CLINICAL, HORMONAL AND METABOLIC STUDIES IN PATIENTS UNDERGOING SECOND TRIMESTER ABORTION WITH PROSTAGLANDIN F2 ALPHA, 15(S)-15-METHYL-PGF2 ALPHA AND HYPERTONIC SALINE

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Introduction

Amniocentesis and the instillation of various abortifacients has become increasingly popular as a simple and acceptable method for mid-trimester abortions. Experience gained from large abortion series and many clinical trials has shown that, if correctly used in properly selected cases, hypertonic saline and prostaglandins (PG) are useful and effective drugs to terminate late first trimester and second trimester pregnancies (Kerenyi, 1971; Bygdeman et al, 1970; Hingorani and Ganesh, 1972).

This study has been conducted to evaluate the relative efficacy, safety and limitations of prostaglandins, PGF2 alpha and 15(S) 15-methyl-PGF2 alpha, and hypertonic saline as abortifacients in pregnancies of 10-20 weeks gestation. An attempt has also been made to study the changes in the levels of hormones during the treatment period. The metabolism of intra-amniotically administered prostaglandin has also been investigated.

Material and Methods

Two hundred and forty women, seeking medical termination of pregnancy at the All India Institute of Medical Sciences Hospital, were selected for this study. The distribution of these patients in the different schedules was as follows:

I. Extra-amniotic
(i) PGF2 alpha—750 µg—2 hourly
100 cases
(ii) 15-methyl—750 µg
- PGF2 alpha
30 cases

II. Intra-amniotic
(i) PGF2 alpha—25 mg (2 doses at 6 hour interval)
70 cases
(ii) 20% saline—200 ml
40 cases

Extra-amniotic Administration of PGF2 alpha and 15-methyl-PGF2 alpha

This route was used in cases of pregnancy of 10-20 weeks' duration. In each
case a Foley’s catheter (No. 8 for 15-methyl-PGF$_2$ alpha cases and No. 14 for PGF$_2$ alpha cases) was introduced through the cervix with due aseptic precautions. The bulb was placed above the internal os, in between the uterine walls and the foetal membranes. The bulb was inflated with 30 ml of normal saline, and 750 μg of the drug in a 3 ml solution was injected every 2 hours for 36 hours. With 15-methyl-PGF$_2$ alpha, 3 ml of solution containing 750 μg of the drug was injected slowly, and the catheter then withdrawn.

**Intra-amniotic Administration—PGF$_2$ alpha and hypertonic saline**

This route was used in subjects with 14-16 weeks pregnancy. With due aseptic precautions, amniotomy was done per abdomen using an 18 gauge needle with stylet, in the mid-line, in the supra-pubic region. The stylet was withdrawn, and after ensuring a free flow of clear amniotic fluid, a polythene catheter was threaded through the needle into the amniotic cavity and the needle was then removed. PGF$_2$ alpha was injected through this catheter. The first dose of 25 mg in a 5 ml solution was injected slowly to avoid untoward reactions like bronchospasm or tetanic uterine contractions. The second dose of 25 mg was given 6 hours later. In the case of saline, 50 ml of liquor was withdrawn, and then 200 ml of 20% saline was injected through the needle over 20 minutes. No indwelling catheter was left.

In each of the four groups, the pulse, blood pressure, temperature and respirations of the patients were regularly recorded. Side effects were noted and treatment was given if needed. Sedation was prescribed when uterine contractions became very painful. Periodic blood samples, including pre-induction and post-abortion ones, were drawn from a few patients in each group, except from those who received PGF$_2$ alpha extra-amniotically. The serum was separated and frozen in aliquot for hormone estimations.

**Clinical Studies**

The results of the clinical trials were analyzed in the following terms

1. **Success rate:**—successful trial in the extra-amniotic and intra-amniotic groups meant abortion (complete or incomplete) within 36 hours or 48 hours of induction, respectively.

2. **Induction-abortion interval:**—This was calculated as the interval between first instillation of abortifacient and occurrence of complete or incomplete abortion.

3. **Side-effects**

4. **Completeness of abortion**

**Success Rate**

The success rate for the 4 schedules used is shown in Table I.

<table>
<thead>
<tr>
<th>Induction Method</th>
<th>No. of cases</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-A PGF$_2$ alpha</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>E-A 15-methyl PGF$_2$ alpha</td>
<td>30</td>
<td>93</td>
</tr>
<tr>
<td>I-A PGF$_2$ alpha</td>
<td>70</td>
<td>88</td>
</tr>
<tr>
<td>I-A 20% saline</td>
<td>40</td>
<td>95</td>
</tr>
</tbody>
</table>

The cumulative abortion rate with the above schedules is illustrated in Figs. 1 & 2.

The methods used for treatment for failures in each group, are shown in Table II.
Cumulative Abortion Rate with Extra-Amniotic PG\textsubscript{2}K and 15-Methyl-PGF\textsubscript{2}K

Cumulative Abortion Rate with Intra-Amniotic PG\textsubscript{2}K and 20\% Saline

**Fig. 1**
Disappearance of 3 prostaglandin F\textsubscript{2} alpha and its metabolites from the amniotic fluid.

**Fig. 2**

Induction—Abortion Interval

The induction—abortion interval in the 4 groups is shown in Table III.

Thus, in each group, the induction—abortion interval was shorter in case of multigravidas except with hypertonic saline, where primigravidas responded faster to the drug. This seems to be a useful advantage of 20\% saline as a mid trimester abortifacent, specially as 43\%
TABLE II

Additional Method for Failed Trial

<table>
<thead>
<tr>
<th>Additional Method used</th>
<th>Induction</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-A</td>
<td>I-A</td>
</tr>
<tr>
<td>Syntocinon drip</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Syntocinon + evacuation</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Vacuum aspiration</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hysterotomy + ligation</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>More drug</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Delayed abortion with no additiopal treatment</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Total cases: 17

TABLE III

Induction—Abortion Interval in Relation to Induction Method

<table>
<thead>
<tr>
<th>Induction Method</th>
<th>Primis</th>
<th>Multis</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-A PGF$_2$ alpha</td>
<td>25</td>
<td>00</td>
<td>15</td>
</tr>
<tr>
<td>E-A 15-Methyl PGF$_2$ a.</td>
<td>20</td>
<td>00</td>
<td>14</td>
</tr>
<tr>
<td>I-A PGF$_2$ alpha</td>
<td>25</td>
<td>00</td>
<td>21</td>
</tr>
<tr>
<td>I-A 20% saline</td>
<td>22</td>
<td>00</td>
<td>32</td>
</tr>
</tbody>
</table>

of women in this latter group were primigravidas.

Side-effects

The side-effects noted were mainly gastro-intestinal and were marked more amongst patients who received prostaglandin than those who received saline. In the former group, the incidence of side-effects seemed to be dose-related being more marked amongst patients who received the methyl analogue (which is known to be more potent) and PGF$_2$ alpha intra-amniotically. One serious complication alone occurred in one patient in the saline-group in a multigravida 35 year old patient, who collapsed 2 hours before abortion, but was resuscitated soon with intravenous fluids and oxygen inhalation. E.C.G. and skiagram of chest blood coagulation studies, serum electrolytes and blood urea were all within normal limits. The various side-effects observed are shown in the Table IV.

Completeness of Abortion

Nature of abortion in the four schedules is shown in Table V and Fig. 3. Abortion tended to be complete in more cases in the intra-amniotically treated cases i.e. with mid-trimester rather than first trimester pregnancies. There were significantly more complete abortions with saline treated cases.

In each of the 4 schedules, no significant change in the vital signs namely
TABLE IV
Side Effects in Relation to Induction Method

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Extra-amniotic</th>
<th>Intra-amniotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PGF(_2) alpha</td>
<td>15-methyl PGF(_2) alpha</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flush</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

In the extra-amniotic group, the methyl analogue seems to be a better abortifacient than PGF\(_2\) alpha. Besides, the single dose administration of the methyl compound is distinctly advantageous, as compared with the two hourly schedule for PGF\(_2\) alpha, necessitating an indwelling catheter which is both cumbersome and attended by a greater risk of infection (Gupta et al, 1974).

In the intra-amniotic group, hypertonic saline seems to have some advantages over PGF\(_2\) alpha, except for its slightly longer induction-abortion interval. There was faster response in primigravidas as compared to multigravidas in saline inductions. Prostaglandin is costlier and not...

TABLE V
Complete and Incomplete Abortions in Relation to Induction Method

<table>
<thead>
<tr>
<th>Induction Method</th>
<th>Complete abortion</th>
<th>Incomplete abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>E-A PGF(_2) alpha</td>
<td>9</td>
<td>10.8</td>
</tr>
<tr>
<td>E-A 15-methyl PGF(_2) alpha</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>I-A PGF(_2) alpha</td>
<td>30</td>
<td>49.2</td>
</tr>
<tr>
<td>I-A 20% Saline</td>
<td>31</td>
<td>81.6</td>
</tr>
</tbody>
</table>
as readily available as saline. Hyper-tonic saline may, therefore, be confidently used as a reasonably safe mid-trimester abortifacient and as a good substitute for the more scarcely available prostaglandin in large abortion series. However, the unexplained vasomotor collapse which occurred in one saline treated case, indicates that the danger of hypernatraemia pointed out by Cameron and Dayan (1966) and of amniotic fluid embolism documented by Pathak (1968) must not be taken lightly.

Hormonal Studies

Hormone Assay Method

Serum estradiol-17β, progesterone and human placental lactogen (HPL) levels were estimated by specific radioimmunoassays. Antiserum, raised against estradiol-6-(O-carboxy-methyl)-oxime BSA in rabbits, and 2,4,6,7-3H-estradiol-17β as tracer were used to develop radioimmunoassay for estradiol. The radioimmunoassay for progesterone was developed using antiserum raised against progesterone-11 alpha-hemisuccinate-BSA in rabbits at 1/15000 final dilution and 1,2,6,7-3H-progesterone as tracer. Using 125I-HPL as tracer and HPL-NIH as reference preparation, a double antibody radioimmunoassay was developed for the estimation of serum HPL.

Effect of PGF2 alpha on Hormone Levels

Intra-amniotic administration of PGF2 alpha for the termination of second trimester pregnancy caused a significant decrease in the serum estradiol, progesterone and HPL levels. The decline in estradiol (Fig. 4) and progesterone (Fig. 5) values started 4-6 hours after the induction phenomena and by the time the fetus was expelled their values had decreased by 40-60 per cent of pre-administration values. Interestingly in case (DP) in which the pregnancy was terminated after 21.30 hours, no change in the serum estradiol or progesterone levels was observed. In this patient serum estradiol and progesterone levels at the time of abortion was 0.6 ng and 28 ng/ml, respectively. The decrease in HPL levels also started 6-8 hours of PGF2 alpha administration and by the time of abortion, it had decreased by 60-70 per cent of preinstillation values (Fig. 6). However, in patient (EP) though the pregnancy was terminated successfully, yet no significant change in serum HPL levels was observed.
Effect of 15 (S)-15-methyl-PGF$_2$ alpha on Hormone Levels

Extra-amniotic administration of 750 µg of 15-methyl-PGF$_2$ alpha caused significant fall in serum estradiol (Fig. 7), progesterone (Fig. 8) and HPL (Fig. 9) levels. In most of the cases the decline in estradiol and HPL levels started immediately after the instillation of the drug and by the time the fetus was expelled their levels had decreased by 40-60 per cent of the preinstillation values. The decline in the levels of these hormones was more rapid in patients with shorter induction-abortion time than in cases with longer induction-abortion time. The decrease in progesterone was observed about six hours after the 15-methyl-PGF$_2$ alpha administration and in the next 6-12 hours its values fell to 50 per
Effect of Hypertonic Saline on Hormone Levels

Intra-amniotic administration of 230 ml of 20 per cent saline caused a significant decrease in the serum estradiol levels in all the cases investigated (Fig. 10). The decrease in estradiol ranged from 60 to 70 per cent of the preadministration values. Interestingly in patient (FMP) 15-methyl-PGF2 alpha failed to terminate pregnancy. In this patient, the levels of all these three hormones, estradiol, progesterone and HPL, remained unaffected.

Metabolic Studies

To study the disappearance of PGF2 alpha from the amniotic fluid 30 to 40 \( \mu \)Ci of (9B-3H)-PGF2 alpha was injected into the amniotic fluid along with 25 mg of PGF2 alpha in 5 ml of normal saline through a polythene catheter, in six patients between 16-20 weeks' gestation.
HORMONAL AND METABOLIC STUDIES

EFFECT OF INTRA-AMNIOTIC HYPERTONIC SALINE ON SERUM ESTRADIOL IN WOMEN.

As shown in Fig. 13, PGF₂ alpha and its metabolites had a very slow disappearance from the amniotic fluid. Near the termination of pregnancy 50 per cent or even more of radioactivity was still left in the amniotic fluid. In one case, with an induction abortion interval of 22 hours, only 10-15 per cent of radioactivity disappeared from the amniotic fluid in 18 hours. No correlation was observed between the amniotic fluid volume, the disappearance rate of PGF₂ alpha and its metabolites and the induction-abortion interval.

Amount of PGF₂ alpha left in the amniotic fluid at different time intervals was determined after necessary extraction and chromatographic separation. Amniotic fluid was acidified to 3N with hydrochloric acid and extracted thrice with diethyl ether. The pooled ether extract was washed and evaporated to dryness. The dried extract was subjected to silicic acid (Caldwell et al, 1972) or reversed phase partition chromatography using hydrophobic hyflo super cell columns and sol-
EFFECT OF INTRA-AMNIOTIC HYPERTONIC SALINE ON SERUM HPL IN WOMEN.

As shown in Fig. 14, PGF$_2$ alpha has a very slow rate of metabolism. In all the cases investigated, 36 to 60 per cent of PGF$_2$ alpha was still left in the amniotic fluid after 24 hours of its administration. No detectable amounts of PGF$_2$ alpha were found in the peripheral blood collected at different time intervals. However, within one hour of the administration of $^3$H-PGF$_2$ alpha, the radioactivity started excreting through urine. These findings along with slow disappearance of radioactivity from the amniotic fluid and the slow rate of metabolism of PGF$_2$ alpha support a direct action of PGF$_2$ alpha on the feto-placental unit of the myometrium.

Summary

240 cases of medical termination...
of pregnancy, between 10-20 weeks, abortions were induced with prostaglandins and hypertonic saline. One hundred patients received PGF₂ α by extra-amniotic route with dose of 750 µg every two hourly. Thirty patients received single dose of 750 µg of 15-methyl PGF₂ alpha extra-amniotically. Seventy patients received PGF₂ α by intra-amniotic route, in the dose schedule of 25 mg followed by 25 mg after 6 hours. In 40 cases, abortions were induced with 200 ml of 20% saline given intra-amniotically. Trial was considered successful if patients aborted incompletely or completely in 48 hours in intra-amniotic group and 36 hours in extra-amniotic group. Success rate was 83%, and 93% in the extra-amniotic group of PGF₂ α and 15-methyl-PGF₂ α, and 88% and 95% in the intra-amniotic group of PGF₂ α and hypertonic saline respectively. Induction Abortion Interval was 23 hr. 30 min.; 18 hrs., 25 hr. and 26 hr. 30 min. respectively in the four groups. Side effects in the form of fever, nausea and vomiting were observed in some cases in prostaglandins groups. Severe side effects, in the form of collapse, cyanosis, dyspnoea were observed in one patient in hypertonic saline group.

Intra-amniotic PGF₂ α and extra-amniotic 15-methyl-PGF₂ α decreased the serum progesterone, estradiol and HPL levels. However, intra-amniotically administered hypertonic saline had no definite effect on serum progesterone and HPL levels till labor, whereas a definite decrease in serum estradiol levels was assumed.

Studies on the Metabolism and PGF₂ α alpha, after intra-amniotic administration, showed that PGF₂ α together with its metabolites gradually decreased to 40-50% after 24 hours, but PGF₂ α alone decreased by 15-30% in 24 hours. When 3H-PGF₂ α was given intra-amniotically to saline group, the initial decrease in radioactivity was sharper, than in the cases where abortions were induced with PGF₂ α. No detectable amount of PGF₂ α was found in peripheral blood. However, radioactivity was detected in the urine within one hour of induction phenomenon.

References