Appearance of Prostaglandin $F_{2\alpha}$ in Human Blood during Labour*

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Brit. med. J., 1968, 4, 618-621

Summary: Blood samples from over 70 pregnant women have been examined for the presence of four prostaglandins. Samples obtained from women not in labour at different gestation periods and at term contained no detectable amounts of prostaglandins. Prostaglandin $F_{2\alpha}$ was present in samples of blood obtained during normal spontaneous labour. The appearance of this substance in the blood preceded the uterine contraction. Whether prostaglandins play a part in the process of normal labour is still conjectural.

Introduction

The mechanism of parturition has for many years been the subject of investigation, and the search for oxytocic substances in blood, urine, and amniotic fluid has been one of the main lines of approach. The presence of smooth-muscle-stimulating substances in maternal blood during pregnancy and in human amniotic fluid has been variously reported (Palmisano, 1950; Suzor *et al.*, 1952; Stamm and Monnier, 1954; Hanon *et al.*, 1955; Armstrong and Stewart, 1960; Centaro *et al.*, 1961; Croxatto *et al.*, 1961; Driessche, 1961; Hawker *et al.*, 1961). As a result of these studies several chemically different substances have been thought to play a part in the initiation and maintenance of labour. These include oxytocin (Fitzpatrick, 1961; Hawker, 1961; Coch *et al.*, 1965), 5-hydroxytryptamine (Koren *et al.*, 1965), and bradykinin (Martinez *et al.*, 1962; Periti *et al.*, 1962). In spite of numerous reports of the presence of different smooth-muscle-active substances in the blood and in amniotic fluid, their role in parturition remains obscure.

The identification of four prostaglandins in human amniotic fluid obtained during normal labour and during spontaneous abortion has been recently reported (Karim, 1966; Karim and Devlin, 1967). Because some prostaglandins have a potent uterine-muscle-stimulating action in vitro (Bygdeman and Eliasson, 1963; Pickles and Hall, 1963; Pickles *et al.*, 1965; Eliasson, 1966), and because these prostaglandins appear in the amniotic fluid during labour, the possibility that they are involved in the process of normal labour has been suggested (Karim and Devlin, 1967). In the present investigation maternal venous blood has been examined for the possible presence of four prostaglandins (E_1 , E_2 , $F_{1\alpha}$, $F_{2\alpha}$). In this paper the finding of prostaglandin $F_{2\alpha}$ in the blood during labour is reported and the possible physiological significance is discussed.

Materials and Methods

The study was carried out on more than 70 pregnant women apparently free from any complications of pregnancy such as toxæmia and diabetes. They were divided into three groups: (1) those between the 12th week of pregnancy and term but not in labour, (2) women in full-term normal labour, and

(3) post-mature women undergoing caesarean section for uterine inertia.

Twenty millilitres of venous blood was withdrawn from the antecubital vein into a sterile polyethylene syringe and transferred to a centrifuge tube containing 500 units of heparin. The blood was centrifuged at 2,000 r.p.m. for 10 minutes and the plasma separated. The plasma was extracted for prostaglandins by a method based on that described by Samuelsson (1963) for the extraction of these substances from the seminal fluid. Briefly this consisted in extracting the plasma pH 3 with three volumes of ethyl acetate, evaporation of the ethyl acetate phase at 40° C. under reduced pressure, and a two-stage distribution of the residue between petroleum spirit (40-60°) and 70% aqueous alcohol. The alcohol phase was evaporated to a small volume, diluted with water, acidified to pH 3, and extracted with ethyl acetate as before. The residue obtained after evaporation of the ethyl acetate contained prostaglandins. This method was used with known concentrations of pure prostaglandin E_2 and $F_{2\alpha}$ added to samples of plasma, and it was found that 80-90% of the added prostaglandins were present in the final extract. The method used for the identification of prostaglandins in pooled samples of blood was similar to the one previously described (Karim, 1966). Prostaglandins in individual samples of blood were identified by means of thin-layer chromatography in solvent system AII of Green and Samuelsson (1964), markers of known prostaglandins on plates coated with silica gel G containing 5% of silver nitrate being used. Biological estimation of chromatographically separated prostaglandins was carried out with the isolated ascending colon preparation from the jird, *Meriones libycus* (Karim *et al.*, 1967).

When samples of blood were taken during normal labour uterine contractions were also recorded by means of an external tocodynamometer (Smythe, 1957).

Results

Blood from Pregnant Women not in Labour

Individual samples of venous blood from 38 women not in labour, between the 12th week of pregnancy and term, were extracted and assayed for prostaglandins. None of these samples contained any detectable amounts of prostaglandin (less than 0.2 mμg. of E_2 or $F_{2\alpha}$ per ml.). Blood samples from four women who were four to five weeks post-mature also did not contain any prostaglandin, neither did the blood from seven women at term who were delivered by caesarean section before the onset of labour.

Blood from Women in Labour (First Stage)

In the first series of experiments four samples were taken from each of 10 women in established labour when the uterine contractions were one every four to six minutes. The samples were taken as follows (see also Diagram): A, during contraction of the uterus; B, during the minute immediately after the uterine contraction; C, two minutes after the end of uterine contraction; and D, during the minute preceding the next uterine contraction.

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From this series of experiments it was found that the sample of blood taken during uterine contraction contained the highest concentration of prostaglandin $F_{2\alpha}$ (6.3 $\mu\text{g./ml.}$ of plasma). The sample taken during the minute following the uterine contraction (sample B) contained on an average less than a quarter of that present in sample A. Sample C from eight patients taken during the rest period of the uterus contained no detect-

Diagrammatic representation of uterine contractions in established labour. Time interval between contractions is four to six minutes. Samples of blood for the estimation of prostaglandins were taken at A, during the contraction of the uterus; B, during the minute following the contraction; C, two minutes after the end of the contraction; and D, during the minute preceding the next uterine contraction.

able concentration of prostaglandin and the other two contained less than sample A, B, or D. In all 10 women the blood taken during the minute preceding the uterine contraction (sample D) contained almost as much prostaglandin $F_{2\alpha}$ as did sample A obtained during the uterine contraction. Detailed results of these experiments are shown in Table I.

Blood at Different Stages of Labour.—In order to establish whether there is any relation between blood prostaglandin levels and the intensity or character of uterine contractions blood from 15 women at different stages of labour was examined. The following samples of blood were taken: I, during established labour (sample during uterine contraction, first stage); II, during expulsion of the foetus (second stage); III, during expulsion of the placenta (third stage); and IV, three hours post-partum.

The blood from five of these patients at each stage of labour was pooled and the prostaglandin content of the pooled sample estimated. In the other cases the prostaglandin content of individual samples was estimated. Detailed results of these experiments are shown in Table II.

TABLE I.—Prostaglandin $F_{2\alpha}$ in Maternal Venous Blood in Established Labour

Subject	Sample A	Sample B	Sample C	Sample D
1	4.4	0.4	—	4.0
2	6.8	1.2	—	5.4
3	12.4	2.3	0.3	11.9
4	2.3	—	—	2.4
5	3.9	—	—	3.6
6	18.0	3.1	0.35	14.4
7	2.0	1.1	—	1.0
8	7.4	2.1	—	6.4
9	3.3	—	—	1.6
10	2.9	1.3	—	0.8
Mean	6.34	1.15	0.065	5.15

— Indicates no prostaglandin $F_{2\alpha}$ detected (less than 0.2 $\mu\text{g./ml.}$). All concentrations are expressed in $\mu\text{g./ml.}$ of plasma. The results are uncorrected for recovery.

TABLE II.—Concentrations of Prostaglandin $F_{2\alpha}$ in Maternal Venous Blood at Different Stages of Labour

Subject	Sample I	Sample II	Sample III	Sample IV
1	6.4	12.4	18.0	—
2	3.3	6.8	4.2	—
3	1.5	22.8	6.9	—
4	6.3	10.5	1.9	—
5	2.1	3.6	2.8	—
6	3.9	5.8	3.4	—
7	8.3	17.9	6.6	0.5
8	2.2	8.4	9.3	—
9	1.8	3.6	3.4	—
10	7.6	10.0	21.0	1.2
Pooled sample of blood from 5 subjects	7.4	18.9	6.9	0.2
Mean of 15 samples	3.38	8.04	6.36	0.013

— Indicates no prostaglandin $F_{2\alpha}$ detected (less than 0.02 $\mu\text{g./ml.}$). All concentrations are expressed in $\mu\text{g./ml.}$ of plasma. The results are uncorrected for recovery.

In the majority of these women there was more prostaglandin $F_{2\alpha}$ in blood taken during the second stage of labour than in the first-stage sample. The blood taken during expulsion of the placenta contained less prostaglandins than the second-stage samples in 7 out of 10 individual samples. The other three contained more. Only 2 out of 10 samples taken three hours postpartum contained detectable concentrations of prostaglandin $F_{2\alpha}$.

Discussion

Prostaglandin was the name given to a vasodepressor and smooth-muscle-stimulating substance found in extracts of human seminal fluid (Euler, 1935). After isolation and elucidation of the chemical structure of prostaglandin it became apparent that this was not a single substance but a family of closely related substances (Bergström and Sjövall, 1957, 1960; Bergström *et al.*, 1962). Six of these have been isolated from human semen. The occurrence of prostaglandins is, however, not restricted to the male accessory glands and their secretions as the name suggests. These substances have been found in thymus, pancreas, brain, and kidney (Bergström and Samuelsson, 1965; Samuelsson, 1965), menstrual fluid (Eglinton *et al.*, 1963), human umbilical cord, amniotic fluid, and decidua (Karim, 1966, 1967; Karim and Devlin, 1967), and in many other animal and human tissues (Karim *et al.*, 1967, 1968; Williams *et al.*, 1968).

The physiological role of prostaglandins is largely unknown, but many have been suggested (Horton, 1965; Pickles *et al.*, 1965; Bergström, 1967; Karim, 1967; Karim and Devlin, 1967).

The presence of prostaglandin $F_{2\alpha}$ in the maternal blood during labour is of interest in view of the potent uterine-muscle-stimulating action of this substance in vitro (Bygdeman and Eliasson, 1963; Pickles and Hall, 1963; Pickles *et al.*, 1965; Eliasson, 1966). It is of particular interest because the sensitivity of the uterus to prostaglandin $F_{2\alpha}$ increases with the progression of pregnancy until finally at term the uterus is most sensitive to it (Eliasson, 1966).

It may be argued that the presence of prostaglandin $F_{2\alpha}$ in blood during labour could be a consequence of the process of labour instead of a cause of it. Davies *et al.* (1967) have shown that stimulation of the sympathetic nerve to the spleen in the cat results in the contraction of the spleen and appearance of prostaglandin E_2 in the splenic venous blood. When the contractions of the spleen are blocked with adrenergic blocking drugs stimulation of the nerve no longer results in the release of prostaglandin. The release of prostaglandin E_1 from the rat phrenic nerve diaphragm preparation on stimulation of the nerve as shown by Ramwell *et al.* (1965), however, is not abolished when the contractions of the diaphragm are blocked with D-tubocurarine. In the present investigation the fact that prostaglandin $F_{2\alpha}$ is present in the sample of blood taken before the onset of uterine contraction and that very little is present in the sample taken at the end of contraction suggests that it is not released as a result of contraction. It is hoped to estimate prostaglandin $F_{2\alpha}$ in samples of uterine vein blood obtained during labour to clarify this point further.

The source of prostaglandin found in the blood during labour is difficult to establish. Decidua contains a high concentration of prostaglandins, and this has been suggested as a possible source of prostaglandins found in the amniotic fluid during labour (Karim and Devlin, 1967). Considerable evidence has now accumulated to show the release of prostaglandins on stimulation of sympathetic as well as parasympathetic nerves. The work of Davies *et al.* (1967) and of Ramwell *et al.* (1965) with splenic and phrenic nerve preparations has already been quoted. Shaw (1966) found a release of prostaglandin from adipose tissue in vitro in response to sympathetic nerve stimulation and Ramwell *et al.* (1966) demonstrated the release of

prostaglandin from adrenals stimulated with acetylcholine. Prostaglandins have been shown to be present in both sympathetic nerves in man and animals (Karim *et al.*, 1967, 1968). It is therefore conceivable that the prostaglandin found in maternal blood is of neural origin. It has recently been shown that the concentrations of adrenaline and noradrenaline in maternal blood are raised during labour and increase with the progression of labour (Beard and Karim, 1967), suggesting an increase in sympathetic activity at this time.

Apart from prostaglandin F_{2a} reported here, the presence of other smooth-muscle-active substances in blood during labour have been recorded. The increase in plasma kinin level during labour has been demonstrated, and it was thought that kinins activated during that time would act synergistically with oxytocin on the uterus (Armstrong and Stewart, 1960; Centaro *et al.*, 1961; Periti *et al.*, 1962; Martinez *et al.*, 1962). Bradykinin and kinins derived from the plasma of women in labour, however, have no oxytocic effect on the human uterus in vitro (Berde and Saarneli, 1961; Centaro and Periti, 1963), and the increase in kinin level during labour is no longer considered to have a physiological significance by virtue of oxytocic activity (Periti and Gasparri, 1966).

Koren *et al.* (1966) suggested that 5-hydroxytryptamine plays a part no less important than that of oxytocin in the initiation of parturition. This suggestion is based on their observation (Koren *et al.*, 1965) that the 5-hydroxytryptamine content of placenta gradually increases during pregnancy and that the enzymatic activity of placental monoamine oxidase which destroys 5-hydroxytryptamine shows a reverse tendency. However, Driesche (1961) found no increase in free plasma 5-hydroxytryptamine concentration during pregnancy or labour.

The substance most frequently suggested to be responsible for the onset of labour is oxytocin. Crucial evidence for the participation of oxytocin in the process of labour is lacking, however, in spite of numerous attempts to clarify this point. The hypothesis that oxytocin plays an essential part in parturition has been largely based on the similarity between spontaneous labour and that induced by oxytocin (Caldeyro-Barcia and Poseiro, 1959). It is supported by the observation of milk ejection during parturition in women (Gunther, 1948) and rabbits (Cross, 1958). On the other hand, it has been maintained that hypophysectomy fails to cause any serious impairment of parturition on several species (Dott, 1923; Allan and Wiles, 1932; Smith, 1932; Little *et al.*, 1958) and that induction of labour with oxytocin is not always successful.

The reports of increase in oxytocin concentration of blood during pregnancy and labour are conflicting. The findings of Suzor *et al.* (1952) of 30–50 milliunits (mU) of oxytocin per ml. during the last month of pregnancy has been thought to be too high, and Driesche (1961) has shown that the oxytocic activity reported by Suzor *et al.* was due to the release of 5-hydroxytryptamine from the disintegrating platelets and not due to oxytocin. Hawker (1961) also reported an average of 10.64 mU of oxytocin per ml. of blood during the third trimester. However, Caldeyro-Barcia (1961) considers that such high activity could not be due to oxytocin alone because in order to achieve an oxytocin level of 1 mU/ml. blood he had to infuse several thousand mU of oxytocin per minute, a dose which would invariably produce abnormal uterine contractions never seen in normal pregnancy. Caldeyro-Barcia also pointed out that he himself had failed to detect even 0.1 mU of oxytocin per ml. of blood at term. Some investigators believe that oxytocin is responsible for the onset of labour, but the concentration in blood is too small to measure with existing bioassay methods. Whether prostaglandins are involved in the process of normal labour is only conjectural at this stage. The available evidence is mainly circumstantial.

It is worth mentioning here that extracts of thymus have been shown to start labour (Halfpap, 1965), and this organ has

been proved recently to contain prostaglandins (Samuelsson, 1965; Karim *et al.*, 1967, 1968).

It is necessary to establish more accurate time relations between uterine contraction and concentrations of prostaglandins. This might be achieved, as has been suggested, by measuring levels in uterine vein blood during labour. The next stage would appear to be the observations of the effect of infusing prostaglandin F_{2a} in a patient at term.

I would like to thank Mrs. Jean Devlin for technical assistance and Dr. E. Pike (Upjohn Co., Michigan) for a gift of pure prostaglandin. My thanks are also due to Professor S. G. Clayton, Professor C. J. Dewhurst, and Mr. R. W. Beard for advice and encouragement; to the medical and nursing staff of Queen Charlotte's Maternity Hospital, London, for their assistance in collecting the material for this project; and to Professor R. R. Trussell for useful comments on the manuscript.

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Response of Pregnant Human Uterus to Prostaglandin- $F_{2\alpha}$ -induction of Labour*

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Brit. med. J., 1968, **4**, 621-623

Summary: Labour was successfully induced in 10 women at or near term with prostaglandin $F_{2\alpha}$ infusion. In no case was there an increase in the resting tone of the myometrium, and complete relaxation between contractions was recorded.

Introduction

The identification of four prostaglandins in human amniotic fluid obtained during labour and spontaneous abortion has been reported (Karim, 1966; Karim and Devlin, 1967). Prostaglandin $F_{2\alpha}$ has proved to have a potent uterine-muscle-stimulating action on isolated strips of pregnant human myometrium (Bygdeman, 1964, 1967). Karim (1968) has further shown that prostaglandin $F_{2\alpha}$ appears in the maternal venous blood in variable amount during labour, and that the concentration of this prostaglandin is highest immediately before a uterine contraction.

This work has prompted the suggestion that prostaglandin $F_{2\alpha}$ may play a part in parturition (Karim, 1966, 1968). In order to gain additional evidence for this suggestion, the effect of the intravenous infusion of prostaglandin $F_{2\alpha}$ on the uterine activity of pregnant women at or near term was studied. The investigation was carried out in three parts. (1) A pilot study to investigate the effect of infusion of prostaglandin $F_{2\alpha}$ on the cardiovascular system of five male and one non-pregnant female volunteers was carried out, in view of reports that some prostaglandins have a vasodepressor effect in man (Bergström *et al.*, 1959, 1965; Carlson, 1967). (2) The effect of prostaglandin $F_{2\alpha}$ infusion on the pregnant human uterus in vivo in two women with intrauterine death of the foetus was studied and the foetuses were delivered. (3) Labour was successfully induced in eight women at or near term with prostaglandin $F_{2\alpha}$ infusion. Labour appeared to be normal, and live children were delivered in all cases.

Materials and Methods

Ten women were studied between the 34th and 44th weeks of pregnancy. Uterine activity was measured by recording changes in the amniotic fluid pressure by using an external guard-ring tocodynamometer (Stanley Cox Ltd.) attached to a Honeywell electronic recorder (Smyth, 1957). The tocograph was sited over the upper part of the fundus uteri and held in

this position by a strap attached around the patient's waist. The relation of the foetal head to the pelvic brim and the condition of the cervix uteri were recorded before administration of prostaglandin. Spontaneous uterine activity was recorded for at least one hour before the infusion of prostaglandin. Prostaglandin $F_{2\alpha}$ was administered continuously at rates of 0.025-0.05 $\mu\text{g./kg./min.}$ by means of a Palmer infusion pump. The volume of the fluid injected did not exceed 15 ml./hour. Maternal blood pressure and foetal heart rate were measured and recorded every 10 minutes. Progress in labour was assessed by observation of the descent of the foetal head and dilatation of the cervical os.

Results

The results of the first part of the investigation to study the cardiovascular effects of prostaglandin $F_{2\alpha}$ infusion have been separately reported (Karim *et al.*, 1968), and only a brief summary is given here. Within the concentration 0.01-2 $\mu\text{g./kg./min.}$ prostaglandin $F_{2\alpha}$ had no significant effect on the heart rate, systolic and diastolic pressures, respiration rate, or the E.C.G. pattern in the six volunteers studied.

Intrauterine Deaths

Intrauterine death had occurred in two cases (Nos. 1 and 2). One of the babies had died three weeks before induction. The second patient had ruptured her membranes before the induction of labour and the cord had prolapsed. Both were multi-gravid patients and were not in labour. Infusion of prostaglandin, 0.05 $\mu\text{g./kg./min.}$, initiated uterine contractions after a latent period of 18 and 20 minutes respectively. The contractions were well spaced and showed no tendency to summation. The resting tone returned to normal between contractions. The induction delivery intervals were 10 and 6 hours respectively. Fig. 1 shows the record of uterine activity in Case 1.

Induction of Labour at or near Term

Only one of the series of eight patients was a primigravida (Case 6). She was four weeks post-mature, and a trial of labour was planned for possible minor disproportion. Uterine contractions started 15 minutes after prostaglandin infusion, contractions were good from the outset, and relaxation was excellent. Progress, however, was slow, and in spite of 12 hours of good contractions labour was terminated by caesarean section for disproportion with a mentoposterior presentation. The child weighed 8 lb. 10 oz. (3,910 g.), and showed no evidence of distress either before or after delivery. The remaining

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