ON THE ABORTIFACIENT MECHANISM OF 15(S)15-METHYL-PROSTAGLANDIN $F_{2\alpha}$ IN EARLY PREGNANCY

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SUMMARY

To induced abortion serial intramuscular injections of 15(S)15-Methyl-Prostaglandin $F_2\alpha$ were given to twelve volunteering women, in their eighth to eleventh week of gestation. The abortifacient effectiveness and changes in foeto-placental function during the treatment were evaluated. The uterine activity began from 15 to 50 minutes and vaginal bleeding started from 1.9 to 7.5 hours after the start of the procedure. All patients aborted within 24 hours. The oestradiol, progesterone, human chorionic somatomammotropin and beta subunit of human chorionic gonadotropin plasma values significantly dropped three hours after the first injection; the alpha-fetoprotein plasma levels significantly rose after six hours. These results suggest that 15(S)15-Methyl-Prostaglandin $F_2\alpha$ oxytocic effect plays an important role to induce first trimester abortion.

INTRODUCTION

Naturally occurring prostaglandins are safer and more effective in interrupting early pregnancy ([1, 2]) than other existing methods. The uterine response to a single administration of these compounds is comparatively short-lived due to rapid enzymatic inactivation. Analogues of the naturally occurring prostaglandins have been synthetized and examined to find a prostaglandin with a more prolonged activity. The 15(S)15-Methyl-Prostaglandin $F_2\alpha$ (15-ME-$PGF_2\alpha$) , whichis resistant to degradation by the enzyme 15-hydroxydehydrogenase ([3, 4]), has proved to be the most effective so far; this compound is also 20-100 times more potent than its parent compound prostaglandin $F_2\alpha$ ([5, 6]). Therefore 15-ME-$PGF_2\alpha$ has been successfully used for early pregnancy interruption ([7, 8, 9]) and several studies have been made on its abortifacient effectiveness ([10, 11]), but the mechanism of action is still unclear ([12]). Powell et al. ([13]) suggested that Prostaglandin $F_2\alpha$ has a physiologic role in human luteolysis and Csapo et al. ([14]) explained the abortifacient action of the same compound by a prostaglandin luteolytic effect. The present study was designed to clarify the abortifacient mechanism of 15-ME-$PGF_2\alpha$ in early gestation; to this purpose, the maternal levels of oestradiol, progesterone, human chorionic somatomammotropin (HCS), beta subunit of human chorionic gonadotropin (β-HCG) and alphafetoprotein (AFP) were evaluated.

MATERIAL AND METHODS

Twelve healthy women, who volunteered for induced abortion, were treated with serial intramuscular injections of 15-ME-$PGF_2\alpha$, in a dose schedule of 250 μg every three hours until twelve hours after the first injection or until the time of abortion. The gestational age varied between eight and eleven weeks. All patients were premedicated with antiemetic and antidiarrhoea agents: 10 mg of metoclopramide monochlorhydrate intramuscularly; 5 mg of dyphenoxylate hydrochloride and 0.05 mg of atro-

pine sulfate orally. In order to minimize the gastrointestinal side-effects, this therapy was repeated regularly every six hours until the abortion. These patients were carefully examined at regular intervals to determine the onset of vaginal bleeding and to detect embryonal parts in the vagina. Blood samples were collected prior to the first injection of 15-ME-$PGF_{2\alpha}$, at 1, 3, 6, 9, 12 and 18 hours following the beginning of the procedure. Plasma was separated and stored frozen at — 20 °C until the assay. Each sample was assayed in triplicate for HCS, β-HCG and AFP by radioimmunoassay (Biodata, Italy); serum oestradiol and progesterone concentrations were measured by a radioimmunoassay following extraction with ether (Cea-Ire-Sorin, Italy). The statistical analysis was performed by Student's test. When the cervix was dilated, without the product of conception being expelled completely, the patient was submitted to suction evacuation.

RESULTS

Abortifacient efficacy. The results obtained from the twelve patients are summarized in table 1. By using the described schedule of serial intramuscular injections of 15-ME-$PGF_{2\alpha}$ eight women aborted completely and four, who aborted incompletely, required suction evacuation. The interval between the first injection and complete or incomplete expulsion ranged from 6.0 to 23.5 hours with a mean of 16.4 hours. Uterine activity initiated within 15 to 50 minutes following the first injection with a mean of 22.4 minutes and the successive injections resulted in further increments of activitv. The onset of vaginal bleeding ranged from 1.9 to 7.5 hours with a mean of 4.4 hours. The total amount of 15-ME-$PGF_{2\alpha}$ used to induce abortion varied from 500 to 1250 μg (mean 1104.2μg). Side effects were noted in many patients but no serious complications occurred. Nausea (83.3 %) and vomiting (41.7 %) were only partially alleviated by the antiemetics; whereas by administering antidiarrhoic drugs only 16.7 % of the patients developed diarrhoea.

Effect on hormone plasma levels. Oestradiol, progesterone, HCS, β-HCG and AFP plasma changes are shown in table II. Before the serial intramuscular injections of 15-ME-$PGF_{2\alpha}$ (time 0) the hormone values were in the normal range for the gestational age.

Oestradiol. Serum oestradiol concentrations did not significantly vary an hour after the first injection of 15-ME-$PGF_{2\alpha}$ and dropped to 60 % of the basal levels at three hours, to 35 % at six hours, 25 % at nine hours, 20 % at twelve hours and to 10 % at eighteen hours. The statistical analysis showed a significant difference at three ($P<0.05$), six, nine, twelve and eighteen hours ($P<0.0005$) from the initial levels.

Progesterone. Progesterone mean values showed a gradual and consistent decrease during 15-ME-$PGF_{2\alpha}$ treatment, as was found for oestradiol. They remained unchanged one hour after the first injection but dropped to 70 % at three hours, 50 % at six and nine hours, 35 % at twelve hours, and to 30 % at eighteen hours. The fall in serum progesterone was statistically significant ($P<0.005$ at three hours and $P<0.0005$ at the following times).

HCS. During treatment the serum HCS concentrations dropped gradually and significantly (at three hours $P<0.05$) to 60 % at six and nine hours ($P<0.005$), 35 % at twelve hours ($P<0.0005$) and to 18 % at eighteen hours ($P<0.0005$) as compared with the initial control levels.

βHCG. The β-HCG plasma concentrations decreased similarly to HCS; they remained unchanged at one hour and significantlv dropped at the successive control times ($P<0.05$ at three hours and $P<0.0005$ at the following times).

AFP. The AFP levels, unchanged for three hours, rose progressively later and were significantly higher than the initial mean values at six ($P<0.005$) nine and twelve hours ($P<0.0005$) at eighteen hours ($P<0.005$).

Table 1 — *Induction of abortion by serial intramuscular injections of 15-ME-PGF$_{2\alpha}$ in early pregnancy.*

Case/Age	Gestation weeks	Parity	Total dose (µg)	Uterine activity (minutes)	Bleeding (hours)	Abortion (hours)	Results
1/22	11	5	500	15	1.9	6.0	Complete
2/19	10	0	1250	30	4.5	20.0	Complete
3/27	8	2	1250	17	2.4	12.1	Complete
4/21	10	0	1250	15	5.1	12.1	Complete
5/27	9	6	1250	15	6.6	14.0	Incomplete
6/16	9	0	1250	50	2.3	23.5	Complete
7/24	8	2	1250	15	6.1	22.1	Incomplete
8/38	10	5	750	35	2.4	6.5	Complete
9/31	10	2	1250	20	6.0	22.0	Incomplete
10/18	9	0	1250	15	4.0	20.0	Complete
11/42	11	5	1250	20	7.5	21.5	Incomplete
12/29	10	4	750	15	5.5	6.5	Complete
Mean ± SEM			1104.2 ± 78.2	22.4 ± 3.3	4.4 ± 0.6	16.4 ± 1.8	

Table 2. — *Changes in hormone plasma levels (Mean±SEM) induced by serial intramuscular injections of 15-ME-PGF$_{2\alpha}$ in early pregnancy (8 to 11 weeks).*

Hormone	Time of control (hours) 0	1	3	6	9	12	18
Oestradiol 17-β (ng/ml)	1.55 ± 0.19 ($\bar{12}$)+	1.48 ± 0.22 ($\bar{12}$)	1.14 ± 0.13* ($\bar{12}$)	0.61 ± 0.11*** ($\bar{12}$)	0.48 ± 0.12*** ($\bar{9}$)	0.30 ± 0.09*** ($\bar{9}$)	0.18 ± 0.04*** ($\bar{6}$)
Progesterone (ng/ml)	22.65 ± 1.67* ($\bar{12}$)	20.47 ± 2.02 ($\bar{12}$)	16.11 ± 1.10** ($\bar{12}$)	10.92 ± 1.07*** ($\bar{12}$)	10.09 ± 1.05*** ($\bar{9}$)	7.89 ± 8.86*** ($\bar{9}$)	7.00 ± 0.84*** ($\bar{6}$)
HCS (ng/ml)	255.0 ± 13.5 ($\bar{12}$)	256.2 ± 8.9 ($\bar{12}$)	215.0 ± 13.9* ($\bar{12}$)	151.6 ± 21.4** ($\bar{12}$)	153.0 ± 21.3** ($\bar{9}$)	118.6 ± 13.3*** ($\bar{9}$)	43.0 ± 4.6*** ($\bar{6}$)
β-HCG (U/ml)	142.1 ± 15.2 ($\bar{12}$)	136.0 ± 15.6 ($\bar{12}$)	117.1 ± 16.4* ($\bar{12}$)	85.6 ± 14.5*** ($\bar{12}$)	80.4 ± 18.9*** ($\bar{9}$)	62.7 ± 11.1*** ($\bar{9}$)	57.6 ± 11.6*** ($\bar{6}$)
AFP (ng/ml)	20.80 ± 3.14 ($\bar{12}$)	18.70 ± 5.41 ($\bar{12}$)	27.94 ± 4.37 ($\bar{12}$)	47.01 ± 7.43** ($\bar{12}$)	44.37 ± 10.02*** ($\bar{9}$)	58.17 ± 9.51*** ($\bar{9}$)	62.06 ± 10.50** ($\bar{6}$)

+ number of cases

* $P < 0.05$; ** $P < 0.005$; *** $P < 0.0005$ (statistical significance between the time 0 and the other times)

DISCUSSION

In this study we have seen that serial intramuscular injections of 15-ME-$PGF_2\alpha$ have successfully induced abortion in all patients within less than 24 hours; 66% of the cases aborted completely and required no surgical evacuation. This experience is too limited for us to recommend a large use of this compound in the termination of early pregnancy, but these results are very encouraging. By this simple technique there is no risk of exposing the patient to the possible hazards and traumas encountered in other procedures. The disadvantage is that this drug certainly entails high percentage of nausea and vomiting, despite the uses of antiemetics. There is disagreement among the investigators regarding the moment of the onset of uterine contractions and the significance of the decrease observed in plasma steroid and proteic hormones. It is well known that the luteal and placental progesterone production ([15]) is an essential factor for the maintenance of first trimester pregnancy; this is based on the evidence that luteectomy in early pregnancy results in serum progesterone decrease followed by abortion ([16]). Several studies have been made in order to investigate the abortifacient mechanism of prostaglandins: it is generally agreed that prostaglandins have luteolytic ([17]) and oxytocic ([18]) effects and act by suppressing the placental steroidogenesis; the subsequent drop in steroid hormones converts the uterus into a more reactive organ ([19, 20]) and develops the uterine activity ([14]). Whereas several authors ([21, 22, 11]) have reported that prostaglandins-induced termination of pregnancy is unrelated to the drop of progesterone but the result of a strong myometrial activity.

Our results show that the uterine contractions began from 15 to 50 minutes (mean 22.4) after first injection of 15-ME-$PGF_2\alpha$, while the serum progesterone, oestradiol, HCS and β-HCG were unchanged after one hour. They progressively dropped three hours after the beginning of the experiment, while the AFP plasma levels unchanged during the first three hours, significantly rose at the successive control times. From these data there is evidence that the oxytocic effect can be considered a most important factor in 15-ME-$PGF_2\alpha$-induced termination of early pregnancy. The following fall of the endocrine placental function can be related to the severe hypoxia determined by a substained vasoconstriction of the utero-placental vessels, as referred to by Pulkkinen et al. ([23]). Moreover the progesterone, oestradiol, HCS and β-HCG drop in serum could also reflect a disruption of the implanted placenta, as testified by the onset of vaginal bleeding (mean time 4.4 hours). The progesterone drop, however, may have facilitated the uterine activity increase during the 15-ME-$PGF_2\alpha$ treatment. The delayed rise of plasma values of AFP, which is an index of foetal status ([24, 25, 26]) could be explained by a severe foetal distress or intrauterine death, as a consequence of the placental damage induced by 15-ME-$PGF_2\alpha$ treatment.

In conclusion, we believe that 15-ME-$PGF_2\alpha$ abortifacient action is mainly mediated by a direct oxytocic effect leading to a placental steroidogenesis decrease, which could subsequently enhance myometrial responsiveness to 15-ME-$PGF_2\alpha$.

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