USE OF INTRAMYOMETRIAL INJECTION OF PROSTAGLANDIN $F_{2\alpha}$ IN THE MANAGEMENT OF INTRACTABLE HEMORRHAGE DUE TO UTERINE ATONY

E. VINCENTI (**), B. TAMBUSCIO (**),
D. MARCHESONI (*), A. GRAZIOTTIN (*),
L. DI LENARDO (*), M. CHIARANDA (**)

(*) Department of Obstetrics and Gynecology
(**) Institute of Anaesthesiology and Resuscitation
University of Padua (Italy)

SUMMARY

Prostaglandin $F_{2\alpha}$, in doses varying from 1 to 5 mg was injected transabdominally, transvaginally or intraabdominally (during caesarean section) into the myometrium in ten patients affected by metrorrhagias not responsive to conventional uterotonic drugs. In all cases but one the result was excellent. Important side effects were observed in only one patient, because of the inadvertent intravascular injection of 5 mg Prostaglandin into the endocervix. An adequate treatment of this patient brought her to complete recovery in a short time.

According to our experience, the intramyometrial injection of $PG_{F2\alpha}$, in doses varying from 1 to 2 mg, is a simple, safe and effective method in the control of severe hemorrhage due to uterine atony not responding to conventional treatment.

The systemic use of conventional uterotonic drugs, such as synthetic oxytocin (Syntocinon) and methylergometrine maleate (Methergin) is sometimes inadequate to control the severe blood loss due to uterine atony or hypotonia that appears sometimes after uterine curettage for spontaneous or induced abortion, in postpartum or in puerperium.

It is well known that prostaglandins induce strong contractions of human pregnant uterus "in vitro", even if it does not respond to the oxytocin under the same experimental conditions ([1]). From a biological point of view, the main difference between the effects of prostaglandins and oxytocin consists in the more regular and more continuous reaction induced by prostaglandin $F_{2\alpha}$ compared to oxytocin ([2, 3]). Moreover, prostaglandins sensitize the human uterus to the stimulating action of oxytocin ([4, 5]). Experimentally, it was also demonstrated that:

1) oxytocin i.v. (3 I.U.) induces a rapid and strong increase of myometrial tone, nevertheless this effect is of short duration ([6]);

2) methergin i.v. (0.2 mg) induces a much smaller elevation of tone which persists for several hours ([6]);

3) prostaglandins i.v. (100 μg) cause a rapid rise of tone which slowly returns to a normal level within 40-50 minutes ([6]).

Preliminary studies on the control of post-partum hemorrhage conducted by Takagi *et al.* ([7]) using prostaglandin $F_{2\alpha}$, administered either by systemic or local route showed that:

1) Single intramuscular injection of prostaglandin $F_{2\alpha}$ (0.5-1.0 mg) induces forceful uterine contractions after 35 min $\pm$ 20 in multiparas. These results indicate that there is no rapid hemostasis caused by intramuscular prostaglandin $F_{2\alpha}$. In addition this method produces severe pain at the site of injection and strong side effects.

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2) Continuous intravenous drip infusion at the rate of 80-100 μg/min induces forceful uterine contractions after 10 min ± 4 in primiparas and 13 min ± 5 in multiparas. Both the amount of blood loss and time of contraction induction decreased if compared with the i.m. injection. However frequent complaints of facial flushing and headache appeared.

3) Intramyometrial injection of prostaglandin $F_{2\alpha}$ (1 mg) either transabdominally or transvaginally causes uterine contractions within 3 min ± 1 in primiparas and multiparas. The total blood loss after local treatment (during the first two hours after injection) is significantly reduced compared to the systemic administration route and side effects are greatly reduced.

Paoletti [1] had already mentioned that the local route of administration is particularly important because it reduces the maximal destruction of prostaglandins. Ninety per cent of the injected prostaglandins are in fact metabolized at the pulmonary level before passing from the venous to the arterial system.

After the pioneer study of Takagi *et al.* [7] on the use of intramyometrial prostaglandin $F_{2\alpha}$ in the treatment of post-partum hemorrhage (3 cases), Jacobs and Arias [8] have recently proposed its clinical use by the transabdominal route (1 mg) reporting the results obtained in 3 patients with severe post-partum hemorrhage due to uterine atony.

The purpose of this paper is to evaluate the optimal doses and indications of use of prostaglandin $F_{2\alpha}$ in a number of patients and in different obstetric conditions.

MATERIAL AND METHODS

From december 1980 to december 1981 ten women admitted to the Gynaecologic and Obstetric Clinic of Padua University were treated with intramyometrial injection of prostaglandin $F_{2\alpha}$ for intractable metrorrhagias due to uterine atony. Such massive metrorrhagias were diagnosed as "intractable" after failure of conventional treatments, i.e. when continuous intravenous drip infusion of 10 I.U. of oxytocin and 0.4 mg of methyl-ergometrine injected either i.v. during caesarean section or i.m. in the other cases were ineffective. The methyl-ergometrine was not administered to preeclamptic patients [9, 10].

The detailed case series is summarized in table 1.

Prostaglandin $F_{2\alpha}$ (Upjohn) in 1 ml vials (5 mg) was used for intramyometrial injections after dilution with saline in order to obtain concentrations of 1 mg/ml of prostaglandin. During caesarean section 22G×1½″ needles were used and the injections were carried out in the upper segment of the myometrium [11]. which showed well marked spasmogenic effects after prostaglandin administration. Single use spinal needles (21G×3½″) were used in the transabdominal and transvaginal administration. Prostaglandin $F_{2\alpha}$ was administered in doses varying from 1 to 5 mg.

The most important clinical parameters, e.g. heart rate, blood pressure, respiratory rate and body temperature were controlled before and after local administration of prostaglandin. Possible side effects were accurately searched. Surgical procedures were performed under intravenous general anaeshesia complemented by nitrous oxide.

RESULTS AND DISCUSSION

The essential results obtained after intramyometrial administration of prostaglandin $F_{2\alpha}$ in the treatment of intractable hemorrhage due to uterine atony are summarized in table 2.

An early spasmogenic effect was observed in all cases and in all but one the uterine contraction persisted for the next hours. In this single case (No. 10) of short lasting effect it was necessary to repeat the dose, but this also was without satisfactory effects.

According to Takagi *et al.* [7] and to Jacobs and Arias [8] a 1 mg prostaglandin $F_{2\alpha}$ dose was sufficient to guarantee a valid uterine contracture with a consequent stop of the blood loss. Under direct visual and manual control, during caesarean section, it was possible to notice that contractions begin at the injection site and spread all over the uterine muscle in 60-90 seconds. Greater effects were not noticed with double doses. Therapeutic effects

Table 1. — *Case-series and details.*

Case (No.)	Age (years)	Para	Weeks of pregnancy or puerperium (p)	Obstetric surgical condition	Anaesthesia	Observations
1	17	0000	37	Caesarean s.	General	—
2	50	0000	38	Caesarean s.	General	Pregnancy-induced hypertension
3	34	1001	40	Caesarean s.	General	—
4	28	1001	p	Uterine evacuation	General	Fragments of placenta and membranes removal (*)
5	24	0101	11	Uterine evacuation	General	Trophoblastic fragments after abortion (**)
6	33	0000	30	None	None	Delivery of dead foetus
7	29	1203	p	Uterine evacuation	General	Fragments of placenta and membranes removal (***)
8	22	0000	8	Abortion	General	—
9	26	0000	39	Caesarean s.	General	Preeclampsia
10	21	0000	37	Caesarean s.	General	Preeclampsia

(*) 24 days after delivery; (**) 30 days after abortion; (***) 22 days after delivery.

were immediate and impressive with 5 mg doses of prostaglandin $F_{2\alpha}$: a very strong contracture (marmoreal uterus) was observed within 30 seconds.

Unfortunately, in patient No. 7, part of the prostaglandin dose was inadvertently injected in a blood vessel just after the uterine curettage at the end of intravenous anaesthesia. Immediately a dramatic picture appeared, characterized by head, neck and superior chest cutaneous flushing, signs of seizure, intense bronchospasm, engorged neck veins with cyanosis, hypertensive crisis (210/110 mmHg) and tachycardia (about 140 beats/min). A pharmacological treatment (thyopentone 175 mg and phentolamine 4 mg) was immediately initiated. Within two mi-

Table 2. — *Results relative to the patients treated with intramyometrial prostagalndin $F_{2\alpha}$ for the management of intractable uterine atony.*

Case (No.)	Blood loss (ml)	$PG_{F2\alpha}$ (mg)	Administration way	Spasmogenic effect	Side effects
1	>1000	1	Laparotomic	+++	None
2	<500	1	Laparotomic	+++	None
3	500-1000	2	Laparotomic	+++	None
4	>1000	5	Transabdominal	++++	None
5	>1000	5	Transvaginal	++++	None
6	>1000	2	Transvaginal	+++	None
7	500-1000	5	Transvaginal	++++	*Suddendly after administration*: seizures, bronchospasm, hypertension, tachycardia, engorged neck veins with cyanosis. *Later*: slight increase of body temperature
8	500-1000	1	Transvaginal	+++	None
9	500-1000	2	Laparotomic	+++	None
10	500-1000	2+2	Laparotomic	+	None

+ slight; ++ moderate; +++ strong; ++++ very strong.

nutes, the patient's conditions markedly improved with decrease of the bronchospasm, disappearance of the neck veins dilation, blood pressure normalization (120/80 mmHg) and decrease of the tachycardia (110 beats/min). After 15 minutes the symptoms completely disappeared; only rectal temperature was 38°. The patient was sent to her ward, perfectly conscious and in good general conditions, 30 minutes after the onset of the side effects. No further therapy was necessary. Excellent uterine contracture was still evident on the following hours.

The i.v. threshold dose of prostaglandin $F_{2\alpha}$ needed to produce uterine contracture is 100 micrograms. At these dose levels prostaglandin $F_{2\alpha}$ shows no systemic or subjective side effects ([12, 13]). Bygdeman *et al.* ([14]) found that when small doses of prostaglandin $F_{2\alpha}$, i.e. 200 micrograms are administered i.v., no influence on pulse rate or blood pressure and no side effects are observed. It is necessary to increase the i.v. dose of prostaglandin $F_{2\alpha}$ to 500 micrograms or more to induce mild side effects, that is ill-defined chest discomfort, occasional vomiting and a slight increase in pulse rate.

Therefore one can conclude that intramyometrial administration of prostaglandin $F_{2\alpha}$ limited to a thousand micrograms cannot cause important side effects, even if inadvertently injected intravascularly.

As a matter of fact, prostaglandins such as E_1, E_2 and $F_{2\alpha}$ are rapidly metabolized at pulmonary level, since they are very labile compounds. To determine the inactivation of these prostaglandins, it is normally sufficient just one passage through the vessels of the bronchial tree and the pulmonary tissue, very rich of metabolizing enzymes such as 15-hydroxydehydrogenase, a NAD^+-linked enzyme ([15]). However, although many Authors regard prostaglandins as freely diffusing agents. some reports of apparent uptake suggested for prostaglandin $F_{2\alpha}$ a saturation process ([16]). Thus it seems likely that a dependence of pulmonary prostaglandin metabolism exists on carrier mediated transport processes ([17]). Circulating concentration of prostaglandins, not metabolized while passing through lungs, is increased by possible interferences with the mediated transport ([18]). Several agents, including some non-steroidal highly concentrated antiinflammatory ones ([19]), are capable of interfering with this transport and metabolism.

So it is possible that prostaglandin $F_{2\alpha}$ intramyometrially administered to patient No. 7 reached the lungs through blood stream in such elevated quantity as to overcome the carrier-mediated transport process of cells in charge of prostaglandin metabolism. More elevated doses of prostaglandin $F_{2\alpha}$ would therefore reach the arterial system determining the dramatic systemic effects, such as intense bronchospasm with pulmonary and systemic arterial hypertension. The timely administration of phentolamine to antagonize the alpha-mimetic effects of prostaglandin $F_{2\alpha}$, prostaglandin that induces heaping up of cGMP, a strongly contractile cyclic nucleotide ([1]), proved to be quite correct.

The side effects were extremely short lasting, because of the high metabolization operated at each passage through lungs.

As far as the administration way is concerned, it was seen that intramyometrial injection of 5 mg of prostaglandin $F_{2\alpha}$ to pregnant monkey does not cause necrosis or histological changes in the myometrium ([20]). Therefore there is no doubt that the intramyometrial injection of prostaglandin $F_{2\alpha}$ is a safe process.

Ultimately, the intramyometrial injection of prostaglandin $F_{2\alpha}$ in doses from 1 to 2 mg can be suggested for the following cases:

1) treatment of uterine atony after failure of parenteral administration of both oxytocin and methylergometrine maleate to healthy patients or after failure of pa-

renteral administration of oxytocin alone to patients with preexisting hypertension or pregnancy induced hypertension;

2) during caesarean section as prophylactic or therapeutic antihemorrhage method alternative to conventional drugs.

Five mg doses of prostaglandin $F_{2\alpha}$ are indicated only for selected cases when a massive uterine response is needed. Nevertheless, in such cases adequate therapeutical means must be set up to take care of such eventual major effects. Frequent aspiration tests should be performed during the intramyometrial injection in order to avoid inadvertent intravascular injection of prostaglandin $F_{2\alpha}$. In short, the use of such high doses of prostaglandin $F_{2\alpha}$ requires the most competent skill.

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