TERMINATION OF SECOND TRIMESTER PREGNANCY WITH SINGLE INTRA-AMNIOTIC AND EXTRA-AMNIOTIC INSTILLATION OF PROSTAGLANDIN F_2 ALPHA & 15-METHYL PROSTAGLANDIN F_2 ALPHA

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Termination of pregnancy in second trimester poses a challenging problem to the obstetrician. Intrauterine administration of prostaglandins constitutes the most significant recent advance in terminating second trimester pregnancy. Initial studies with natural compound proved excellent in termination of midtrimester pregnancy (Bygdeman, 1971; Anderson, 1972). However, as the natural compound metabolises quickly, repeated administrations were required to achieve a high success rate which involved a potential risk of introducing infection into uterine cavity. With the aim of evolving a "single shot" procedure, further trials were conducted with high doses of PGF_2 alpha (Brenner *et al,* 1973) and with its 15-methyl analogues (Wiquist *et al,* 1973, Hingorani *et al,* 1976) which metablise slowly and thus have longer duration of action.

Present study was carried out to have more experience with the recommended single dosage schedules and to compare the relative effectiveness and safety of intra-amniotic and extra-amniotic routes.

Material and Methods

The material comprised 200 healthy women between 10 and 20 weeks of gestation who sought medical termination of pregnancy at Safdarjang Hospital, New Delhi. Distribution of patients in the different schedules is given below:

Route	Drug & Dose	No. of cases
1. Intra-amniotic	(a) PGF_2 alpha 50 mgm.	49
	(b) 15-methyl PGF_2 alpha 2.5 mgm	51
2. Extra-amniotic	15-methyl PGF_2 alpha 1.0 mgm mixed with viscous medium (Hyscon)	100

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Technique of Administration

Intra-amniotic: Drug was administered by transabdominal amniocentesis via a polyethylene catheter threaded through an 18 gauze needle. The drug was administered only if clear liquor was obtained.

In case of bloody tap, injection was given provided the stained amniotic fluid tended to clear.

Extra-amniotic: Extra-amniotic instillation was done via a polyethylene catheter (No. Fr. 8) introduced through the cervix into the lower uterine segment, so that the tip of the catheter was just within the internal os. After instillation the patient was kept lying down for 20 minutes to avoid expulsion of the drug.

Patients were carefully observed till the time of abortion. No additional oxytocics or surgical intervention was used within the trial period or till the patient had aborted the foetus. Analgesics for uterine pain (Inj. Pethidine 50 to 100 mgm, 1/m), antiemetic (Prochlorperazine, 5 to 10 mgm) and anti-diarrhoeal (Retardin—5 mgm, diphenoxylate chloride and 50 mgm. atropine) were used as and when required. Cervical swab cultures for bacteriological study were taken prior to instillation of drug, at the time of abortion and 24 hours after abortion, to assess the risk of infection by intra- and extra-amniotic routes.

The trial was considered as successful when abortion occurred, either complete or incomplete, within 48 hours following intra-amniotic instillation and within 36 hours following extra-amniotic instillation. Abortion was considered as complete, if the foetus and placenta were expelled through the cervical canal without interference and as incomplete when any part of the placenta was retained inside the uterine cavity. Induction abortion interval was calculated as time interval between injection of the drug and expulsion of the foetus.

Observations

Patient Characteristics: Fifty-nine young unmarried or primigravidae and 119 multigravidae sought medical termination of pregnancy at later weeks of gestation necessitating intra-amniotic instillation.

Most of the patients were Hindus, belonging to urban areas (Table I).

TABLE I
Age, Parity, Weeks of Gestation, Marital States and Religion

	Intra-amniotic N = 100	Extra-amniotic N = 100
1. **Age (Years)**		
— 20	35	13
21 — 30	51	68
— 30	14	19
2. **Parity**		
Nulli	61	20
Multi	39	80
3. **Gestation (Wks)**		
10 — 12	—	41
14 — 16	35	56
18 — 20	65	1
4. **Residence**		
Urban	87	95
Rural	4	2
Urban Outside	5	3
5. **Marital Status**		
Married	47	79
Unmarried	44	15
Formerly married	9	6
6. **Religion**		
Hindu	90	96
Muslim	3	2
Christian	7	2

Success Rate: As seen in Table II, the success rates with intra-amniotic PGF_2 alpha and 15-methyl PGF_2 alpha were 93.9 per cent and 98 per cent respectively. The difference was not statistically significant ($P < 0.05$). The success rate with extra-amniotic 15-me-F_2 alpha, being 86 per cent was significantly less as compared to the intra-amniotic route.

Complete/Incomplete Abortion: Table III shows that number of incomplete abortions were significantly higher in

TABLE II
Success Rate

Outcome	1. Intra-amniotic				2. Extra-amniotic	
	(A) PGF_2		(B) 15-me-F_2		15-me-F_2 alpha	
	No.	%	No.	%	No.	%
Success	46	93.9	50	98.0	86	86.0
Failure	3	6.1	1	2.0	14	14.0
	1(A)	Vs.	1(B)	— p 0.05		
	1	Vs.	2	— p 0.05		

TABLE III
Complete/Incomplete Abortion

Abortion	1. Intra-amniotic				2. Extra-amniotic	
	(A) PGF_2 alpha		(B) 15-me-F_2 alpha		15-me-F_2 alpha	
	No.	%	No.	%	No.	%
Complete	35	76.1	36	72.0	17	19.8
Incomplete	11	23.9	14	28.0	69	80.2
	1(A)	Vs.	1(B)	p 0.05		
	1	Vs.	2	p 0.05		

extra-amniotic group than intra-amniotic group, being 80.2 per cent with extra-amniotic 15-me-F_2 alpha as compared to 28.0 per cent with intra-amniotic 15-me-F_2 alpha and 23.9 per cent with intra-amniotic F_2 alpha. The higher incidence of complete abortions in the intra-amniotic group was probably due to the fact that placenta is completely formed in later weeks of gestation and more women in this group were registered at later weeks (after 14 weeks of gestation).

Induction-Abortion Interval: The mean induction-abortion interval (depicted in Table IV-A) was 14.5 hours with extra-amniotic 15-me-F_2 alpha, 20.4 hours with extra-amniotic 15-me-F_2 alpha and 19.8 hours with intra-amniotic F_2 alpha. Although the mean induction-abortion interval was shortest with extra-amniotic

TABLE IV(A)
Induction—abortion Interval

I.A.I.	1. Intra-amniotic				2. Extra-amniotic
	(A) PGF_2 alpha		(B) 15-me-F_2 alpha		15-me-F_2 alpha
Mean	19.8 Hrs.		20.4 Hrs.		14.5 Hrs.
S.D.	10.3276		8.7990		7.6180
	1(A)	Vs.	1(B)	p 0.05	
	1	Vs.	2	p 0.01	

15-me-F_2 alpha, there was no significant difference between the number of abortions occurring within 24 hours of instillation in the three groups (Table IV-B).

Effect of Parity on Outcome of the Trials: Table V reveals that parity had no significant co-relation with the success rate or the type of abortion (complete or incomplete). Induction-abortion interval was shorter in multipara as compared to nullipara with all dosage schedules. The difference, however, was significant only with PGF_2 alpha.

Effect of Period of Gestation on Outcome of the Trials: Present study revealed that no significant co-relation existed between the period of gestation and success rate, complete or incomplete abortion, induction-abortion interval (Table VI).

Supplementary Therapy for Incomplete Abortions: In case of incomplete abortions, the process could be completed easily by intravenous oxytocin or evacuation. Evacuation was carried out easily by a finger or an instrument (Ovum-forceps or curette) inserted into the uterine cavity. None of the cases required general anaesthesia (Table VII).

TABLE IV(B)

I.A.I.	1. Intra-amniotic (A) PGF_2 alpha No.	%	(B) 15-me-F_2 alpha No.	%	2. Extra-amniotic 15-me-F_2 alpha No.	%
24 Hrs.	33	71.7	36	72.0	77	89.5
24 Hrs.	13	28.3	14	28.0	9	10.5
Within Trial	1(A),	1(B),	2	—p	0.01	
Between	1(A)	& 1(8)		—p	0.05	
	1	& 2		—p	0.05	

TABLE V
Parity in Relation to Outcome of Trials

	Intra-amniotic PGF_2 alpha Primi	Multi	15-me-F_2 alpha Primi	Multi	Extra-amniotic 15-me-F_2 alpha Primi	Multi
Success	92.6% (25/27)*	95.5% (21/22)	100% (34/34)	94.6% (16/17)	80.0% (16/20)	87.3% (70/80)
Complete abortions	84.0% (21/25)	66.6% (14/21)	79.4% (27/34)	56.2% (9/16)	14.3% (2/16)	21.4% (15/70)
Induction abortion interval (Hrs.)	23.5	15.8	22.3	18.1	17.4	13.8

* Figures in parentheses indicate the number of cases.

TABLE VI

Period of Gestation in Relation to Outcome of Trial

	Intra-amniotic				Extra-amniotic	
	PGF_2 alpha		15-me-F_2 alpha		15-me-F_2 alpha	
	14-16 Wks	17-20 Wks.	14-16 Wks.	17-20 Wks.	10-13 Wks.	14-16 Wks.
Success	95% (19/20)*	93.1% (27/29)	93.3% (14/15)	100% (36/36)	86.1% (37/43)	85.7% (48/56)
Complete abortions	73.7% (14/19)	77.8% (21/27)	35.7% (5/14)	86.6% (31/36)	16.2% (6/37)	20.8% (10/48)
Induction abortion interval (Hrs.)	17.2	21.7	18.1	21.3	16.5	13.0

* Figures in parentheses indicate the number of cases.

TABLE VII

Supplementary Therapy for Incomplete Abortions

Therapy	Intra-amniotic		Extra-amniotic
	PGF_2 alpha	15-me-alpha	15-me-F_2 alpha
I.V. Oxytocin	4	5	2
Evacuation			
—Digital	2	4	22
—Surgical	2	3	30
Oxytocin + Evacuation	3	2	15
	11	14	69

Management of Cases Who Failed to Abort: Eighteen cases failed to abort. Failure of abortion in these cases was due to unresponsiveness of the uterus to the drug. Twelve patients aborted after the cut off time with or without interference. Of the 6 patients who left the hospital without termination, 4 patients got the pregnancy terminated at private clinic by suction evacuation, 1 had a spontaneous abortion one month after discharge. One patient continued the pregnancy to term, she had failed to abort after extra-amniotic instillation of 15-me-F_2 alpha at 12 weeks gestation. She refused interference after the cut off time and delivered a 2.2 kgm. female baby at 38 weeks of gestation. Baby had no obvious congenital abnormalities (Table VIII).

Side Effects

Table IX shows that no side effects occurred in 22.4 per cent cases with PGF_2 alpha, 29.4 per cent with intra-amniotic 15-me-F_2 alpha and 35 per cent with extra-amniotic 15-me-F_2 alpha.

Most common side effects were vomiting and diarrhoea. Their incidence did not differ significantly in the three groups. Vomiting and diarrhoea were easily controllable and did not cause negative fluid or electrolyte balance in any case.

Two patients with intra-amniotic PGF_2

TABLE VIII
Management of Cases who Failed to Abort

	Intra-amniotic		Extra-amniotic
	PGF_2 alpha	15-me-F_2 alpha	15-me-F_2 alpha
(1) Aborted after cut-off time without interference	—	—	4
(2) I.V. Oxytocin	—	1	1
(3) Hypertonic saline	1	—	—
(4) Repeat Prostaglandin	—	—	1
(5) Surgical Evacuation	—	—	3
(6) Hysterotomy	—	—	1
(7) Patient left Hospital after unsuccessful procedure No. 2	2	—	2
(8) Patient left Hospital after cut off time without any supplementary procedure	—	—	2
Total	3	1	14

TABLE IX
Side Effects

Side-effect	Intra-amniotic				Extra-amniotic	
	PGF_2 alpha		15-me-F_2 alpha		15-me-F_2 alpha	
	No.	%	No.	%	No	%
No	11	22.4	15	29.4	35	35.0
Yes	38	77.6	36	70.6	65	65.0
1. Vomiting	28	57.1	26	51.0	56	56.0
ME/T	2.5		2.7		2.7	
2. Diarrhoea	19	38.8	19	37.3	41	41.0
ME/T	2.7		3.5		3.3	
3. Dyspnoea	—	—	—	—	1	1.0
4. Flush	2	4.1	—	—	8	8.0
5. Fever:						
Upto 38°C	2	4.1	2	3.9	3	3.0
38°C	2	4.1	2	3.9	1	1.0
6. Blood Loss						
0 — 100 ml	44	95.7	48	96.0	85	98.8
100 — 300 ml	2	4.3	2	4.0	1	1.2

alpha and 8 with extra-amniotic 15-me-F_2 alpha complained of flushing of face and feeling of uneasiness immediately after instillation of the drug which lasted only for few minutes and did not require any therapy. One patient in extra-amniotic group had mild broncho-spasm immediately after instillation of the drug. She was relieved with injection aminophylline and oxygen inhalation with 15-20 minutes.

Other side effects noted occas'onally were epigastric pain (8), headache and giddiness (4), excessive salivation (1), Macular rash (1). No seizures were noted.

Pulse and blood presure showed no

change in majority of the patients. Three cases had bradycardia immediately following instillation of extra-amniotic 15-me-F_2 alpha. Bradycardia was probably a vasovagal effect due to uterine hypertonous and returned to normal within 5-10 minutes without any therapy.

Seven patients showed temperature rise upto 38°C which returned to normal on its own without antibiotic therapy. Five patients had temperature rise more than 38°C. One was attributed to malaria, other 4 were due to endometritis, following postabortional curettage (2 cases), early rupture of membranes (1 case) and 1 patient had, had interference done earlier by a 'dai'. All these patients responded to antibiotics within 48 hours.

Blood loss was less than 100 ml in 178 of 182 cases who aborted successfully. Of the 5 cases with blood loss more than 100 ml, 1 patient had bleeding one hour after instillation of intra-amniotic PGF_2 alpha. This patient had successful amniocentesis on third attempt which might have led to placental separation. Two patients were grand multiparous who lost blood at the time of abortion. None of the patients lost more than 300 ml or required blood transfusion.

Major complications as cervical trauma was seen in only 1 case. It was a small cervical laceration (not requiring suturing) seen in a 20 year old nulliparous patient who had intra-amniotic instillation of 2.5 mgm. of 15-me-F_2 alpha and aborted 26 hours after instillation. Ballooning of the cervix at the time of abortion was seen in 3 patients who had intra-amniotic PGF_2 alpha. Cervix was normal at follow up in these cases.

Follow up

Table X shows the response to follow up. 90 per cent of patients reported for follow-up 4-6 weeks after abortion.

90 per cent of those followed up had no complaints. 9 (5.0 per cent) complained of vaginal discharge and lower abdominal pain. Pelvic examination was normal in these cases. One patient had high grade fever after discharge from the hospital, following extra-amniotic administration of 15-me-F_2 alpha. She had grown Staph. aureus in the cervical culture taken after abortion.

Vaginal bleeding following abortion lasted for less than 5 days in 78.9 per cent patients. 15.6 per cent had slight bleeding for 15 days and 5.5 per cent continued to have intermittent spotting for more than 15 days. Two patients from the extra-amniotic group who had intermittent bleeding for almost one month were re-admitted for dilatation and curettage. There were no retained products of conception. Histopathology of endometrial curettings revealed mixed secretory and prolifertive pattern.

Re-establishment of menstrual cycle occurred within 4 weeks of 84.4 per cent cases and within 5-8 weeks in 11.6 per cent. There was no change in duration and flow of menstrual period in 77.3 per cent, 14.4 per cent had slightly heavier periods and 8.3 per cent had scanty flow (Table X).

Bacteriological Study: Pre-instillation cultures showed the presence of organisms in 18 per cent of patients with extra-amniotic and 20 per cent of patients with intra-amniotic instillation. Organisms isolated included Staph. aureus (12), Staph. albus (8), Strep. aureus (1), Diptheroids (3), Candida (3), E. Coli (4) and Micrococci (7).

As depicted in Table XI, cultures taken during the course of abortion showed that

TABLE X
Follow Up

	Intra-amniotic		Extra-amniotic	Total No.	%
	PGF_2 alpha	15-me-F_2 alpha	15-me-F_2 alpha		
No. of cases	49	51	100	200	
Cases reported for follow-up	42	45	93	180	90.0
1. **Vaginal Bleeding following abortion**					
5 days	37	34	76	142	78.9
6-15 days	7	9	12	28	15.6
15 days	3	2	5	10	5.5
2. **Complaints**					
—None	38	40	84	162	90.0
—Vaginal discharge	2	3	4	9	5.0
—Fever	—	—	4	1	0.5
Lower abdominal pain	2	2	4	8	4.5
3. **Pelvic Examination**					
—Normal fiindings	42	45	93	180	100.0
—Abnormal	—	—	—	—	—
4. **Re-admission to Hospital** Reason:					
—Bleeding	—	—	2	2	1.1
—Retained products	—	—	—	—	—
—Sepsis	—	—	1	1	0.5
5. **Menstrual Pattern**					
(a) Cycle: Occurred					
—within 4 Weeks	34	40	78	152	84.4
—within 5-8 Weeks	6	3	12	21	11.6
—more than 8 Weeks after abortion	2	2	3	7	4.0
(b) **Flow and Duration**					
—No change	34	35	70	139	77.2
—Increased	5	6	15	26	14.4
—Decreased	3	4	8	15	8.3

TABLE XI

Route of Administration	No. of Cases	No Pathogen throughout		Pathogens grown during abortion		Pathogens grown 24 hours after abortion	
		No.	%	No.	%	No.	%
Intra-amniotic	80*	71	88.7	7	8.7	2	2.7
Extra-amniotic	82*	70	85.4	7	8.9	5	6.4

* Rest of the cases not included as pathogens were grown in pre-instillation cervical culture.

85.4 per cent patients in extra-amniotic group and 88.7 per cent patients in intra-amniotic group remained sterile throughout. 8.9 per cent of extra-amniotic and 8.7 per cent of intra-amniotic cases harboured the organisms during the course of abortion. 6.4 per cent of extra-amniotic and 2.7 per cent of intra-amniotic cases harboured pathogens 24 hours after abortion. The difference between the intra-amniotic and extra-amniotic routes was not significant.

The most common organisms isolated in both the groups was Esch. coli. Other organisms isolated were Pseudo. pyocyaneus, Kleibsella and Staph. aureus. No anaerobic organisms were isolated (Table XI).

Conclusion

1. A single intra-uterine instillation of prostaglandins F_2 alpha and its 15-methyl analogue either via trans-abdominal intra-amniotic or trans-cervical extra-amniotic route for termination of pregnancy between 10 to 20 weeks of gestation is an effective and safe procedure.

2. The successful outcome of abortion and the incidence of complete abortions were higher with intra-amniotic as compared to extra-amniotic route. The trans-cervical extra-amniotic route has the added advantage of being useful for the cases between 10 to 14 weeks of gestation where trans-abdominal intra-amniotic approach is not technically feasible. The incidence of major side effects as vomiting and diarrhoea were comparable and clinically acceptable.

3. 15-me-F_2 alpha administered via intra-amniotic route does not appear to have a distinct advantage over naturally occurring PGF_2 alpha administered by same route for induction of midtrimester abortion. The success rate, induction-abortion interval incidence of complete abortion and the major side effects are almoost similar with both drugs.

4. The risk of aquisition of pathogens during abortion is minimal after intra-amniotic as well as extra-amniotic instillation. Presence of pathogens like Staph. aureus, Staph. albus and Strep. aureus does not increase the risk of complications if the termination of pregnancy is carried out in their presence.

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