EVALUATION OF A LOWER DOSE SCHEDULE OF INTRAMUSCULAR 15(S)-15-METHYL PROSTAGLANDIN 'F'2 ALPHA FOR INDUCTION OF EARLY MIDTRIMESTER ABORTION

by

R. RAJAN,* M.B.,B.S., M.D., D.G.O.

M. SUBHADRA NAIR,** M.B.,B.S., M.S., D.G.O.

A. K. SARADA,*** M.B.,B.S., M.D., D.G.O.

L. USHA DEVI,† M.B.,B.S.

and

ROSSAMA JOHN,†† M.B.,B.S., D.G.O.

Termination of pregnancies after the first trimester is more satisfactorily accomplished with prostaglandins, especially their 15 methyl analogues, administered by a variety of routes, than by employing the presently available pharmacologic and surgical methods. While intraamniotic administration of prostaglandin $F_{2\alpha}$ is the only approved method for inducing abortion, different prostaglandins by several routes and in a variety of doses have been investigated. Generally, the effective doses of prostaglandins by systemic routes must be continuously or frequently administered and are associated with higher rates of side effects when compared to effective intrauterine routes.

Toppozada *et al* (1972), reporting on the uterine effects of 15 (S)-15-methyl-prostaglandin $F_{2\alpha}$, demonstrated that intramuscular injection of this compound in midtrimester subjects produced a sustained increase in uterine activity for 5 to 7 hours without any local reaction. Clinical effectiveness of intramuscular dose schedule of 15-methyl analogues was initially determined by Karim (1972) in his preliminary studies with a small series of patients. Although intramuscular administration is not as convenient as the oral or vaginal techniques, it has potential advantages over the other systemic and intrauterine methods. Especially, this route of administration is applicable to gestational ages and clinical conditions in which amniocentesis is impractical.

Intramuscular administration of 15 (S) 15-methyl prostaglandin $F_{2\alpha}$ has been tried in several effective dose schedules (Table I). However, many of these investigators employ a large dose of the drug with the frequent side effects of nausea, vomiting, and diarrhoea which may limit the usefulness of these schedules. The purpose of our study was to investigate the effectiveness of intramuscular administration of 15 (S) 15-methyl prostaglandin $F_{2\alpha}$ in a lower dose schedule to reduce the incidence of side effects. The main objective of our series was to establish the practicability of this method

*Assistant Professor, Obstetrics & Gynaecology.

**Director and Professor, Obstetrics & Gynaecology.

***Profelsor, Obstetrics & Gynaecology.

†Senior Researcd Fellow, I.C.M.R.

††Post gradudte Student Medical College Hospital, Gandhinagar, Kottayam 686 008, Kerala.

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for aborting patients between 13 to 16 menstrual weeks' gestation.

Materials and Methods

Abortion was induced in 50 physically healthy gravidas, 16 to 45 years of age and 13 to 20 menstrual weeks' gestation, with serial intramuscular doses of 15 (S) 15-Me-PG F_2 alpha, at the Contraceptive Testing Unit of I.C.M.R., Medical College Hospital, Kottayam. One milliliter of the undiluted solution contained 250 μ gm of 15 (S) 15-Me-PG F_2 alpha as tromethamine salt. All subjects were treated with the same dose schedule, and the drug was injected deeply into the gluteus muscle. Initially 125 μ gm 0.5 ml) of PG was injected for 2 doses, every 3 hours. Thereafter the dose was increased to 250 μ gm (1 ml) administered every 3 hours. The drug administration was terminated with the expulsion of the foetus or when the trial was declared a failure after 30 hours. Thirty minutes before the first dose of PG, the patients were administered 5 mgms of Siquil intramuscularly, and 2 tablets of lomotil orally. Lomotil therapy was repeated for the 2nd and 3rd dose schedules of the PG.

The patients were monitored for vital signs during the period of drug administration and until abortion was complete. Pulse rate, blood pressure, oral temperature and any side effects were recorded regularly. The incidence and frequency of the gastrointestinal complications were carefully noted. The patients were also observed for the uterine contractions, leaking membranes and any vaginal bleeding. A vaginal examination was performed after the fourth dose, to determine the cervical dilatation. If the vomiting and diarrhoea were severe, intravenous infusions were started.

TABLE I

Serial Intramuscular Administration of 15-me-PG F_2 α

Author & Year	Dose Schedule	Abortion rate (%)	Vomiting (%)	Diarhoea (%)
Leibman et al. (1974)	250μ every 8 hours	56.00	—	—
Robins and Mann (1975)	250μ every 2 hours	74.00	82.00	66.00
Laursen and Wilson (1975)	250μ every 2 hrs. for 2 doses			
	500μ every 2 hrs. for 24 hrs.	86.00		
	750μ every 2 hrs. until abortion occurred	100.00	91.00	71.00
Ylikorkala and Jarvinen (1975)	300μ every 3 hrs.	80.00	80.00	30.00
Gruber et al. (1976)	250μ every 2 hrs. for 24 hrs.	74.00		
	500μ every 2 hrs. for 48 hrs.	95.00	80.00	30.00
Hingorani et al. (1977)	400μ every 3 hrs. for 30 hrs.	76.60	70.00	76.60
Hingorani et al. (1977)	300μ every 3 hrs. for 30 hrs.	88.50	45.70	74.30
Present series	125μ every 3 hrs. for 2 doses 250μ every 3 hrs. for 30 hrs.	78.00	20.00	56.00

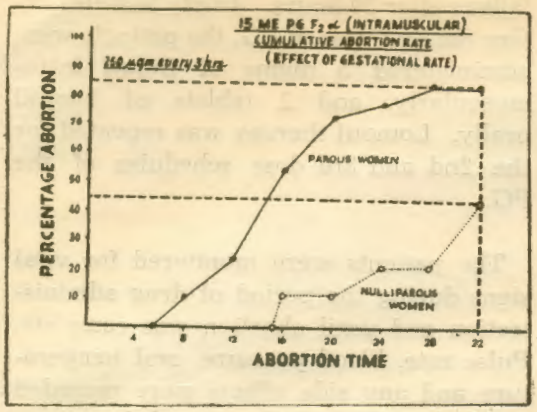

Fig. 1

Induction-to-abortion time was the period from the initial PG injection to abortion of the foetus. If the placenta was not expelled within 1 hour, the same was removed with ovum forceps. Within 30 hours if the patient did not show imminent signs of abortion the trial was declared as failure. Depending on the nature of cervix, the failed cases were managed either by surgical evacuation or intraamniotic urea instillation.

Results

Within 30 hours 78 per cent of the 50 midtrimester subjects aborted after they received 250 μ gm of 15 (S)-15-methyl-prostaglandin F_2 alpha intramuscularly every 3 hours. The induction-to-abortion time of the successful cases ranged from 5 hours 35 minutes to 30 hours, with a mean duration of 16 hours and 10 minutes. The number of injections required for effecting abortion ranged from 2 to 10 with a mean of 5.5, and the quantity of drug ranged from 1 ml to 9 ml with a mean of 4.5 ml.

The blood loss was within normal limits in these patients and there was no potentially dangerous complications associated with this method of abortion. The repeated intramuscular injections were not associated with any local irritation or discomfort. The patients in this study experienced remarkably little discomfort in the presence of quite strong uterine contractions, and analgesics were not required routinely except in 1 nulliparous woman.

The only complication witnessed was the typical gastro-intestinal disturbance in the form of nausea, vomiting and diarrhoea. However, the incidences of these complications were comparatively less, with 20 per cent developing vomiting and 56 per cent developing diarrhoea. Among them only 12 per cent had 3 or more episodes of vomiting, and 22 per cent 3 or more episodes of diarrhoea.

Abortion was incomplete in 38.40 per cent of the successful cases. Of the 11 failures, the PG administration had made the cervix effaced and favourable in 5 subjects, enabling easy surgical evacuation of the uterus. The remaining 6 patients required intraamniotic instillation of urea for completion of abortion.

Effect of Gestational Age (Table II)

The abortion rate was almost identical in subjects between 13 to 16 weeks' gestation and those above 16 weeks' gestation. However, the mean abortion time, the number of injections and the quantity of drug required were less in the former group. Incidence of incomplete abortion was more when the duration of pregnancy was more than 16 weeks.

Effect of parity

The cumulative abortion rate of parous and nulliparous subjects is given in Fig.1. There were 41 parous and nulliparous women in this group. The low dose schedule appeared to be more practicable for parous women, with an abortion rate

TABLE II
Effect of Gestational Age

Particulars	13 to 16 weeks	after 16 weeks
Total number of patients	30	20
Abortion rate	74.50%	80.00%
Induction-to-abortion time (mean)	14 hrs 45 mts	17 hrs 30 mts
Quantity of drug used (average)	4 ml (1000 μ gm)	5 ml (1250 μ gm)
Number of injections (average)	5	6
Incomplete abortion	35.00	50.00
Vomiting	14.00	25.00
Diarrhoea	46.00	65.00

of 85.40 per cent and a mean induction-to-abortion time of 15 hours and 45 minutes. For nulliparous women, the failure rate was as high as 55 per cent, and the induction abortion time was, on an average, more than 24 hours.

Comments

The development of prostaglandin analogues administered by a variety of routes, has initiated clinical speculation that intrauterine application of chemicals may be potentially eliminated in the induction of midtrimester abortion. Intramuscular administration of 15 (S) 15-methyl-prostaglandin F_2 alpha appears to be an effective and practicable method for aborting midtrimester subjects, and it seems to have several advantages over the intra-amniotic route. Essentially, intramuscular administration is a less cumbersome and simpler procedure which saves the patient from the inherent complications of amniocentesis. Probably this method is more applicable for early midtrimester pregnancies and patients with ruptured membranes where amniocentesis is impractical. The occasional dangerous complications such as rupture uterus reported for intraaminiotic administration of PG (Rajan, 1978) are not seen with intramuscular method. By contrast to intraamniotic route, the patients receiving intramuscular PG experience remarkably little discomfort in the presence of quite strong uterine contraction and the course of abortion is very smooth. Serial intramuscular injections do not produce any pain or erythema at the injection sites.

The protocol of the present study was designed to gain experience with serial intramuscular administration of 15-me-Pg F_2 alpha in a lower dose schedule. Abortion was effectively induced in a dose schedule of 250 μ gm every 3 hours for 30 hours. Seventy eight per cent of the 50 midtrimester subjects aborted within 30 hours, and another 10 per cent had easy vaginal evacuation following the intramuscular administration. The mean induction-to-abortion time was 16 hours and 10 minutes, and the average quantity of the drug required (4.5 ml) and average number of injection given (5.5) were comparatively less. No patients developed any serious complications, and the blood loss was within normal limits in all of them.

One disadvantage of the intramuscular use of the 15 methyl analogues is the almost universal gastrointestinal toxicity. With the effective dose schedule, which involve larger quantity of the drug, the incidence of vomiting and diarrhoea appears to be very frequent (Laursen and Wilson, 1975 and Gruber *et al* 1976). Hingorani *et al* (1977), employing 300 to

400 μ of PG at less frequent intervals of 3 hours, could not reduce the incidence of these complications. However, our schedule of 250 μ every 3 hours for 30 hours appears to reduce the incidence of these side effects considerably. Only 20 per cent of the patients had vomiting, with 12 per cent having 3 or more episodes and 56 per cent had diarrhoea with only 22 per cent having 3 or more episodes. When the results of the other authors are compared, this remarkable reduction in gastrointestinal toxicity appears to be dose related.

However, the reduced dose schedule has not affected the efficacy of the procedure. Of the 41 parous women who were induced, 85.40 per cent aborted within 30 hours, with a mean induction-to-abortion time of 15 hours and 45 minutes. But nulliparous women did not respond satisfactorily to this dose schedule, and they recorded a high failure rate of 55 per cent.

While gestational age did not appear to have any influence on the abortion rate, early midtrimester pregnancies responded with a shorter induction-to-abortion time (14 hours and 45 minutes), and smaller quantity of PG (4 ml), than the pregnancies above 16 weeks' duration. This is an added advantage, and thus intramuscular administration of 15-me-Pg F_2 alpha makes abortion extremely easy at the 13 to 16 weeks' period. Since the risk of uterine rupture is not associated with this method of administration, multiparous women can be confidently induced, and as mentioned earlier they respond more promptly and quickly than nulliparous women.

Conclusion

Serial intramuscular administration of 15 (S) 15-methyl-prostaglandin F_2 alpha is an effective and safe method of midtrimester abortion. This is particularly applicable for pregnancies between 13 and 16 weeks, where amniocentesis is impractical. A low dose schedule, employing 250 μ gm of PG every 3 hours for 30 hours, has considerably reduced the incidence of gastrointestinal side effects and appears to be ideally suited for multiparous women who have responded promptly without any serious complications. The response of the nulliparous women was poor and they took a longer time to abort. From this evaluation it appears that a smaller dose schedule should be tried initially in all subjects, and if favourable response is not obtained within a reasonable period of 24 to 30 hours, then the dose may be enhanced. This study also signifies the role of intramuscular method in multiparous subjects who stand a greater risk with the other method of termination.

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