows:

Favourable Cervix

1. Cervix more than 2 fingers dilated, partly effaced.
2. Cervix 1 to 2 fingers dilated, well effaced, soft and stretchable.

Unfavourable Cervix

1. Cervix long (uneffaced), less than 1 finger dilated.
2. Cervix partly effaced but tight, less than 1 finger dilated.

Intermediate Cervix

All cases not falling into either of the above groups.

The author felt, however, that in primigravidae the degree of effacement of the cervix is of major importance in assessing the cervix and the response to induction. He felt that insufficient attention has been given to this in the literature and no reference to an attempt at scientific measurement of this factor has been given. Bishop (1964) did however, include an assessment of effacement as a factor when devising his scheme for giving a total pelvic score in order to assess the favourability of the outcome of elective induction of labour. In this thesis the author regarded the length of the primigravid cervix to be 3cm at the onset of labour. The technique of measurement is described on page 30.

'Effacement-grams' besides 'cervico-grams' were kept and it was clearly shown that the major portion of the latent phase of labour is concerned with cervical effacement. Applying statistics to the results it was found that if the cervix was not 75% effaced 8 hours after induction 13 out of 18 cases will not deliver or be 5cm dilated within 12 hours as shown in Table 34 below:

TABLE 34

RATE OF EFFACEMENT OF PRIMIGRAVID CERVIX ON OUTCOME OF INDUCTION

	Delivery or 5cm Dilatation within 12 hours	
	Yes	No
Cervix 75% effaced after 8 hours	59	5
Cervix not 75% effaced after 8 hours	5	13

$p < 0.001$

This is in complete disagreement with Anderson et al (1971) who in discussing induction with prostaglandin solutions, found that with a Bishop score of 4 or less (unripe cervix) contractions occurred which were strong and regular for 6 to 8 hours, without any discernible change in cervical dilatation and effacement. The

patient would then be found to be 2 to 4cm dilated and delivery would occur in the next 1 to 2 hours. They felt that this might be representative of the type of labour one might expect from prostaglandin inductions in difficult cases. The reason for the lack of cervical change is not apparent but may be due to the fact that the patients in their series were multiparous patients (up to para 4) and primigravidae, who are more predictable, were excluded. Again, in this study the only difference in the labour pattern between the ripe and unripe cervix was the longer latent phase in the latter during which increasing effacement took place. Thus it was found that the latent phase of labour between induction and the acceleratory phases of labour varies with the state of the cervix and that effacement is of major importance. Embrey & Anselmo (1962) provide corroboratory evidence for this as they felt that the latent period between induction and the onset of labour varies with the ripeness of the cervix. A modification of Embrey's classification was thus devised and employed in this study:

Favourable Cervix

More than 2cm dilated and/or more than 66% effaced.

Unfavourable Cervix

Less than 2cm dilated and/or under 66% effaced.

It is felt that this is more precise in that it quantitates, rather than qualitates, effacement.

Using these criteria to assess the cervix, it can be seen from Table 35 that the success rate did vary with the ripeness of the cervix. Although no justification for a cervical score was found by the author in the literature, these findings would lend credence to the evidence based on first principles.

TABLE 35

EFFECT OF STATE OF THE CERVIX

ON OUTCOME OF INDUCTION

State of Cervix	Prostaglandin $F_{2\alpha}$ Success %	Oxytocin Success %
Unripe Cervix	75	64
Ripe Cervix	94	80

These findings support the work of Embrey & Anselmo (1962) mentioned above. A differing definition of favourability was derived by them for primigravidae and

multiparae. Anderson et al (1971), who did not find the state of the cervix significant, did not distinguish between them and furthermore, multiparous labour is known to be more rapid (Friedman, 1967).

Each patient in this thesis was also assessed according to Bishop's scoring system (1964) and it was found that using this method a score of 9 or more, which was a favourable prediction for labour by his criteria, agreed with the author's assessment for a ripe cervix, using the criteria of ripeness listed above, in only 68% of cases.

This lack of close agreement may be due to several factors. No statistical validation of the Bishop score was found. The statement that 'experience has convinced us that elective induction may be successfully and safely performed when the pelvic score totals 9 or more' (Bishop, 1964) highlights this contention. A high pelvic score, however, is, by first principles, more likely to be associated with an easy induction. The factors used in any non-parametric scoring system are not equivalent and may even be interrelated as is probable in Bishop's system with such factors as consistency, position of the cervix and engagement of the fetal head. These are directly related to effacement of the cervix. For this reason, and because of the close correlation found with Embrey's classification (Embrey, 1962) it was thought that cervical effacement was the best available guide to the ease of induction of labour.

7.6 THE EFFECT OF AMNIOTOMY ON PROSTAGLANDIN AND OXYTOCIN INDUCED LABOUR

Confusion and contradiction punctuate the obstetric literature with regard to the influence of the chorio-amniotic membranes on the course of labour. No true physiological prospective studies were found by the author in the world literature which used cases matched for factors affecting the response to induction, with the state of the membranes being the only variable. Further, no published study is as yet available on the effect of rupturing the membranes on labour induced with prostaglandins.

The results of this thesis show quite clearly that elective artificial rupture of the membranes speeds up the onset of labour and accelerates the latent phase of labour. This enhancement occurs to a statistically significant degree where prostaglandin $F_{2\alpha}$ is the agent used, and to a numerical degree only when oxytocin is used. The reason for this improvement may be the pressure of the head on the cervix, acting via Ferguson's reflex (Ferguson, 1941).

Further, it has been shown that rupturing the membranes artificially increases uterine activity (Brotanek, 1966; Brotanek et al, 1969), and this may be an additive factor.

Why Friedman (1967) found an adverse effect from rupturing the membranes may be that he obtained his results from a large computer study involving every case entering the labour ward. Amongst these would be patients with early rupture of the membranes because of abnormal positions and patients with abnormal uterine activity. Some cases, however, would conform to our results. If all these cases are put together and averaged out no effect on labour may be found, which is a fault of large computer studies.

Infection was not encountered in the cases studied. A further advantage to rupture of the membranes is the provision of an additional parameter (the appearance of the liquor amnii) by which we can monitor the fetus in labour.

7.7 SIDE EFFECTS PRODUCED BY PROSTAGLANDINS

Many side effects have been reported following the use of prostaglandins to induce labour. The main ones noted were diarrhoea, vomiting and a red line along the area draining the infusion site, which will be referred to as 'phlebitis', uterine hypertonus and inco-ordinate uterine action (Karim & Filshie, 1970b; Roberts & Turnbull, 1971; Roth-Brandel & Adams, 1970).

DIARRHOEA

From the results described above on page 66 it was shown that the amount of diarrhoea recorded during induction with the 2 drugs was not statistically different. Rupturing the membranes also had no effect on this. It must be remembered that in some obstetric units patients routinely receive an enema prior to induction. This may have aggravated the amount of diarrhoea in both groups. Prostaglandins occur naturally in the gut wall, however, and may therefore be involved in normal motor activity of the gastro-intestinal tract (Bennett, 1971). Furthermore, prostaglandins are released during peristalsis (Bennett et al, 1967; Coceani et al, 1967). A pathological role for circulating prostaglandins on gut motility is provided by the possible diarrhoeal effects of prostaglandins released from certain tumours (Williams et al, 1968). From this evidence it would seem likely that too high dosages of prostaglandins may be a cause of diarrhoea.

VOMITING

There was no statistical difference in the amount of vomiting between the 2 groups. When the membranes were ruptured electively at induction, however, this resulted in a significant increase in the amount of vomiting in both groups. The reason for this is not clear.

'PHLEBITIS'

A tissue reaction at the infusion site occurred with statistical significance ($p < 0.001$) in the prostaglandin $F_{2\alpha}$ treated group. It appeared as a reddening overlying the vein draining the infusion site (See Colour Plate page 67). This effect was transient and faded rapidly on discontinuing the infusion. Only 1 patient complained of a burning discomfort at the infusion site. It was not tender to pressure. Hillier & Embrey (1972) used higher doses of prostaglandin $F_{2\alpha}$ for induction of abortion and obtained the same findings, except that they found the prostaglandin $F_{2\alpha}$ induced reaction caused a reddening of the tissues around the infusion site, rather than along the vein. The explanation for this reaction, which has been variously described as 'phlebitis','venous erythema' or 'chemical vasculitis' (Hillier & Embrey, 1972), is not clear.

Solomon et al (1968) studied the effect of injected PGE_1 on the skin of the fore-arms of 8 healthy human subjects. They found it was a potent vasodilator of human cutaneous vessels and its effect was only partially dose-dependent, as when the injected dose was lowered from 5 µg to 1 µg the reaction was less marked but otherwise the same. It caused a transient erythema which was tender to pressure. In these patients there was an inflammatory streak leading away from the injection site which they felt may have been due to leakage of PGE_1 from the lymphatic vessels.

Greaves et al (1971) have recovered prostaglandins E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ from inflamed areas of human skin, and they feel that prostaglandins may be mediators of human cutaneous inflammation. This is supported by the fact that skin from man is capable of prostaglandin synthesis (Jonsson & Angård, 1972; Zibohr et al, 1973).

BLOOD UREA

In those cases where the membranes had been ruptured electively a statistically significant rise in the blood urea occurred after delivery in the prostaglandin group as compared to the patients who had received oxytocin. This suggests that prostaglandin $F_{2\alpha}$ was not anti-diuretic. Prostaglandin $F_{2\alpha}$ has been identified within the renal medulla and there is evidence that the reno-medullary prostaglandins may normally participate in an anti-hypertensive and naturetic function (Lee et al,

1967). The excretion of water may account for the rise in blood urea. This may be of great advantage in labour induction where fluid retention may be critical.

There were no statistical differences in the effects of the 2 drugs on the haemoglobin level, total white blood cell count, differential count and platelet count. Platelet functions were not performed.

HYPERTONUS

Dewhurst (1972) feels that hypertonus is likely to occur during prostaglandin infusion in the main circumstances discussed below:

1. An Initial High Dose

Roberts & Turnbull (1971) reported 4 cases of uterine hypertonus following amniotomy in 18 women induced at term when given 0.75 - 3 µg per minute of PGE_2 intravenously; their initial dose was high, however, and in 1 case the uterine hypertonus encountered was definitely due to too high a dose.

2. A High Dose Reached by Frequent and Large Increases

Beazley (1971) had found that a latent period of 15 to 30 minutes exists with the prostaglandins when used for labour induction. Embrey (1969) found a latent period of 15 to 20 minutes when prostaglandins were administered intravenously in late pregnancy. If this delay in response is not appreciated, one dose could coincide with the next dosage increase and hypertonus may therefore result. This effect is illustrated by the cardiotocograph tracings on page 51. From these it can

be seen that the author overcame this problem by observing a 30 minute interval between incremental dosages of prostaglandin $F_{2\alpha}$.

Embrey (1969) does not report hypertonus using E and F prostaglandins in the only other series where equivalent doses of oxytocin and prostaglandin were used, except in 1 case where overdosage occurred (8 µg per minute of PGE_2 was given, the previous range being between 2 - 6 µg PGE_2 per minute).

In this study no hypertonus was encountered using prostaglandin $F_{2\alpha}$ in 43 patients who received it up to a maximum dose of 40 µg per minute. Karim (1970), with a dose not exceeding 10 µg per minute of prostaglandin $F_{2\alpha}$ to induce labour, did not encounter hypertonus in 200 patients. Beazley & Gillespie (1971) found no hypertonus in 150 patients receiving prostaglandin $F_{2\alpha}$, even though they used a highest dose of 6.7 µg per minute of prostaglandin E_2 (equivalent to 67 µg prostaglandin $F_{2\alpha}$ per minute). This strength was reached, however, only after 5 increases at hourly intervals. Embrey (1970) did not encounter hypertonus in 23 cases at or near term using PGE_1 and PGE_2 to induce labour.

Uterine over-stimulation is a potential risk with both oxytocin and prostaglandin (Beazley & Gillespie, 1971) and care must be taken to infuse them cautiously if the problem is to be avoided. Anderson et al (1972) concur with this view which supports the findings of this thesis.

QUALITY OF LABOUR

Karim et al (1970) found that the uterine activity produced by prostaglandin infusion resembled that of normal spontaneous labour and no unphysiological increase in uterine tonus was observed.

Roth-Brandel & Adams (1970), using lower doses of prostaglandin $F_{2\alpha}$ than the author, however, recorded episodes of inco-ordinate uterine activity. The examples illustrated are not convincing. They admit that mid-pregnancy may not be equivalent to late pregnancy, and in the only example of late pregnancy inco-ordinate activity occurred after 410 minutes of a constant infusion of prostaglandin $F_{2\alpha}$ 0.7 µg per minute. If labour had supervened before this time, this may well have been an excessive dose. The more usual pattern of response, common to prostaglandins $F_{2\alpha}$, PGE_1 and PGE_2, was an initial increase in frequency of contractions, followed more slowly by an increase in intensity.

Using the formula of Effer et al (1969), discussed on page 60, which is a measure of the quality of labour, this was not found. The quality of the labour produced was similar to that obtained with oxytocin, whether amniotomy was performed or not.

HAEMATOLOGICAL EFFECTS

No alteration was found in the haemoglobin, white blood cell count, differential count or platelet count of any patient tested. A leucocytosis has been reported following high dose intravenous prostaglandins $F_{2\alpha}$ and PGE_2 used for mid-trimester abortion (Hillier & Embrey, 1972). The doses used, however, are far in excess of those used for the term induction of labour. The effects of prostaglandins on erythropoeisis are still not certain. It has recently been reported, however, that prostaglandins modulate the effects of the hormone erythropoeitin on erythroid differentiation in marrow cell cultures (Dukes, 1972).

BLOOD PRESSURE, PULSE RATE AND RESPIRATION

No significant change was noted in the blood pressure, pulse rate or respiration of any patient receiving prostaglandin $F_{2\alpha}$ or oxytocin. Karim et al (1969a) and Karim & Filshie (1970a) found this to be the

case in male volunteers employing doses of prostaglandin $F_{2\alpha}$ up to 150 µg per minute. These are higher dosages than those used in this series. Embrey (1969), using a maximal total dose of prostaglandin $F_{2\alpha}$, also found no changes in these parameters.

It appears from the lack of effects on the parameters discussed above that prostaglandin $F_{2\alpha}$ has a very selective effect on the pregnant myometrium (Karim et al, 1969a).

EFFECTS ON THE FETUS

No abnormalities of the fetal heart rate occurred in this study employing either prostaglandin $F_{2\alpha}$ or oxytocin. Figures 8 and 9 on page 80 show the cardiotocograph tracings from 1 patient which illustrate that it is the placental reserve which is important in determining the response of the fetus to labour (Scher & Baillie, in press).

In summarising the toxic effects of prostaglandin $F_{2\alpha}$ when compared to oxytocin in equivalent dosages, it is reasonable to conclude that the only side effect significantly associated with prostaglandin $F_{2\alpha}$ administration is the transient 'red line' at the infusion site. This agrees with Embrey's findings for prostaglandins E_1 and E_2 (1970).

7.8 THE EFFECTS OF PROSTAGLANDIN $F_{2\alpha}$ AND OXYTOCIN ON FLUID BALANCE DURING INDUCTION IN PATIENTS SUFFERING FROM PRE-ECLAMPSIA

Oxytocin is anti-diuretic (Gupta & Cohen, 1972) and water intoxication has been reported as a complication (Liggins, 1962; Whalley & Pritchard, 1963; Potter, 1964; Self, 1966; Silva & Allan, 1966; Lilien, 1968; Josey et al, 1969; Goodlin et al, 1969; Bilck & Dorr, 1970; Gupta & Cohen, 1972).

It has been reported that in pregnant women having a continuous intravenous infusion of oxytocin, anti-diuresis starts at an infusion rate of about 15 m-u per minute and is maximal at 45 m-u per minute (Abdul-Karim & Assali, 1961). The measurement of fluid balance in labour presents considerable difficulties because of the lack of a steady state. In this study a greater amount of water was retained when oxytocin was used to induce labour than when prostaglandin $F_{2\alpha}$ was used. The metabolic effects of the pre-eclamptic process are probably the most important variables in determining the amount of fluid retained (Hytten & Leitch, 1971). This may account for the wide variation encountered in this study, despite great care in selecting cases and in establishing comparability before induction.

Pain and fear may reduce the renal plasma flow and glomerular filtration rate (Hytten & Leitch, 1971). In order to avoid this, a lumbar epidural anaesthetic was used (Turnbull, personal communication) in cases 4, 5, 6, 7, 11, 12, 13 and 16. This produced variable results, however, the reason for which is not understood. This variability of response may be due to the variability of dermatone analgesia produced by an epidural block. Renal blood flow is probably enhanced by a block extending to T8 and T9 (Crawford, 1972), whereas a block extending more cranially may well cause sympathetic blockade and a decrease in renal flow, on occasion even extending to a systemic hypotension (Willocks & Moir, 1968). No systemic hypotension was recorded in this series, but effects on renal blood flow could not be excluded.

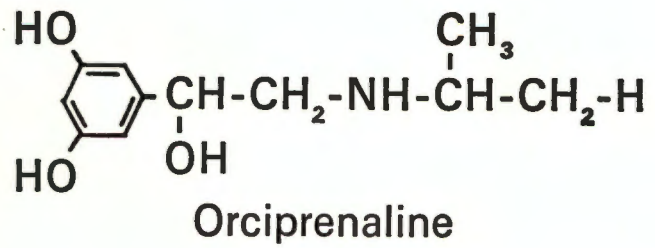
Another factor which may affect urinary output is the position adopted by the pregnant woman. In the supine position the pregnant woman shows a decreased urine flow, decreased electrolyte excretion, decreased glomerular filtration rate and also a decreased renal plasma flow. Further, Klopper (1964) noted that the reduction in diuresis after a water load when a pregnant woman lay on her back versus her side, was particularly marked in hypertension. In labour it is particularly trying for the patient to lie in a fixed position on her side.

Isotopic studies were not attempted because it is unethical to use isotopes in a pregnant woman. The measurement of urine volume and osmolality is the best guide to fluid status under clinical conditions (Pitts, 1968). In this study, despite a significantly higher intake of fluid in the oxytocin group, the urinary volumes were almost identical. This is contrary to expectation if there were no differences between $F_{2\alpha}$ and oxytocin.

Furthermore, as the osmolality of the urine of the 2 groups was similar, it would appear that water was being retained in the oxytocin group, an action compatible with an anti-diuretic effect (Strauss, 1957). This is well known for oxytocin (Abdul-Karim & Rizik, 1970), and although by no means conclusive, this study offers further objective evidence that prostaglandins are superior to oxytocin in cases of pre-eclampsia where induction is necessary. As a result of difficulty in measuring fluid balance in labour a further study has been devised, with special attention being given to the initial state of hydration and standardisation of the amount of fluid given to each patient per unit time.

7.9 THE ROLE OF PROSTAGLANDINS IN SPONTANEOUS LABOUR

The findings of this thesis suggest that prostaglandin $F_{2\alpha}$ has a physiological role in the acceleratory phase of labour. An in vivo situation was used to test this. In order to avoid patient to patient variation both drugs were used in the same subject. In the titration schedules uterine activity analogous to early labour was obtained by using comparable titration schemes for oxytocin and prostaglandin $F_{2\alpha}$. Orciprenaline, the formula of which is shown below,



Orciprenaline

a resorcyl ethanolamine and beta-adrenergic stimulant, was less effective in decreasing uterine activity stimulated by prostaglandin $F_{2\alpha}$ than by oxytocin.

There are several possible explanations for this. Firstly, the effect of the prostaglandin may be on the sarcoplasm via a calcium mechanism (Carstens, 1972), thereby bypassing the site of action of beta-adrenergic agents and oxytocin. Secondly, prostaglandin stimulated labour may be less affected by Orciprenaline because of the known alpha-adrenergic effect of prostaglandin. This effect was not noted, however, as seen by reference to the pulse rate in Table 32 on page 98. Thirdly, the other possible mechanism is that prostaglandins stimulated oxytocin release, leading to an augmented effect (Gillespie et al, 1972) which would be less easily depressed by Orciprenaline.

These findings would conform with the hypothesis that the prostaglandins may be implicated in the stage of rapid cervical dilatation, as beta-adrenergics are known to be less effective in this stage of premature labour and the result of this study reinforces the possibility that prostaglandins may have a physiological role in parturition. Consequently, a new approach in the management of premature labour is suggested in that anti-prostaglandins may be effective at a later stage in premature labour, thereby enabling many more cases to be treated. It is the author's intention to assess this possibility.

PART 8

SUMMARY AND GENERAL CONCLUSIONS

The prostaglandins are an important new group of local hormones. They have found their first clinical application in obstetrics. The clinical role for these agents has not been decided and has received inadequate scientific consideration. In particular, the place of prostaglandins in obstetrics in a country which does not have an abortion law, such as South Africa, has not received attention.

The comparison of the oxytocic properties of prostaglandin with oxytocin in the induction of labour has not always been undertaken with due regard to matching patients for the factors determining a patient's response to induction, and, in particular, scant attention has been given to using equivalent dosages of the two drugs.

It was thus considered that a study directed towards clarifying the true clinical role of prostaglandins in obstetrics, and comparing it with oxytocin, should be undertaken and was necessary. Accordingly the aims of this thesis, as outlined in Part 2, were:

1. To determine comparable dosage schedules of prostaglandin $F_{2\alpha}$ and oxytocin for labour induction, so that real comparisons could be made.

2. To determine the success rate of labour induction in a physiological study on matched patients receiving oxytocin or prostaglandin $F_{2\alpha}$, initially without performing amniotomy, and then subsequently to study patients where amniotomy is carried out at the time of induction of labour, in order to evaluate the effect of rupturing the membranes on labour induced by oxytocin or prostaglandin $F_{2\alpha}$,

3. To determine if the advantage claimed for prostaglandin in induction of labour with an unripe cervix is real or spurious,

4. To study the side effects which are a supposed disadvantage of prostaglandins, namely diarrhoea, vomiting, 'phlebitis', hypertonus and abnormal uterine action,

5. To study the effects of prostaglandin $F_{2\alpha}$ and oxytocin on the blood urea and blood count,

6. To study the effects of prostaglandin $F_{2\alpha}$ and oxytocin on fluid balance in primigravidae suffering from classical pre-eclampsia,

7. To determine the physiological role for prostaglandins in spontaneous labour.

To provide a background to these studies the historical background and chemistry of the prostaglandins was reviewed.

Primigravid patients requiring induction of labour were selected and compared for the criteria known to influence the response to induction. As there was no difference in these criteria in the oxytocin and prostaglandin groups, the results obtained could be compared.

In a separate study equivalent titration schedules for oxytocin and prostaglandin $F_{2\alpha}$ were determined by direct intra-amniotic pressure recordings. These practical schedules were used throughout this thesis.

Following initial evaluation of the criteria of inducibility mentioned above, the blood urea, haematocrit and total and differential white blood cell counts were determined. The carefully selected patients, 83 in number, received either prostaglandin $F_{2\alpha}$ or oxytocin, depending on whether their folder number ended in an odd or even figure. A method of assessing cervical ripeness was determined and 'cervico-grams' and 'effacement-grams' were kept during labour. Parameters by which the success rate of different methods of induction could be compared were determined. All the

patients were constantly 'specialled' by a single research midwife and all the cervical assessments were performed by the author personally throughout the trial. All data were recorded on special trial forms (See Appendix A) and the data ultimately transferred to computer cards for analysis and statistical evaluation.

The following results were obtained:

1. The success rate of induction of labour using oxytocin or prostaglandin $F_{2\alpha}$, although numerically better with the latter, shows no statistical difference.

2. Prostaglandin $F_{2\alpha}$ is statistically superior to oxytocin where an unripe cervix exists and the membranes are ruptured, but this is felt to be an effect of amniotomy.

3. Amniotomy significantly enhances the success rate of induction with prostaglandin $F_{2\alpha}$.

4. There is no statistically significant difference in the amount of diarrhoea and vomiting produced by the 2 drugs. The only significant side effect of prostaglandin $F_{2\alpha}$ is a transient red line along the area draining the infusion site.

5. Prostaglandin $F_{2\alpha}$ produces a normal quality of labour.

6. Amniotomy statistically significantly accelerates labour in both prostaglandin $F_{2\alpha}$ and oxytocin induced labour.

7. The major part of the latent phase of labour in primigravid patients is concerned with effacement of the cervix, and if the cervix is not 75% effaced 8 hours after induction 13 out of 18 cases will not deliver, or be 5cm by 12 hours.

8. Neither administering prostaglandin $F_{2\alpha}$ nor oxytocin causes a change in the blood urea, haematocrit, white blood cell or differential count.

9. Neither administering prostaglandin $F_{2\alpha}$ or oxytocin for labour induction causes a change in the systolic or diastolic blood pressure.

10. This thesis shows that oxytocin is anti-diuretic when compared to prostaglandin $F_{2\alpha}$ in the induction of labour at term in patients suffering from classical pre-eclampsia. These 17 patients are not included in the 83 inductions described above.

11. Prostaglandin $F_{2\alpha}$ is not anti-diuretic when compared with oxytocin in the induction of primigravid patients suffering from classical pre-eclampsia.

12. The use of a beta-adrenergic agent (Orciprenaline) in stopping labour induced with oxytocin or prostaglandin $F_{2\alpha}$ suggests that the latter has a physiological role in the acceleratory phase of labour.

A rapidly changing biological equilibrium such as the onset of labour, and the factors governing it, is difficult to study because many unknown or unquantifiable variables affect this equilibrium. Precise conclusions are therefore difficult to make.

The following conclusions, however, may be made:

1. This carefully controlled physiological study has shown that prostaglandins are as effective as oxytocin in the routine induction of labour at term but have a latent period which must be respected. They may be more effective where an unripe cervix is found and the membranes are ruptured.

2. The side effects obtained when using prostaglandins are not a major disadvantage. The only significant side effect of prostaglandin $F_{2\alpha}$ is a transient red line over the area draining the infusion site. The other side effects usually ascribed to prostaglandins are thought to have been exaggerated. Further, the development of synthetic analogues may overcome these side effects.

3. Prostaglandins cause less fluid retention and hence must be considered the drug of choice in the induction of patients where fluid balance is critical e.g. pre-eclamptics, hypertensives and patients with renal or cardiac disease.

4. Comparable dosage schedules of prostaglandin $F_{2\alpha}$ and oxytocin must be used when comparing the 2 agents.

5. Rupturing the membranes at amniotomy statistically significantly improves the success rate of induction with prostaglandin $F_{2\alpha}$.

6. Prostaglandins may be implicated in the acceleratory phase of labour.

PART 9

FUTURE STUDIES OF PROSTAGLANDINS IN OBSTETRICS SUGGESTED BY THIS THESIS

1. Fluid balance studies comparing oxytocin and prostaglandin with equivalent intakes of fluid.

2. Similar comparisons of effectiveness in induction of labour using PGE_1, PGE_2 and synthetic analogues as they become available. Total chemical synthesis has been achieved (Corey, 1969) and natural and synthetic analogues are being developed which may be more successfully used in obstetrics with fewer undesirable side effects.

3. The use of antiprostaglandins and relaxant prostaglandins in the management of premature labour.

4. The role of prostaglandins in intra-uterine death where induction is a problem. A preliminary trial has been completed using PGE_2 in cases having an intra-uterine death and it suggests that this is a useful application for prostaglandins in obstetrics (See Addendum page 168).

PART 10

REFERENCES

REFERENCES

ABDUL-KARIM, R. & ASSALI, N.S. (1961). Effects of oxytocin on renal haemodynamics and water and electrolyte secretion. J. Lab. clin. Med. 57, 522-532.

ABDUL-KARIM, R. & RIZIK, P.T. (1970). The effect of oxytocin on renal haemodynamics, water and electrolyte secretion. Obstet. Gynec. Surv. 25, 805-813.

ANDERSON, G., HOBBINS, J., CORDERO, L. & SPEROFF, L. (1971). Clinical use of prostaglandins as oxytocin substances. Ann. N.Y. Acad. Sci. 180, 499-512.

ANDERSON, G., HOBBINS, J. & SPEROFF, L. (1972). Intravenous prostaglandins E_2 and $F_{2\alpha}$ for the induction of term labour. Am. J. Obstet. Gynec. 112, 382-386.

ANDERSON, M.M. (1965). The state of the cervix and surgical induction of labour. J. Obstet. Gynaec. Br. Commonw. 72, 711-716.

ARMITAGE, P. (1971). Statistical Methods in Medical Research, p. 135. Oxford and Edinburgh: Blackwell Scientific Publications.

BAILLIE, P., MEEHAN, F.P. & TYACK, A.J. (1970). Treatment of premature labour with Orciprenaline. Br. med. J. 4, 154-155.

BAILLIE, P., MILTON, P. & MILTON, J. In press. The causes and effects of delay in the treatment of premature labour.

BATTEZ, G. & BOULET, L. (1913). C. r. Seanc. Soc. Biol. 74, 8. Cited by Von Euler, U.S. (1936). J. Physiol. 88, 213-234.

BEAZLEY, J.M., DEWHURST, C.J. & GILLESPIE, A. (1970). The induction of labour with prostaglandin E_2. J. Obstet. Gynaec. Br. Commonw. 77, 193-199.

BEAZLEY, J.M. (1971). The induction of labour with prostaglandins. Research in Prostaglandins, Worcester Foundation for Experimental Biology 1, 1-3.

BEAZLEY, J.M. & GILLESPIE, A. (1971). Double-blind trial of prostaglandin E_2 and oxytocin in induction of labour. Lancet, 1, 152-155.

BENNETT, A., FRIEDMAN, L.A. & VANE, J.R. (1967). Release of prostaglandin E_1 from the rat stomach. Nature, Lond. 216, 873-876.

BENNETT, A. (1971). Effects of kinins and prostaglandins on the gut. Proc. R. Soc. Med. 64, 12-13.

BERGSTRÖM, S. (1949). Prostaglandinets kerni. Nord. Med. 42, 1465-1466.

BERGSTRÖM, S. & SJÖVALL, J. (1960a). The isolation of prostaglandin F from sheep prostate glands. Acta chem. scand. 14, 1693-1700.

BERGSTRÖM, S. & SJÖVALL, J. (1960b). The isolation of prostaglandin E from sheep prostate glands. Acta chem. scand. 14, 1701-1705.

BERGSTRÖM, S., RYHAGE, R., SAMUELSSON, B. & SJÖVALL, J. (1962). The structure of prostaglandin E, $F_{1\alpha}$ and $F_{2\alpha}$. Acta chem. scand. 16, Part 1, 501-502.

BERGSTRÖM, S. & SAMUELSSON, B. (1962). Isolation of prostaglandin E_1 from human seminal plasma. J. biol. Chem. 237, 3005-3006.

BERGSTRÖM, S. (1966). The prostaglandins. Recent Prog. Horm. Res. 22, 153-175.

BERGSTRÖM, S. (1967). Isolation, Structure and Action of the Prostaglandins, Nobel Symposium 2, Prostaglandins, p. 21-30. Stockholm: Almqvist and Wiksell.

BERGSTRÖM, S., CARLSON, L.A. & WEEKS, J.R. (1968). Prostaglandins. Pharmac. Rev. 20, 1-48.

BERGSTRÖM, S. & SAMUELSSON, B. (1968). Prostaglandins. Stockholm: Almqvist and Wiksell.

BERGSTRÖM, S. (1973). Advances in the Biosciences 9, International Conference on Prostaglandins, Pergamon Press, Vieweg, Braunschweig.

BILCK, W. & DORR, P. (1970). Water intoxication and grand mal seizures due to oxytocin. Can. med. Ass. J. 103, 379-382.

BISHOP, E.H. (1964). Pelvic scoring for elective induction. Obstet. Gynaec. 24, 266-268.

BROTANEK, V. (1966). Intrauterine Dangers to the Fetus, Proceedings of a Symposium. Excerpta Medica Monograph p. 147-149, Prague.

BROTANEK, V., HENDRICKS, C.H. & TOSHIRO YOSHIDA (1969). Changes in uterine blood flow during contractions. Am. J. Obstet. Gynec. 103, 1108-1116.

BRUMMER, H.C. (1971). Interaction of E prostaglandins and syntocinon on the pregnant human myometrium. J. Obstet. Gynaec. Br. Commonw. 78, 305-309.

BYGDEMAN, M. (1964). The effect of different prostaglandins on human myometrium in vitro. Acta physiol. scand. 63, suppl. 242.

BYGDEMAN, M. (1967). Studies of the Effects of Prostaglandins in Seminal Plasma on Human Myometrium in vitro, Prostaglandins, Nobel Symposium 2, p. 71-77. Stockholm: Almqvist and Wiksell.

CALDEYRO-BARCIA, R., MENDEZ-BAUER, G., POSEIRO, J.J., ESCARCENA, L.A., POSE, S.V., BIENIARZ, J., ARNT, I.C., GULIN, L. & ALTHALSE, O. (1966). Control of Human Fetal Heart Rate During Labour. Heart and Circulation in the Newborn and Infant, Ed. D.E. Cassels. New York: Grune and Stratton.

CALKINS, L.A. (1934). Discussion of Jackson, D.G. Rupturing the membranes to induce labour. Am. J. Obstet. Gynec. 27, 349-355.

CANUS, L. & GLEY, E. (1907). C. r. Seanc. Soc. Biol. 63, 204. Cited by Von Euler, U.S. (1936). J. Physiol. 88, 213-234.

CARSTENS, M.E. (1972). Effects of Prostaglandins on Calcium Transport in Uterine Sarcoplasmic Reticulum. Conference of the Federation of American Societies for Experimental Biology: Atlantic City, New Jersey.

CHASSAR MOIR, J. & MYERSCOUGH, P.R. (1971). Munro Kerr's Operative Obstetrics, 8th edn., p. 68. London: Bailliere, Tindall and Cassell.

COCEANI, F., PACE-ASCIAK, C., VOLTA, F. & WOLFE, L.S. (1967). Effect of nerve stimulation on prostaglandin formation and release from the rat stomach. Am. J. Physiol. 213, 1056-1064.

COREY, E.J. (1969). Total Synthesis of Prostaglandins. Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research XII. Organic Synthesis, p. 51-79. Ed. W.O. Milligan: Houston, Texas.

CRAFT, I.L., CULLUM, A.R., MAY, D.T.L., NOBLE, A.D. & THOMAS, D.J. (1971). Prostaglandin E_2 compared with oxytocin for the induction of labour. Br. med. J. 3, 276-279.

CRAWFORD, J.S. (1972). Principles and Practice of Obstetric Anaesthesia, 3rd edn. p. 146-160. Oxford: Blackwell Scientific Publications.

DEWHURST, C.J. (1972). In discussion following Prostaglandin $F_{2\alpha}$ for induction of labour. Vakhariya, V.R. & Sherman, A.I. Am. J. Obstet. Gynec. 2, 212-222.

DONALD, I. (1969). Practical Obstetric Problems, 4th edn. London: Lloyd-Luke Ltd.

DUBOIS, C. & BOULET, L.C. (1911). C. r. Seanc. Soc. Biol. 71, 536. Cited by Von Euler, U.S. (1936). J. Physiol. 88, 213-234.

DUBOIS, C. & BOULET, L. (1919). Ibid 82, 1054. Cited by Von Euler, U.S. (1936). J. Physiol. 88, 213-234.

DUKES, P.P. (1972). Modulating effects of erythropoietin, prostaglandins and cyclic 3' - 5' nucleotides on erythroid differentiation in marrow cell cultures. Fedn. Proc. 31, 487.

EFFER, S.B., BERTOLA, R.P., VRETTOS, A. & CALDEYRO-BARCIA, R. (1969). Quantitative study of the regularity of uterine rhythm in labour. Am. J. Obste. Gynec. 105, 909-915.

EGLINGTON, G., RAPHAEL, R.A., SMITH, G.N., HALL, W.J. & PICKLES, V.R. (1963). Isolation and identification of 2 smooth muscle stimulants from menstrual fluid. Nature, Lond. 200, 960 and 993-995.

ELIASSON, R. (1959). Studies on prostaglandin occurrence, formation and biological actions. Acta physiol. scand. 46, suppl. 158, 1-73.

EL-SAHWI, S., GAFAAR, A.A. & TOPPOZADA, H.K.C. (1967). A new unit for evaluation of uterine activity. Am. J. Obstet. Gynec. 98, 900-905.

EMBREY, M.P. (1962). The effects of intravenous oxytocin on uterine contractility: Part 1, J. Obstet. Gynaec. Br. Commonw. 69, 910-917.

EMBREY, M.P. & ANSELMO, J.F. (1962). The effects of intravenous oxytocin on uterine contractility: Part 2. J. Obstet. Gynaec. Br. Commonw. 69, 918-923.

EMBREY, M.P. & MORRISON, D.L. (1968). The effect of prostaglandins on human pregnant myometrium in vitro. J. Obstet. Gynaec. Br. Commonw. 75, 829-832.

EMBREY, M.P. (1969). The effect of prostaglandins on the human pregnant uterus. J. Obste. Gynaec. Br. Commonw. 76, 783-789.

EMBREY, M.P. (1970). Induction of labour with prostaglandins E_1 and E_2. Br. med. J. 2, 256-258.

EMBREY, M.P. (1971a). PGE compounds for induction of labour and abortion. Ann. N.Y. Acad. Sci. 180, 518-523.

EMBREY, M.P. (1971b). Induction of abortion by prostaglandin E (prostaglandins E_1 and E_2). J. Repr. Med. 6, 256-259.

EMBREY, M.P. & HILLIER, K. (1971). Therapeutic abortion by intrauterine instillation of prostaglandins. Br. med. J. 1, 588-590.

FERGUSON, J.K. (1941). A study of the motility of the intact uterus at term. Surgery, Gynec. Obstet. 73, 359-366.

FRIEDMAN, E.A. (1967). Labour : Clinical Evaluation and Management. New York : Appleton - Century - Crofts.

GARRETT, W.J. (1960). Prognostic signs in surgical induction of labour. Med. J. Aust. 47, 929-931.

GILLESPIE, A., DEWHURST, C.J. & BEAZLEY, J.M. (1971). Prostaglandin induced labour. Br. med. J. 2, 222.

GILLESPIE, A. (1972). Prostaglandin and oxytocin enhancement and potentiation and their clinical applications. Br. med. J. 1, 150-152.

GILLESPIE, A., BRUMMER, H.C. & CHARD, T. (1972). Oxytocin release by infused prostaglandin. Br. med. J. 1, 543-544.

GOLDBLATT, M.W. (1933). A depressor substance in seminal fluid. J. Soc. Chem. Ind., Lond. 52, 1056-1057.

GOLDBLATT, M.W. (1935). Properties of human seminal plasma. J. Physiol. 84, 208-218.

GOODLIN, R.C., McLENNAN, C.E., CHOYCE, J.M. et al (1969). Therapeutic abortion with hypertonic intra-amniotic saline : a clinical experience in a combined university hospital. Obstet. Gynec. 34, 1-6.

GÖTZL, A. (1910). Z. urol. Chir. 4, 743. Cited by Von Euler, U.S. (1936). J. Physiol. 88, 213-234.

GREAVES, M.W., SONDERGAARD, J. & McDONALD-GIBSON, W. (1971). Recovery of prostaglandins in human cutaneous inflammation. Br. med. J. 2, 258-260.

GUPTA, D.R. & COHEN, N.H. (1972). Oxytocin, 'salting out' and water intoxication. J. Am. med. Ass. 220, No. 5, 681-683.

HAMBERG, M. & SAMUELSSON, B. (1966). Prostaglandins in human seminal plasma. J. biol. Chem. 241, 257-263.

HAMBERG, S. (1973). A Note on Nomenclature, Advances in the Biosciences 9, International Conference on Prostaglandins, p. 847-850. Ed. S. Bergström. Pergamon Press, Vieweg, Braunschweig.

HILLIER, K. & EMBREY, M.P. (1972). High dose intravenous administration of prostaglandin E_2 and $F_{2\alpha}$ for the termination of mid-trimester pregnancies. J. Obstet. Gynaec. Br. Commonw. 79, 14-22.

HORTON, E.W. (1965). Biological activities of pure prostaglandins. Experienta 21, 113-118.

HORTON, E.W. (1968). The Prostaglandins : Recent Advances in Pharmacology, 4th edn. Ed. R.S. Stacey and J.M. Robson. London : Churchill.

HORTON, E.W. (1969). Hypotheses on physiological roles of prostaglandins. Physiol. Rev. 49, 122-161.

HYTTEN, F.E. & LEITCH, I. (1971). The Physiology of Human Pregnancy, 2nd edn., p. 132-164. Oxford : Blackwell Scientific Publications.

JAPELLI, G. & SCAFA, G.M. (1906). Archs. ital. Biol. 45, 165. Cited by Von Euler, U.S. (1936). J. Physiol. 88, 213-234.

JONSSON, C.-E. & ANGÅRD, E. (1972). Biosynthesis and metabolism of prostaglandin E_2 in human skin. Scand. J. clin. Lab. Invest. 29, 289-296.

JOSEY, W.E., PINTO, A.P. & PLANT, R.F. (1969). Oxytocin-induced water intoxication. Am. J. Obstet. Gynec. 104, 926.

KARIM, S.M.M. (1966). Identification of prostaglandins in human amniotic fluid. J. Obstet. Gynaec. Br. Commonw. 73, 903-908.

KARIM, S.M.M. & DEVLIN, J. (1967). Prostaglandin content of human amniotic fluid during pregnancy and labour. J. Obstet. Gynaec. Br. Commonw. 74, 230-234.

KARIM, S.M.M. (1968a). Appearance of prostaglandin $F_{2\alpha}$ in maternal blood during labour. Br. med. J. 4, 618-621.

KARIM, S.M.M. (1968b). The Role of Prostaglandin $F_{2\alpha}$ in Human Parturition, Prostaglandins, Peptides and Amines, p. 65. London : Academic Press.

KARIM, S.M.M., TRUSSEL, R.R., PATEL, R.C. & HILLIER, K. (1968). Response of pregnant human uterus to prostaglandin $F_{2\alpha}$-induction of labour. Br. med. J. 4, 621-623.

KARIM, S.M.M., SOMERS, K. & HILLIER, K. (1969a). Cardio-vascular actions of prostaglandin $F_{2\alpha}$ infusion in man. Europ. J. Pharmacol. 5, 117-120.

KARIM, S.M.M., TRUSSELL, R.R., HILLIER, K. & PATEL, R.C. (1969b). Induction of labour with prostaglandin $F_{2\alpha}$. J. Obstet. Gynaec. Br. Commonw. 76, 769-782.

KARIM, S.M.M. (1970). Action of prostaglandin in the pregnant woman. Ann. N.Y. Acad. Sci. 180, 499-512.

KARIM, S.M.M. & FILSHIE, G.M. (1970a). Therapeutic abortion using prostaglandin $F_{2\alpha}$. Lancet 1, 157-159.

KARIM, S.M.M. & FILSHIE, G.M. (1970b). Use of prostaglandin E_2 for therapeutic abortion. Br. med. J. 3, 198-200.

KARIM, S.M.M. & HILLIER, K. (1970). Prostaglandins and spontaneous abortion. J. Obstet. Gynaec. Br. Commonw. 77, 837-839.

KARIM, S.M.M., HILLIER, K., TRUSSELL, R.R., PATEL, R.C. & TAMUSANGE, S. (1970). Induction of labour with prostaglandin E_2. J. Obstet. Gynaec. Br. Commonw. 77, 200-210.

KARIM, S.M.M. (1971). Action of prostaglandin in the pregnant woman. Ann. N.Y. Acad. Sci. 180, 483-498.

KARIM, S.M.M. (1972). Prostaglandins in the control of parturition and menstruation. J. Reprod. Fert. supp. 16, 105-119.

KEETEL, W.C., DIDDLE, A.W., & PLASS, E.D. (1940). Premature elective rupture of the membranes. Am. J. Obstet. Gynec. 40, 225-233.

KING, A.G. (1940). New concepts of dry labour. J. Am. med. Ass. 114, 238-241.

KLOPPER, A. (1964). Changes in renal function in late pregnancy. Lancet 2, 565-566.

KURZROK, R. & LIEB, C. (1930). The action of semen on the human uterus. Proc. Soc. exp. Biol. Med. 28, 268-272.

LEE, J.B., CROWSHAW, K., TAKMAN, B.H., ATTREP, KATHERINE A. & GONGOUTAS, J.Z. (1967). The identification of prostaglandins E_2, $F_{2\alpha}$ and A_2 from rabbit kidney medulla. Biochem. J. 105, 1251-1260.

LIGGINS, G.C. (1962). The treatment of missed abortion by high dosage syntocinon intravenous infusion. J. Obstet. Gynaec. Br. Commonw. 69, 277-281.

LIGGINS, G.C., GRIEVES, S.A., KENDALL, J.Z. & KNOX, B.S. (1972). The physiological role of progesterone, oestradiol 17 and prostaglandin $F_{2\alpha}$ in the control of ovine parturition. J. Reprod. Fert. supp. 16, 85-103.

LILIEN, A.A. (1968). Oxytocin-induced water intoxication. J. Obstet. Gynec. 32, 171-173.

O'DRISCOLL, K., JACKSON, R.J.A. & GALLAGHER, J.T. (1969). Prevention of prolonged labour. Br. med. J. 2, 477-480.

PAUERSTEIN, C.J. & ZAUDER, H.L. (1970). Autonomic innervation sex steroids and uterine contractility. Obstet. Gynaec. Surv. 25, 617-630.

PHILPOTT, R.H., SAPIRE, K.E. & AXTON, J.H.M. (1972). Obstetrics, Family Planning and Paediatrics, p. 15. The Family Planning Association of Rhodesia.

PICKLES, V.R. & HALL, W.J. (1963). Some physiological properties of the menstrual stimulant substances A1 and A2. J. Reprod. Fert. 6, 315-317.

PICKLES, V.R., HALL, W.J., BEST, F.A. & SMITH, G.N. (1965). Prostaglandins in endometrium and menstrual fluid from normal and dysmenorrhoeic subjects. J. Obstet. Gynaec. Br. Commonw. 72, 185-192.

PICKLES, V.R. (1967). The prostaglandins. Biol. Rev. 42, 614-652.

PICKLES, V.R. (1969). Prostaglandins. Nature, Lond. 224, 221-225.

PITTS, P.F. (1968). The Physiology of the Kidney and Body Fluids, p. 220-225. Chicago : Yearbook Medical Publishers.

POTTER, R.R. (1964). Water retention due to oxytocin. Obstet. Gynec. 23, 699-702.

PULKINEN, M.O. (1970). Regulation of uterine contractility. Acta obstet. gynec. scand. 49, supp.1, 19-41.

QUEEN CHARLOTTE TEXTBOOK OF OBSTETRICS (1970). 12th edn., p. 77, Ed. J.S. Tomkinson. London: J. and A. Churchill.

ROBERTS, G. (1970). Induction of labour using prostaglandins. J. Reprod. Fert. 23, 370-371.

ROBERTS, G., ANDERSON, A., McGARRY, J. & TURNBULL, A.C. (1970). Absence of antidiuresis during administration of prostaglandin $F_{2\alpha}$. Br. med. J. 2, 152-154.

ROBERTS, G. & TURNBULL, A.C. (1971). Uterine hypertonus during labour induced by prostaglandins. Br. med. J. 1, 702-705.

ROTH-BRANDEL, U. & ADAMS, M. (1970). An evaluation of the possible use of prostaglandin E_1, E_2 and $F_{2\alpha}$ for induction of labour. Acta obstet. gynec. scand. 49, supp. 5, 9-17.

ROTH-BRANDEL, U., BYGDEMAN, M., WIQVIST, N. & BERGSTRÖM, S. (1970). Prostaglandins for induction of therapeutic abortion. Lancet 1, 190-191.

RUSSELL, J.G. (1969). Radiological assessment of fetal maturity. J. Obstet. Gynaec. Br. Commonw. 76, 208-219.

SAMUELSSON, B. (1963). Prostaglandins and related factors, Part 17. Structure of prostaglandin E_3^2. J. Am. chem. Soc. 85, 1878-1879.

SAMUELSSON, B. (1964). Identification of prostaglandin $F_{3\alpha}$ in bovine lung. Prostaglandins and related factors 26. Biochim. biophys. Acta 84, 707-713.

SCHER, J., DAVEY, D.A., BAILLIE, P., FRIEND, J. & FRIEND, D.M. (1972). A comparison of prostaglandin $F_{2\alpha}$ and oxytocin in the induction of labour. S. Afr. med. J. 46, 2009-2012.

SELF, J. (1966). Water intoxication induced by oxytocin administration. Am. J. med. Sci. 252, 573-574.

SILVA, P. & ALLAN, M.S. (1966). Water intoxication due to high doses of synthetic oxytocin. Obstet. Gynec. 27, 517-520.

SOLOMON, L.M., JUHLIN, L. & KIRSCHENBAUM, M.B. (1968). Prostaglandin on cutaneous vasculature. J. invest. Derm. 51, 280-282.

STRAUSS, M.B. (1957). Body Water in Man, p. 99-104. London: J. and A. Churchill.

THAON, P. (1907). C. r. Seanc. Biol. 63, 111. Cited by Von Euler, U.S. (1936). J. Physiol. 88, 213-234.

TENNANT, R.A. & BLOCK, M.D. (1954). Surgical induction of labour in modern obstetric practice. Br. med. J. 2, 833-837.

TURNBULL, A.C. (1957). Uterine contractions in normal and abnormal labour. J. Obstet. Gynaec. Br. Emp. 64, 321-333.

TURNBULL, A.C. & ANDERSON, A.B.M. (1967). Induction of labour. J. Obstet. Gynaec. Br. Commonw. 74, 849-854.

TURNBULL, A.C. & ANDERSON, A.B.M. (1968). Induction of labour. J. Obstet. Gynaec. Br. Commonw. 75, 24-31.

VAKHARIYA, V.R. & SHERMAN, A.I. (1972). Prostaglandin $F_{2\alpha}$ for induction of labour. Am. J. Obstet. Gynec. 2, 212-222.

VOGT, W. (1958). Naturally occurring lipid-soluble acids of pharmacological interest. Pharmac. Rev. 10, 407-435.

VON EULER, U.S. (1934). Zur kenntnis der pharmakologeschen wirkungen von nativsekretin und extrakten männlicker accessorischer geschlectsdrüsen. Archs. Med. exp. Anat. path. 175, 78-84.

VON EULER, U.S. (1935). Uber die spezifische blutdrucksenkende substanz des menschlicken prosta-und samenblasensekretes. Klin. Wschr. 14, 1182-1183.

VON EULER, U.S. (1936). On the specific vaso-dilating and plain muscle stimulating substances from accessory genital glands in man and certain animals (prostaglandin and vesiglandin). J. Physiol. 88, 213-234.

VON EULER, U.S. & ELIASSON, R. (1968). Prostaglandins. Medical and Chemical Monographs, Vol. 8. New York : Academic.

WHALLEY, P.J. & PRITCHARD, J.A. (1963). Oxytocin and water intoxication. J. Am. med. Ass. 186, 601-603.

WILLIAMS, E.D., KARIM, S.M.M. & SANDLER, M. (1968). Prostaglandin secretion by medullary carcinoma of the thyroid. Lancet 1, 22-23.

WILLOCKS, J. & MOIR, D.D. (1968). Epidural analgesia in the management of hypertension in labour. J. Obstet. Gynaec. Br. Commonw. 75, 225-228.

WIQVIST, N. & BYGDEMAN, M. (1970a). Induction of therapeutic abortion with intravenous prostaglandin $F_{2\alpha}$. Lancet 1, 889.

WIQVIST, N. & BYGDEMAN, M. (1970b). Therapeutic abortion by local administration of prostaglandin. Lancet 2, 716-717.

ZIBOHR, V.A., McELLIGOT, T. & HSIA, S.L. (1973). Prostaglandin E_2 Biosynthesis in Human Skin: Subcellular Localisation and Inhibition by Unsaturated Fatty Acids and Anti-inflammatory Agents, Advances in the Biosciences 9, International Conference on Prostaglandins, p. 457-460. Ed. S. Bergström, Pergamon Press, Vieweg, Braunschweig.

PART 11

APPENDICES

APPENDIX A

UPJOHN PROTOCOL FORM

Upjohn INDIVIDUAL PATIENT REPORT - PGF_{2a}, PGE_2 OR OXYTOCIN

INDUCTION OF LABOR IN PREGNANT WOMEN

99-543 2/71

INVESTIGATOR'S NAME | PATIENT'S NAME OR NUMBER

DRUG NAME | LOT NO. ___ ___ ___ ___/___ ___/___ | DATE OF START OF TREATMENT ___/___/___ DAY / MONTH / YEAR

AGE | HEIGHT ___ ___(.) ___ ☐ IN. ☐ cm. | WEIGHT ___ ___ ___(.) ___ ☐ LB. ☐ Kg. | RACE ☐ WHITE ☐ ORIENTAL ☐ NEGRO ☐ OTHER ___ (WRITE IN)

GRAVIDA ___ ___ | PARA (IF MORE THAN 6 EXCLUDE FROM STUDY) ___ ___ | ABORTUS ___ | NO. OF LIVING CHILDREN ___ | NO. OF BIRTHS MALFORMED ___

NO. OF MONTHS OR YEARS SINCE LAST DELIVERY OR MISCARRIAGE ___ ___ ☐ MONTHS ☐ YEARS | NO. OF WEEKS OF GESTATION ___ ___

HISTORY AND INITIAL STATUS

HISTORY OF ALLERGY

HIVES ☐ NO ☐ YES | HAY FEVER ☐ NO ☐ YES | ASTHMA ☐ NO ☐ YES | PENICILLIN SENSITIVITY ☐ NO ☐ YES

ALLERGIES (LIST) ☐ NO ☐ YES (WRITE IN) _____

HAVE THERE BEEN ANY PREVIOUS CESAREAN BIRTHS? ☐ NO ☐ YES (IF YES, EXCLUDE FROM STUDY)

HAS THE PATIENT BEEN IN TRUE LABOR WITH THIS PREGNANCY? ☐ NO ☐ YES (IF YES, EXCLUDE FROM STUDY)

HAVE THE AMNIOTIC MEMBRANES SPONTANEOUSLY RUPTURED? ☐ NO ☐ YES (IF YES, EXCLUDE FROM STUDY)

LIST SIGNIFICANT PAST ILLNESSES (IF NONE, CHECK BOX PROVIDED)

☐ NONE (OR)

1.

2.

3.

PRE-TREATMENT PHYSICAL EXAM

GENERAL

☐ NORMAL
☐ ABNORMAL

LIST ABNORMALITIES

PELVIC

☐ NORMAL
☐ ABNORMAL

LIST ABNORMALITIES

CIRCLE APPROPRIATE NUMBER

PELVIC SCORE

Cm	0	1–2	3–4	5–6
DILATATION	0	1	2	3
%	0–30	40–50	60–70	80
EFFACEMENT	0	1	2	3
	–3	–2	–1 0	+1 +2
STATION	0	1	2	3
	Firm	Medium	Soft	
CONSISTENCY	0	1	2	
	Post.	Mild.	Ant.	
POSITION	0	1	2	

TOTAL SCORE _____

INITIATION OF INFUSION DATE ___/___/___ DAY / MO. / YEAR TIME ___:___ HR. MIN.

TOTAL DURATION ___:___ HR. MIN.

TOTAL VOLUME _____ ml

CONCENTRATION OF DRUG _____ mcg/ml

TOTAL DOSE GIVEN _____ ml; _____ mg

INTERVAL FROM START OF INFUSION TO ONSET OF CONTRACTIONS.

INITIAL CONTRACTIONS ___:___ HR. MIN.

ADEQUATE CONTRACTIONS ___:___ HR. MIN.

RATE OF INFUSION AT THE TIME _____ ml/MIN.

RATE OF INFUSION AT THE TIME _____ ml/MIN.

DID CONTRACTIONS BECOME UNDESIRABLY SEVERE?

☐ NO
☐ YES

IF YES, GIVE INTERVAL AFTER ONSET OF INFUSION.

___:___ HR. MIN

___:___ HR. MIN.

INDIVIDUAL PATIENT REPORT CONT'D.

99-543-2 2/71

OBSERVATIONS DURING INFUSION

(RECORD WHEN SIGNIFICANT CHANGES OCCURRED, GIVING THE INTERVAL AFTER START OF MEDICATION INFUSION.)

INTERVALS AFTER START OF INFUSION	INITIAL OR PRETREATMENT	HR. : MIN.	HR. : MIN.	HR. : MIN.	HR. : MIN.	HR. : MIN.	HR. : MIN.
RATE OF INFUSION ml/min.							
INTERVAL BETWEEN CONTRACTIONS (minutes)							
BASELINE UTERINE PRESSURE mmHg							
PEAK UTERINE PRESSURE mmHg							
CERVICAL DILATATION cm							
FETAL HEART RATE							

HOW LONG AFTER ONSET OF INFUSION DID AMNIOTIC MEMBRANES RUPTURE? ____ : ____ HR. MIN.

HOW LONG AFTER INITIAL INFUSION WAS STARTED DID DELIVERY OF FETUS OCCUR? ____ : ____ HR. MIN.

TOTAL DURATION OF LABOR UNTIL DELIVERY OF FETUS ____ : ____ HR. MIN.

CONCOMITANT THERAPY

DRUG NAME	DOSAGE	HOW LONG AFTER ONSET OF INFUSION
		____ : ____ HR. MIN.
		____ : ____ HR. MIN.
		____ : ____ HR. MIN.

ADVERSE EFFECTS

SIDE EFFECT	HOW LONG AFTER ONSET OF INFUSION?	DURATION
	____ : ____ HR. MIN.	____ : ____ HR. MIN.
	____ : ____ HR. MIN.	____ : ____ HR. MIN.
	____ : ____ HR. MIN.	____ : ____ HR. MIN.

MODE OF DELIVERY

☐ SPONTANEOUS VAGINAL ☐ FORCEPS EXTRACTION

☐ CAESARIAN ☐ OTHER _____

COMMENTS:

INVESTIGATOR'S SIGNATURE _____ DATE _____

Upjohn

INDIVIDUAL PATIENT REPORT - PGF_{2a} , PGE_2 OR OXYTOCIN

INDUCTION OF LABOR IN PREGNANT WOMEN

99-544 3/71

INVESTIGATOR'S NAME

PATIENT'S NAME OR NUMBER

DRUG NAME

LOT NO. ___ ___ ___ ___/___ ___/___

DATE OF START OF TREATMENT ___ DAY / ___ MONTH / ___ YEAR

STATUS OF MOTHER

		PRE-TREATMENT	RANGE DURING INFUSION	AT TIME OF DELIVERY	1 HOUR AFTER DELIVERY
TEMPERATURE ☐ ORAL ☐ RECTAL		___ ___ ___•___	___ ___•___ TO ___ ___•___	___ ___ ___•___	___ ___ ___•___
PULSE RATE (BEATS/MIN.)		___ ___ ___	___ ___ ___ TO ___ ___ ___	___ ___ ___	___ ___ ___
RESPIRATION (RATE/MIN.)		___ ___ ___	___ ___ ___ TO ___ ___ ___	___ ___ ___	___ ___ ___
BLOOD PRESSURE (mm Hg.)	SYSTOLIC	___ ___ ___	___ ___ ___ TO ___ ___ ___	___ ___ ___	___ ___ ___
	DIASTOLIC	___ ___ ___	___ ___ ___ TO ___ ___ ___	___ ___ ___	___ ___ ___

ANY MATERNAL SIDE EFFECTS AFTER DELIVERY THOUGHT TO BE RELATED TO MED. INFUSION.I. ☐ NONE ☐ YES (IF YES, WRITE IN)

DELIVERY OF PLACENTA ___ ___ ___ MINUTES FROM DELIVERY OF FETUS

WAS THERE EXCESSIVE HEMORRHAGE? ☐ NO ☐ YES (IF YES ONSET AND DURATION IN MINUTES FROM DELIVERY OF FETUS)

ONSET ___ ___ ___ MIN. DURATION ___ ___ ___ MIN.

WRITE IN SPECIAL TREATMENT _____

STATUS OF FETUS

APGAR SCORE	AT TIME OF DELIVERY	5 MINUTES AFTER DELIVERY
FETAL HEART RATE	BEATS/MIN. ___ ___ ___ ☐0 ☐1 ☐2	BEATS/MIN. ___ ___ ___ ☐0 ☐1 ☐2
RESPIRATORY RATE AND EFFORT	BEATS/MIN. ___ ___ ___ ☐0 ☐1 ☐2	BEATS/MIN. ___ ___ ___ ☐0 ☐1 ☐2
MUSCLE TONE	☐0 ☐1 ☐2	☐0 ☐1 ☐2
RESPONSE TO CATHETER IN NOSTRIL	☐0 ☐1 ☐2	☐0 ☐1 ☐2
COLOR	☐0 ☐1 ☐2	☐0 ☐1 ☐2

DID FETUS SPONTANEOUSLY RESPIRE? ☐ NO ☐ YES (IF YES, TIME IN SECONDS FROM COMPLETE DELIVERY TO ONSET OF RESPIRATION) ___ ___ ___ SECONDS

IF NO, WRITE IN WHAT WAS DONE AND INDICATE TIME IN SECONDS TO ONSET OF SATISFACTORY RESPIRATION. ___ ___ ___ SECONDS

ANY FETAL SIDE EFFECTS AFTER DELIVERY THOUGHT TO BE RELATED TO MEDICATION INFUSION? ☐ NO ☐ YES (IF YES, WRITE IN)

LABORATORY DATA - PGF_{2a} , PGE_2 OR OXYTOCIN

INDUCTION OF LABOR IN PREGNANT WOMEN

99-544-2 2/71

			INITIAL PRE-TREATMENT	12 HOURS AFTER DELIVERY	OTHER
DATE PATIENT EXAMINED (DAY, MONTH, YEAR)			___ / ___ / ___ DAY / MONTH / YEAR	___ / ___ / ___ DAY / MONTH / YEAR	___ / ___ / ___ DAY / MONTH / YEAR
CHEMICAL	BUN (MG.%)				
	SGPT (UNITS)				
HEMATOLOGY	HCT (%)				
	HGB (mg.%)				
	WBC ($\times 10^3$)				
	DIFFERENTIAL	NEUTROPHILS (%)			
		LYMPHOCYTES (%)			
		MONOCYTES (%)			
		ESINOPHILS (%)			
		BASOPHILS (%)			
PLATELET COUNT					
URINALYSIS	ALBUMIN (0 – 4+)				
	SUGAR (0 – 4 +)				
	MICROSCOPIC (SPUN SEDIMENT)	WBC/HPF			
		RBC/HPF			
		CASTS/HPF			
		OTHER (WRITE IN)			
OTHERS (Write In)					

INVESTIGATOR'S SIGNATURE

APPENDIX B

PUNCH CARD CODE

A1 - 6	(6)	Hospital Number	
A7	(1)	Race C - Coloured A - Asian B - Bantu	
A8 - 9	(2)	Age in Years	
A10 - 12	(3)	Height in cms	
A13 - 14	(2)	Pre-delivery Weight in Kgs	
A15 - 18	(4)	Antenatal Haemoglobin	
A19	(1)	Primary Indication for Induction 1 = Raised BP and Albuminuria 2 = Raised BP 3 = Prolonged Pregnancy 4 = Other	
A20 - 23	(4)	Best Estimated Gestational Age i.e. 2 weeks 1 day 1 certain 1 or uncertain 2	
A24	(1)	Associated Diseases	1. Urinary Tract Infection 2. Drugs 3. None
A25	(1)	Enema Given	1. Yes 2. No 3. Unknown
A26	(1)	Oil Given	1. Yes 2. No
A27 - 32	(6)	Average of Last 2 BPs Prior to Infusion Systolic Diastolic	
A33 - 38	(6)	Maximum Systolic and Diastolic BP During Infusion Systolic Diastolic	
A39 - 44	(6)	Minimum Systolic and Diastolic BP During Infusion Systolic Diastolic	
A45	(1)	Drug Used	1. Oxytocin 2. Prostaglandin $F_{2\alpha}$

A46 - 49	(4)	Initial Temperature
A50 - 53	(4)	Maximum Temperature During Infusion
A54 - 56	(3)	Initial Cervical Dilatation cms
A57 - 58	(2)	Initial Cervical Effacement %
A59	(1)	Station 1 = -3 2 = -2 3 = below spines 5 = unknown
A60	(1)	Initial Consistency 1. Firm 2. Medium 3. Soft
A61	(1)	Initial Position 1. Posterior 2. Middle 3. Anterior 4. Unknown
A62 - 64	(3)	Uterine Activity Prior to Infusion (seconds of contraction/10 minutes)
A65	(1)	Anxiety 1. Extreme 2. Relaxed 3. Unknown
A66 - 68	(3)	Commencement of Infusion - I.C. in Minutes
A69 - 71	(3)	I.C. - A.C. Interval in Minutes
A72 - 74	(3)	A.C. - 5 cm Total Interval in Minutes
A75 - 77	(3)	Infusion - 5 cm Total Interval in Minutes
A78 - C7 i.e.	(90)	PVs During Infusion

Time since Onset of Infusion in Minutes	(3)	1 A78-80	2 B13-15	3 B28-30	4 B43-45	5 B58-60	6 B73-75
Cervical Dilatation cm	(3)	B1-3	B16-18	B31-33	B46-48	B61-63	B76-78
Cervical Effacement %	(3)	B4-6	B19-21	B34-36	B49-51	B64-66	B79-C1
Station (As for Initial PV)	(1)	B7	B22	B37	B52	B67	C2
Total Amount Drug	(3)	B8-12	B23-27	B38-42	B53-57	B68-72	C3-7

C 8 - 11 (4) Total Amount of Drug at I.C.

C12 - 15 (4) Total Amount of Drug at A.C.

C16 - 19 (4) Total Amount of Drug at 5 cm

C20 - 23 (4) Total Fluid Intake at 5 cm or End of Trial

C24 - 26 (3) Total Fluid Output at 5 cm or End of Trial

C27 (1) Success or Not 1. Yes
2. No
3. Dubious

C28 (1) Pattern Description (of contractions)

0 = Labour Did Not Occur
1 = Unknown
2 = Very Regular
3 = Regular
4 = Irregular
5 = Very Irregular

C29 (1) Fetal Heart Rate 1. Benign Change
2. Abnormal Change
3. No Change

Side Effects

C30 (1) Hypertonus 1. Yes 2. No

C31 (1) Diarrhoea 1. Yes 2. No

C32 (1) Nausea 1. Yes 2. No

C33 (1) Vomiting 1. Yes 2. No

C34 (1) Phlebitis 1. Yes 2. No

C35 (1) Other 1. Yes 2. No

Sedation in Total Amounts 000 if not Given (Except Nepresol)

C36 - 38 (3) Pethidine mg

C39 - 41 (3) Aterax mg

C42 - 43 (2) Sparine mg

C47 (1) Nepresol 1. Yes 2. No

C48	(1)	Sedation When Given 1. 0 - 5.59 hours 2. 6 - 12 hours 3. Both 4. Neither
C49 - 51	(3)	Interval From Onset of Infusion - Spontaneous Rupture of the Membranes in Minutes (OOO if ARM)
C52	(1)	Operative Delivery 1. Spontaneous Vaginal 2. Forceps/Vacuum 3. Caesarian Section
C53 - 54	(2)	Apgar at 1 Minute
C55 - 57	(3)	Haemoglobin Post-delivery
C58 - 59	(2)	Urea Post-delivery
C60 - 63	(4)	Fetal Weight gms
C64 - 67	(4)	Placental Weight gms
C68 - 69	(2)	Crown - Heel Length cms
C70 - 71	(2)	Head Circumference cms

APPENDIX C

FLUID BALANCE PROTOCOL

PENINSULA MATERNITY HOSPITAL

NAME:..... AGE: ..... RACE: ... FOLDER NO.: .....

DATE:.....

DIAGNOSIS: DRUG:

TIME:																
BLOOD:																
Na																
K																
Osm.																
Creat.																
URINE:																
Vol.																
Osm.																
Na																
K																
Intake																
Vomit																
24 HR URINE:																
Osm.																
Vol.																
Creat.																
SERUM:																
Osm.																

OTHER INFORMATION

PART 12

ADDENDUM

THE USE OF PROSTAGLANDIN E_2 IN THE MANAGEMENT OF INTRA-UTERINE DEATH

INTRODUCTION

The term Intra-uterine Death (I.U.D.) embraces cases before the 28th week of pregnancy (missed abortion), and those occurring later which result in macerated stillbirth (Donald, 1969).

The fetus is considered essential to the onset of labour (Liggins et al, 1972) and the onset of labour in association with intra-uterine fetal death therefore remains a paradox. As a result, the role of prostaglandins in intra-uterine death was studied in an attempt to provide a solution to the problem of management of this condition.

At present prostaglandins are being administered by various routes to induce second trimester abortion (Badraoui et al, 1973) - intravenously, intra-amniotically, extra-amniotically and intra-vaginally (Embrey et al, 1972; Hillier & Embrey, 1972; Hale et al, 1973).

We have investigated the use of prostaglandin E_2 (PGE_2) administered by the extra-amniotic route in patients with an intra-uterine death, in order to find a solution to the management of this problem.

PATIENTS AND METHODS

Twenty six patients with an intra-uterine death, seen over a period of 3 months in Groote Schuur Hospital, were studied.

The diagnosis was made by the following methods:

(1) Clinically: By absence of fetal movements, absence of fetal heart on auscultation and reduction of uterine growth over a period.

(2) Ultrasonically: By progressive reduction in the fetal biparietal diameter, flattening and overlapping of the skull bones with duplication of the skull bone echoes, and reduction in the uterine volume.

(3) Radiologically: The radiological signs include overlapping of the skull bones (Spalding's sign), acute angulation of the fetal spine, and gas shadows in the large vessels and lungs.

The use of ultrasonics over X-ray was favoured as a method of confirmation of the diagnosis for the following reasons:

(a) The diagnosis is made earlier, approximately 2 weeks before radiological signs appear.

(b) It is possible to exclude a normal pregnancy without risk to the live fetus (Kukard, In press).

Immediately prior to induction venous blood was withdrawn from the patient for the estimation of plasma oestradiol, plasma progesterone and human placental lactogen. These investigations were repeated every 2 hours until delivery and then 24 hours later.

METHOD OF PLASMA PROGESTERONE ESTIMATION

Plasma progesterone was measured by a modification of the competitive protein binding mechanism of Johansson (1970).

METHOD OF PLASMA OESTRADIOL MEASUREMENT

Plasma oestradiol was measured by radio-immunoassay. A modification of Abrahams' procedure (1969) without preliminary separation of oestrogens by chromatography was employed. The antibody used was highly specific for oestradiol.

METHOD OF HUMAN PLACENTAL LACTOGEN MEASUREMENT

Human Placental Lactogen (H.P.L.) was measured according to the method of Letchworth et al (1971) using the H.P.L. radio-immunoassay kit obtained from the Radio-Chemical Centre, Amersham.

The method of administration of the extra-amniotic prostaglandin was as described by Embrey et al (1972). A No. 16 Foley's catheter containing a measured, pre-filled Ampicillin and saline solution was introduced through the cervix to lie just within the internal os, between the membranes and the uterine wall. The balloon of the catheter was filled with 30 ml of the same solution.

A prostaglandin E_2 solution was prepared by adding 5 mg of prostaglandin E_2 into 20 ml of sterile water for injection. This gives a solution strength of 250 µg/ml. The solution in the Foley's catheter was then displaced by an equal volume of the prostaglandin E_2 solution. An initial test dose of 125 µg of prostaglandin E_2 was then injected and after 10 minutes a further 250 µg was injected. Thereafter 375 µg (1½ ml) of the prostaglandin E_2 solution was injected every 2 hours until delivery.

The patients were examined vaginally every 2 hours to assess changes in the cervix.

Aseptic precautions were strictly observed throughout the procedure. As an additional precaution against infection the patients received systemic Ampicillin.

RESULTS

All patients were successfully delivered vaginally.

The clinical details of the patients are shown in Table 1 (A) and Table 1 (B).

TABLE 1 (A)

CLINICAL DETAILS OF PATIENTS REPORTED IN THIS SERIES

Case No.	Age	Gravidity	Gestation at Delivery (weeks)	Duration of Intra-uterine Death (Days)	Fundal Height (Weeks)	State of Cervix
1	28	5	35	6	34	Unripe
2	34	6	28	42	20	Unripe
3	41	2	32	7	30	Unripe
4	44	13	28	9	28	Unripe
5	25	1	29		19	Unripe
6	39	9	34	14	34	Unripe
7	29	2	35	7	24	Unripe
8	43	3	28		26	Unripe
9	34	6	30	21	30	Unripe
10	23	1	36	21	34	Ripe
11	30	3	32	3	30	Unripe
12	19	1	29		20	Unripe
13	26	2	34		32	Unripe
14	38	5	40	17	38	Unripe
15	26	3	29	21	25	Unripe
16	25	4	33	5	30	Ripe
17	27	3	35		32	Unripe
18	27	2	26		26	Ripe
19	25	4	37		30	Ripe
20	39	2	20	7	28	Unripe
21	23	1	36		22	Unripe
22	37	5	32	15	26	Unripe
23	19	2	33	27	21	Unripe
24	23	3	29	21	28	Unripe
25	43	3	25	15	20	Unripe
26	39	7	28	9	28	Unripe

TABLE 1 (B)

CLINICAL DETAILS OF PATIENTS REPORTED IN THIS SERIES

Case No.	Induction-Delivery Interval (Hours)	Total dose Prostaglandin E_2 (µg)	Remarks
1	5	1125	Hypertension
2	10½	1125	Nausea
3	11¾	1125	Pre-eclampsia, antepartum haemorrhage, diarrhoea
4	15½	1125	Hypertension, diabetes, previous Caesarian Section, diarrhoea
5	5½	1125	Mitral valvotomy, pre-eclampsia
6	16	1800	
7	11	750	Pre-eclampsia, previous Caesarian Section
8	7¾	1125	Hypertension, previous Caesarian Section
9	15	1125	Hypertension
10	6¾	1500	Diarrhoea
11	8	1125	Hypertension, syphilis, previous Caesarian Section
12	7½	1800	
13	4½	1125	Twins
14	3¾	750	Attempted induction with quinine, stilboestrol and I.V. oxytocin 1 week previously
15	10¼	1875	Rhesus incompatibility
16	2¼	375	Light for dates, proteinuria
17	6¾	1125	Hypertension, diabetes, retained placenta, post-partum haemorrhage
18	2	375	
19	2¼	750	Light for dates
20	4¾	1125	Hypertension, fibromyomata
21	19	1875	
22	8	1125	
23	7	1500	Two previous attempts at induction with quinine, stilboestrol and I.V. oxytocin - the last 1 week previously
24	9	1500	
25	12	1500	
26	11	1875	Accidental haemorrhage, vomited twice.

The mean age of the patients was 31 years. The average gestational maturity of the pregnancy at the time of induction was 31.3 weeks with a mean fundal height of 27.5 weeks. The mean duration between the occurrence of the intra-uterine death and induction, where known, was 14.4 days.

The mean amount of PGE_2 administered to the patients was 1.125 µg (1.8 mg).

Patients experienced their first contractions between 4 and 20 minutes following the intra-uterine extra-amniotic administration of the PGE_2 solution, with a mean of 8.8 minutes. No patients experienced contractions prior to the actual administration of the prostaglandin solution. The contractions became frequent and painful early on during the induction with a sustained increase of basal tone as measured by external tocography using a Hewlett Packard cardiograph, number 8020A. The induction-delivery interval ranged from 2 to 16 hours with a mean of 8.6 hours.

SIDE EFFECTS

The absence of side effects was noteworthy. Patient No. 2 complained of nausea early on in her labour and Case No. 26 vomited twice. Cases 3 and 10 had 2 and 1 diarrhoeal stools respectively.

COMPLICATIONS

Delivery of fetus and placenta was complete, except in Case No. 17, which was complicated by a retained placenta and a post-partum haemorrhage. The placenta had to be removed manually and the patient received a 3 pint blood transfusion. Bleeding was otherwise well within normal limits in all the patients.

No cases of sepsis occurred.

DISCUSSION

In earlier years the accepted management of the dead fetus in utero was one of watchful expectancy (Gochberg & Reid, 1966), and this is often the case today.

This conservative attitude, besides causing inconvenience and grief to the patient (Pritchard, 1959; Wolff et al, 1970), may lead to disturbance of the coagulation mechanism (Hodgkinson et al, 1954; Barry et al, 1955; Pritchard & Ratnoff, 1955; Quinn & Harper, 1955).

The reason for this conservative attitude is that in most patients with an intra-uterine death labour ensues within 2 or 3 weeks (Tricomi & Kohl, 1957), and the risk of the retained fetus becoming infected following surgical induction was too great to attempt it.

Ursell (1972), however, compared cases of intra-uterine death treated with an oxytocin infusion only, with cases in whom amniotomy was used in addition to oxytocin. He found no difference between the 2 groups and a slightly increased incidence of puerperal pyrexia in the group where amniotomy was performed. One patient on a high dose oxytocin drip, which failed to induce labour, had a convulsive episode, probably due to water retention. This anti-diuretic action of oxytocin is well known (Roberts et al, 1970). Liggins (1962) also described a case of severe water retention using oxytocin intravenously in the induction of a 30 week amenorrhoea missed abortion. Using oxytocin alone the induction failed in 43% of cases. This high failure rate and a prolonged induction-delivery interval are the main criticisms of the use of oxytocin to induce patients with an intra-uterine death.

Lower Uterine Segment Caesarian Section or hysterotomy are unacceptable methods of treatment (Filshie, 1971), except under special circumstances.

The instillation of hypertonic saline has potentially dangerous side effects, including maternal death (Wagatsuma, 1965; Cameron & Dayan, 1966). This technique is also associated with a long latent interval before the onset

of labour (Csapo et al, 1963). Hypertonic glucose has an increased incidence of infection and is also associated with a long latent interval (Wood et al, 1962).

In Intra-uterine Death there is only 1 specific study (Filshie, 1971). The other reports are sporadic and incidental (Beazley et al, 1970; Karim et al, 1970; Beazley & Gillespie, 1971). Filshie (1971) reported 7 cases of intra-uterine death successfully treated with an intravenous infusion of PGE_2.

He obtained a mean infusion delivery interval of 8 hours 30 minutes, which is identical to that obtained in this series. The gestational maturity of the cases at the time of induction, however, was 35 weeks, compared to the mean of 31 weeks reported in this series.

He also noted the absence of side effects as reported in this series.

Beazley et al (1970), in a paper on induction of labour with PGE_2, induced 3 cases with an intra-uterine death between 29 and 33 weeks maturity using intravenous PGE_2. One patient required a repeat infusion. The induction-delivery interval ranged between 12 to 23 hours.

Karim et al (1970) in a paper on induction of labour with PGE_2 included cases with an intra-uterine death between 35 and 42 weeks maturity. The induction-delivery interval ranged from 5½ hours to 31 hours and 1 patient required a repeat infusion.

Beazley & Gillespie (1971), in a double blind trial of PGE_2 and oxytocin in induction of labour, induced labour successfully in 5 out of 8 patients with fetal death in utero using PGE_2. Three cases with an intra-uterine death received oxytocin, and the induction failed in 1 of these. Their impression was, from this and their earlier study (Beazley et al, 1970), that PGE_2 is a more useful drug than oxytocin for the induction of labour in these cases.

From the results described above the extra-amniotic route seems to offer advantages over all the other methods discussed. The minimal side effects obtained with this technique of administration is noteworthy, compared with the severe side effects of high dose intravenous infusions of primary prostaglandins for termination of mid-trimester pregnancies (Hillier & Embrey, 1972).

Unfortunately the serial hormone and enzyme analyses were not available at the time of completion of this thesis. Table 2 below gives the results available. It shows the mean $\pm$ S.E of plasma oestradiol and plasma progesterone and H.P.L. immediately prior to induction and 24 hours after delivery.

TABLE 2

MEAN ± STANDARD ERROR OF PLASMA OESTRADIOL, PROGESTERONE AND H.P.L.

	Immediately Prior to Induction Mean ± S.E.	Twenty-four Hours After Delivery Mean ± S.E.
7 Oestradiol	2.65 ± 0.59	0.08 ± 0.04 ng/ml
7 Progesterone	39.47 ± 5.96	2.65 ± 0.92 ng/ml
3 H.P.L.	2.00 ± 0.81	<1 mcg/ml

It is curious that despite the apparent progesterone block (Csapo, 1961) PGE_2 acted faster than the other methods reported above, and this provides further evidence that prostaglandins are involved in the onset of labour.

It is felt that prostaglandins have an important and practical role in the management of the retained dead fetus.

The author wishes to thank Dr. M. Katz, Head of the Gynaecological Endocrine Section, University of Cape Town and Groote Schuur Hospital, for the plasma oestradiol and plasma progesterone estimations.

REFERENCES

ABRAHAM, G.E. (1969). Solid phase radioimmunoassay of oestradiol - 17β. J. clin. Endocr. Metab. 29, 866-870.

BADRAOUI, M.H.H., BONNAR, J., HILLIER, K. & EMBREY, M.P. (1973). Blood coagulation changes during mid-trimester abortion induced by prostaglandin $F_{2\alpha}$. Bri. med. J. 4, 375-379.

BARRY, A.P., GEOGHEGAN, F. SHEA, S.M. (1955). Acquired fibrinopenia in pregnancy. Bri. med. J. 2, 287-290.

BEAZLEY, J.M., DEWHURST, C.J. & GILLESPIE, A. (1970). The induction of labour with prostaglandin E_2. J. Obstet. Gynaec. Bri. Commonw. 77, 193-199.

BEAZLEY, J.M. & GILLESPIE, A. (1971). Double-blind trial of prostaglandin E_2 and oxytocin in induction of labour. Lancet 1, 152-155.

CAMERON, J.M. & DAYAN, A.D. (1966). Association of brain damage with therapeutic abortion induced by amniotic-fluid replacements: Report of 2 cases. Bri. med. J. 1, 1010-1013.

CSAPO, A. (1961). Defence mechanism of pregnancy. In Progesterone and the Defence Mechanism of Pregnancy, p. 3-27, ed. G.E. Wolstenholme and M.P. Cameron, Ciba Foundation Study Group No. 9.

CSAPO, A., JAFFIN, H., KERENYI, T., DE MATOS, C.E.R. & DE SOUSA FILHO, M.B. (1963). Fetal death in utero. Am. J. Obstet. Gynec. 87, 892-905.

DONALD, I. (1969). Practical Obstetric Problems, 4th edn., p. 78. London : Lloyd-Luke.

EMBREY, M.P., HILLIER, K. & MANHENDRAN, P. (1972). Induction of abortion by extra-amniotic administration of prostaglandins E_2 and $F_{2\alpha}$. Bri. med. J. 3, 146-149.

FILSHIE, G.M. (1971). The use of prostaglandin E_2 in the management of intra-uterine death, missed abortion and hydatidiform mole. J. Obstet. Gynaec. Br. Commonw. 78, 87-90.

GOCHBERG, S.H. & REID, D.E. (1966). Early induction of labour in intra-uterine death. New Engl. J. Med. 275, 432-434.

HALE, R.W., PION, R.J. & SCHINER, W.B. (1972). Vaginal administration of prostaglandins to induce early abortion. Advances in Biosciences 9, International Conference on Prostaglandins, p. 561-565. Ed. S. Bergström. Pergamon Press, Vieweg, Braunschweig.

HILLIER, K. & EMBREY, M.P. (1972). High-dose intravenous administration of prostaglandin E_2 and $F_{2\alpha}$ for the termination of mid-trimester pregnancies. J. Obstet. Gynaec. Bri. Commonw. 79, 14-22.

HODGKINSON, G.P., MARGULIS, R.R. & LUZARDE, J.H. (1954). Etiology and management of hypofibrinogenaemia of pregnancy. J. Am. Ass. 154, 557-561.

JOHANSSON, E.D.B. (1970). A Simplified Procedure for the Assay of Progesterones, Karolinska Symposia on Research Methods in Reproduction and Endocrinology, 2nd Symposium, Ed. E. Diczfaluzy. Stockholm.

KARIM, S.M.M., HILLIER, K., TRUSSELL, R.R. & PATEL, U.C. (1970). Induction of labour with prostaglandin E_2. J. Obstet. Gynaec. Bri. Commonw. 77, 200-210.

LETCHWORTH, A.T., BOARDMAN, R., BRISTOW, C., LANDON, J. & CHARD, T. (1971). A rapid radio-immunoassay for human chorionic sommamomatotrophin. J. Obstet. Gynaec. Bri. Commonw. 78, 535-541.

LIGGINS, G.C. (1962). The treatment of missed abortion by high dosage syntocinon intravenous infusion. J. Obstet. Gynaec. Bri. Commonw. 69, 277.

LIGGINS, G.C., GRIEVES, S.A. KENDALL, J.Z. & KNOX, B.S. (1972). The physiological role of progesterone, oestradiol-17β and prostaglandin $F_{2\alpha}$ in the control of ovine parturition. J. Reprod. Fert. Supp. 16, 85-103.

PRITCHARD, J.A. (1959). Fetal death in utero. Obstet. Gynaec. 14, 573-580.

PRITCHARD, J.A. & RATNOFF, O.D. (1955). Studies of fibrinogen and other hemostatic factors in women with intrauterine death and delayed delivery. Surgery, Gynec. Obstet. 101, 467-477.

24 JAN 1975

QUINN, L.J., & HARPER, J.A. (1955). Fibrinogenaemia in an iso-sensitised mother carrying a dead fetus. J. Obstet. Gynaec. Bri. Commonw. 62, 280-282.

ROBERTS, G., ANDERSON, A., McGARRY, J. & TURNBULL, A.C. (1970). Absence of anti-diuresis during administration of prostaglandin $F_{2\alpha}$. Bri. med. J. 2, 152-154.

TRICOMI, V. & KOHL, S.G. (1957). Fetal death in utero. Am. J. Obstet. Gynec. 74, 1092-1097.

TURNBULL, A.C., PATTEN, P.T., FLINT, A.P.F., KEIRSE, M.J.N.C., JEREMY, J.Y. & ANDERSON, ANNE B.M. (1974). Significant fall in progesterone and rise in oestradiol levels in human peripheral plasma before onset of labour. Lancet 1, 101-103.

URSELL, W. (1972). Induction of labour following fetal death. J. Obstet. Gynaec. Bri. Commonw. 79, 260-264.

WAGATSUMA, T. (1965). Intra-amniotic injection of saline for therapeutic abortion. Am. J. Obstet. Gynec. 93, 743-745.

WOLFF, J.R., NEISON, P.E. & SCHILLER, P. (1970). The emotional reaction to a stillbirth. Am. J. Obstet. Gynec. 108, 73-77.

WOOD, C., BOOTH, R.T. & PINKERTON, J.H. (1962). Induction of labour by intra-amniotic injection of hypertonic glucose solution. Bri. med. J. 2, 706-709.

24 JAN 1975

Publications subsequent to completion of this thesis:

SCHER, J. & BAILLIE, P. (1973) The effect of a β-adrenergic agent on prostaglandin stimulated labor, Advances in the Biosciences 9, International Conference Prostaglandins, p. 743-749. Ed. S. Bergström, Pergamon Press, Vieweg, Braunschweig.

SCHER, J., BAILLIE, P., JESSOP, S. & HENDRIE, B. (1973) A comparison between the effects of prostaglandin $F_{2\alpha}$ and oxytocin on fluid balance during induction of labour in patients suffering from Pre-eclampsia. S. Afr.med.J. Supplement - Obstetrics and Gynaecology, 47, 1291-1292.