

ACTION OF PROSTAGLANDINS ON THE CONTRACTILITY OF PREGNANT HUMAN UTERUS

by

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Experimental studies of the action of prostaglandins on human myometrium have shown with minor discrepancy constant pattern of response, the PGE series inhibiting and PGF series stimulating myometrial activity. Bygdeman (1964) reported that PGF group as a whole caused inhibition of human myometrium in vitro, but PGF were relatively inactive, but with high dose they produced stimulation, occasionally inhibition. On the other hand, Pickles *et al* (1963) and Pickles *et al*, (1965) found that PGF invariably increased the contraction of human myometrium in vitro while PGF gave a variety of effects varying from mild stimulation to complete inhibition.

The behaviour of pregnant uterus however, appears to be quite different. Recently, attention has been directed to study of pregnant myometrium in vitro (Embrey and Morrison, 1968). It was found that while lower segment myometrium was relatively inactive, well-marked effects were observed with upper segment myometrium. Not only PGF (F₁ alpha and F₂ alpha) exhibited stimulatory effect but for the first time it was shown

that contrary to expectation the 'E' prostaglandin (PGE₁ and PGE₂) also produced spasmogenic effects on pregnant myometrium. These results which were at first surprising have now been confirmed in a preliminary study of the intact human uterus in pregnancy. Recent experiment by Martin *et al*, (1971) showed that PGE₁ in a low dose was found to stimulate both uterine body and lower segment of pregnant uterus in vitro and a high dose brought about decrease and blockage of such activity.

Due to wide variety of action of prostaglandins, they are going to emerge as an exciting new molecular species. They are exciting because of their extreme potency and powerful action on the pregnant uterus in all stages of pregnancy, which can be utilised for the termination of early pregnancy. The reported discrepancies as regards its in vitro action on pregnant uterus, prompted the authors to study the effect of PGE₁ and PGF₁ alpha on human myometrium in vitro.

Material and Methods

The uterine muscle strips were obtained from the uteri of pregnant women of different age groups, operated upon for caesarean section, hysterectomy and hysterotomy.

The muscle strips from myometrium were immediately preserved after operation in Krebs's solution.

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After recording normal contractions, prostaglandin F_1 alpha was added to the bath in varying concentrations and the effects recorded. The following were studied: (a) amplitude of contraction, (b) frequency of contraction, (c) duration of contraction, (d) contraction phase, and (e) relaxation phase.

Then the drug was washed out by Kreb's solution and again sometime was allowed for normal contractions to appear and the effect of the drug to disappear. The Prostaglandin E_1 in varying concentrations was added to the bath and the effect was recorded.

Sometimes the effect of PGE_1 and PGF_1 alpha were recorded on two different strips of the same tissue and sometimes in the same tissue after allowing sufficient time after washing out the first drug.

Occasionally the effect of ergometrine was noted on the myometrial strips, on which the effect of PGE_1 and PGF_1 alpha were observed for comparison of the action of ergometrine and prostaglandin on human myometrium.

Table I shows the number of pregnant cases according to the period of gestation. Out of 40 pregnant cases, 8 are of first trimester, 12 are of second trimester and 20 are of third trimester or term pregnancy.

Discussion

In the present experiment it is observ-

ed that E_1 in low dose (0.04 ug/ml) stimulated the uterine body and with increased dose there was decrease in the amplitude and frequency of contractions and with further increase complete inhibition (Photographs I, II and III). Table III shows that 0.04 ug/ml. bath fluid of E_1 stimulates 66 per cent cases in the first trimester, 70 per cent in the second trimester and 60 per cent in the third trimester of pregnancy. With increased dose the amplitude and frequency are decreased and with still further increase i.e. with more than 0.3 ug/ml. of bath fluid complete inhibition of normal contractions are seen (100 per cent cases).

In the lower segment PGE_1 in the dose of 0.04 and 0.1 ug/ml. bath fluid produced contractions and with increased dose inhibition was observed (Photograph VI). However, the amplitude of contraction was less than that of upper segment. Table IV shows the action of PGE_1 on lower segment pregnant myometrium. It is seen that 0.04 ug/ml. produced contraction in 50 per cent cases of first trimester of pregnancy, 100 per cent cases of second trimester and 60 per cent cases of third trimester, but with slightly increased dose i.e. 0.1 ug/ml. bath fluid, 100 per cent cases in the first trimester, 100 per cent in the second trimester and 90 per cent in the third trimester showed contraction. Thereafter further increase produced inhibition and with 0.3 ug and more/ml.

TABLE I
Showing the Number of Pregnant Cases According to Different Periods of Gestation

	First trimester	Second trimester	Third trimester and term pregnancy
Strips from corpus	6	10	10
Strips from lower segment	2	2	10
Total	8	12	20

TABLE IV
Shows the Effect of PGE_1 in Different Concentrations on Lower Segment Pregnant Myometrium in Different Trimesters of Pregnancy (Photograph VI)

Concentration of PGE_1 in ug/ml bath fluid	Type of response	1st trimester (2 cases)		2nd trimester (2 cases)		3rd trimester (10 cases)	
		No. of cases showing response	Percent-age	No. of cases showing response	Percent-age	No. of cases showing response	Percent-age
0.04	Stimulation	1	50	2	100	6	60
	Inhibition	0	0	0	0	0	0
	No response	1	50	0	0	0	40
0.1	Stimulation	2	100	2	100	9	90
	Inhibition	0	0	0	0	0	0
	No response	0	0	0	0	1	10
0.2	Stimulation	1	50	0	0	2	20
	Inhibition	1	50	2	100	7	70
	No response	0	0	0	0	1	10
0.3 & more	Stimulation	0	0	0	0	0	0
	Inhibition	2	100	2	100	9	90
	No response	0	0	0	0	1	10

bath fluid complete inhibition (100 per cent) was observed.

The lower segment response differs from that of upper segment in the above mentioned observations. A comparatively high dose is required for stimulation of contraction and the amplitude and the frequency of contraction is less than that of upper segment.

It is observed that PGF_1 alpha in the dose of 0.04 ug/ml. bath fluid produced stimulation in 50 per cent cases in the first trimester, 60 per cent in the second trimester and 70 per cent in the third trimester or term pregnancy. With increased dose the stimulation is more marked. In the dose of 0.3 ug or more/ml. bath fluid there was stimulation (contraction) in 100 cases. Similarly the frequency and amplitude of contraction also increased with increased dose (Photographs No. I, II, III and IV). However, PGF_1 alpha in very low dose (0.04 ug/ml.) does not produce well-marked contraction like that of PGE_1 . In contrast to the action of PGE_1 it does not produce inhibition in increased dose (Photographs I, II, III and IV). The amplitude and frequency of contraction observed with 5 ug/ml. bath of PGF_1 alpha is more than the contraction produced by 5 ug/ml. bath of ergometrine. The significance of this finding is that PGs have got more powerful contractile action on the uterus than ergometrine, a finding which may have got clinical importance (Photographs II and IV).

The lower segment showed varied response. In majority of the cases there was stimulation (Photograph VIII). Table V shows that there was no response in low dose i.e. 100 per cent of the cases in all stages of pregnancy were non-responsive to the dose of 0.04 and 0.1 ug/ml. bath fluid. With increased dose 0.3 or more

ug/ml. bath fluid contractions were seen in 100 per cent cases. However, the amplitude and frequency of contraction was less than that of upper segment. There was no significant difference between the responses obtained from the lower segment strips at different periods of gestation.

These findings are somewhat similar to the observations of different workers with minor discrepancies. Bygdeman (1964) reported that PGF_1 alpha always stimulated the motility of pregnant myometrium in the same way as found for non-pregnant myometrium but the sensitivity of the strips were increased, even a dose of 0.01 ug/ml. bath fluid was enough. The stimulating effect remained even if the dose was increased upto 0.5 ug/ml. The experiments were mostly carried out in strips obtained from early pregnancy and only one case was of term pregnancy. However, he did not mention the difference in response to different periods of gestation and the effect on lower segment.

Embrey and Morrison (1968) reported that on upper segment myometrium PGF_1 alpha in low doses (10 to 20 ug/ml. was without any effect but with high dose 50 to 100 ug/ml) mild stimulation was observed. In the lower segment there was an immediate contraction followed by inhibitory pause usually lasting some minutes i.e. biphasic stimulation inhibition response.

The present result is similar to that of Bygdeman (1964) and there are slight discrepancies with the findings of Embrey and Morrison (1968) as regards the findings on lower segment, which is not marked in the present experiment.

In this study of their effects on human myometrium in vitro, both E_1 and F_1 alpha produced various types of response in

TABLE V
Shows the Action of PGF_1 alpha in Different Trimesters on Lower Segment Pregnant Myometrium in Different Trimesters of Pregnancy (Photograph VII)

Concentration of PGF_1 alpha in ug./ ml response bath fluid	Type of response	1st trimester (2 cases)		2nd trimester (2 cases)		3rd trimester (10 cases)	
		No. of cases showing response	Percent-age	No. of cases showing response	Percent-age	No. of cases showing response	Percent-age
0.1	Stimulation	0	0	0	0	0	0
	Inhibition	0	0	0	0	0	0
	No response	2	100	2	100	10	100
0.2	Stimulation	0	0	1	50	1	10
	Inhibition	0	0	0	0	0	0
	No response	2	100	1	50	9	90
0.3	Stimulation	2	100	2	100	9	90
	Inhibition	0	0	0	0	0	0
	No response	0	0	0	0	1	10
More than 0.3	Stimulation	2	100	2	100	10	100
	Inhibition	0	0	0	0	0	0
	No response	0	0	0	0	0	0

different physiological conditions in different concentrations of the drug. The significant results in the present study were undoubted spasmogenic effect of PGE₁ and PGF₁ alpha on upper segment pregnant myometrium in all stages of pregnancy.

This stimulatory effect of prostaglandins in all stages of pregnancy has prompted many workers to use prostaglandins for the termination of pregnancy or abortion and induction of labour. In fact, Karim *et al.*, (1968) and Embrey (1969) have successfully induced labour by using prostaglandins, and Bygdeman *et al.*, (1968) and Karim *et al.*, (1970) reported that abortion can be done by using PGE and PGF compounds.

The powerful spasmogenic effect of both PGE₁ and PGF₁ in all stages of pregnancy and its marked spasmogenic effect which is more than that of ergometrine indicates the possibility of using the prostaglandins in medical practice for preventing atonic uterine bleeding after abortion or delivery and termination of pregnancy for family planning purpose.

Summary

PGE₁ in the pregnant upper segment myometrium produces powerful contractions in all the trimesters of pregnancy. With increased dose blockage of such activity, either partially or totally occurs.

Action of PGE₁ on lower segment pregnant myometrium is similar to that of upper segment but a comparatively high dose is required for the production of contraction as well as blockage of such action (Inhibition).

PGF₁ alpha always produces contraction in the pregnant myometrium in all trimesters of pregnancy, but a compara-

tively high dose is required for such activity than the dose of PGE₁.

With increased dose of PGF₁ alpha amplitude and frequency of contraction of pregnant myometrium increases and tetanic type of contraction is produced with very high dose. In contrast to the action of PGE₁, it never produces inhibition with increased dose.

Pregnant lower segment myometrium requires high dose of PGF₁ alpha for production of contraction and the amplitude is less than that of the upper segment myometrium. There is no marked difference in response to myometrial strips at different periods of gestation.

The effects of PGE₁ and PGF₁ alpha on pregnant myometrium are more powerful than that of 'Ergometrine' which indicates the possibility of using prostaglandins for atonic uterine bleeding after abortion or delivery.

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See Figs. on Art Paper I-II