Uterine motility and cervical ripening in second trimester elective abortion by two different PGE analogues

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Summary: The clinical effects were studied of two different PGE analogues on the uterine motility and cervical ripening of eighty pregnant women asking for a second trimester elective abortion for fetal abnormalities.

Forty women received vaginal suppositories each containing 1 milligram of 16, 16 - dimethyl-trans-s2-PGE1 (Gemeprost) every 3 hours (5 mg max). Intramuscular injections of 500 micrograms of 16-phenoxy-w 17, 18, 19, 20 tetranor PGE2 methyl-sulphonylamide (Sulprostone) were administered every four hours (2000 mcg max.) to the remaining forty patients.

Thirty-three Gemeprost treated patients (82.5%) and 34 Sulprostone treated patienst (85%) experienced a complete abortion in the mean of 12.92 ± 6.95 hours and 11.88 ± 6.8 hours respectively.

The histological and ultrastructural findings of cervical ripening were similar in both groups, while the tocographic patterns showed different characteristics.

Side effects occurred in 16 Sulprostone (40%), but only in 9 (22.5%) Gemeprost treated patients, demonstrating that Gemeprost, although equally effective, is better tolerated.

Key words: Prostaglandin analogues; Abortion.

INTRODUCTION

Although natural prostaglandins are able to induce cervical ripening and uterine contractions, in clinical use they have recently been replaced by synthetic analogues which are equally effective but have minor side effects. The strength of natural PGs systemic side effects has been the main limit for customary use of these drugs ([1, 2]).

In Obstetrics and Gynecology the interest in this new generation of prostaglandins derivatives has led to the discovery of highly uterus-selective analogues ([3]). These drugs which are resistent to enzymatic degradation, are particularly indicated in the elective mid pregnancy termination, since by allowing different ways of administration, they permit the subdivision and reduction of dosage, thus increasing systemic and particularly gastrointestinal tolerance ([3, 4]).

In the present study, we examined the effectiveness and side effects of two diffe-

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rent PGE analogues, Gemeprost (16, 16-dimethyl-trans-s2-PGE1) and Sulprostone (16-phenoxy-w, 17, 18, 19, 20 tetranor PGE2 methyl-sulphonylamide), in order to evaluate their ability to raise cervical ripening and uterine contractions.

At present, Gemeprost is the only PG analogue available in Italy for vaginal administration; its uterus-stimulating activity seems to be ten times higher than natural PGE1 and PGE2.

The cervical ripening induced by Gemeprost and Sulprostone was evaluated qualitatively and quantitatively by light and electron microscopic study of cervical biopsies.

MATERIALS AND METHODS

The present study was carried out at the Department of Gynecology and Obstetrics of the University of Naples "Federico II", II Medical School.

Eighty pregnant women who were seeking a second trimester elective abortion on account of fetal anomalies (Table 1), were examined.

Table 1. – *Fetal anomalies.*

Down's syndrome	22 (27.50%)
Edward's syndrome	3 (3.75%)
Hurler's syndrome	2 (2.50%)
Klinefelter's syndrome	2 (2.50%)
Neural tube defects	11 (13.75%)
Multiple anomalies	25 (31.25%)
Osteogenesis imperfecta	5 (6.25%)
Cystic fibrosis	2 (2.50%)
Epignathus	1 (1.25%)
Type II mucolipidosis	1 (1.25%)
Type IV mucolipidosis	1 (1.25%)
Toxoplasmosis	4 (5.00%)
X trisomy	1 (1.25%)

Patients' ages went from 33 to 40 years (mean±SD = 36.63±2.15); gestational age was from 16 to 22 weeks (mean±SD = 19.31±2.04), while the global rate of primigravidae was 43.7% (Table 2).

Table 2. – *Patients' characteristics.*

	Range	Mean±SD
No. 80		
Age (years)	33 - 40	36.63±2.15
Gestational Age (weeks)	16 - 33	19.31±2.04
Rate of primigravidae (%)	43.7 (35/80)	

Patients were divided into two groups, named "Gemeprost" and "Sulprostone", equivalent for patients' age and gestational age.

The rate of primigravidae was slightly higher in the first group (Table 3).

Table 3. – *Characteristics of the patients assigned to Gemeprost and sulprostone group.*

	Gemeprost	Sulprostone	P
No.	40	40	
Age (years)	36.77±1.96	36.50±2.35	NS
Primigravidae	19 (47.5%)	16 (40.0%)	
Multiparae	21 (52.5%)	24 (60.0%)	
Gestational age (weeks)	19.22±2.16	19.40±1.93	NS

Gemeprost 1 mg vaginal suppositories were placed in the posterior vaginal fornix every 3 hours (5 mg maximum).

Sulprostone, 500 mcg every 4 hours (2000 mcg maximum), was administered intramuscularly.

The uterine contractions were evaluated and recorded, according to Caldeyro-Barcia, gauging intra-uterine pressures by an intracavitary extra-amniotic catheter, connected to a Cardiff MK3 device.

The cervical score, the body temperature and the heart rate, together with possible side effects such as nausea, vomiting or diarrhoea were also evaluated and recorded.

Cervical biopsies were performed on 30 patients before drug administration and 3 hours and 6 hours later, in order to describe in detail the morphological and ultrastructural changes which happened with cervical ripening.

Every specimen, collected by a bioptic forceps, was divided into two portions which were

examined by light and electron microscopes, respectively.

For light microscopic observation the specimens were stained with hematoxylin-eosin, while for the electron microscopic examination they were fixed in 2.5% glutaraldehyde and 1% osmium tetroxide, stepwise dehydratated with ethanol, Epon 812 embebbed and stained by colloidal steel or Ruthenium Red.

Ultra-thin sections were examined on grids by a Philips 301 electron microscope.

Furthermore, a morphometric evaluation of the ultrastructural characteristics of collagen fibrils and cells which constitute the cervical tissue, in Gemeprost and Sulprostone treated patients was carried out by a Zeiss Videoplan Analysis System, connected to a personal computer (Table 10).

RESULTS

Induction/abortion time

Thirty-three Gemeprost treated patients (82.5%) and 34 Sulprostone treated patients (85%) experienced a complete abortion in the mean time of 12.92±6.95 hours and 11.88±6.8 hours respectively (Tables 4, 5).

Primigravidae underwent the abortion in the mean time of 16.30±6.05 hours in the Gemeprost group and in 15.65± 5.98 hours in the Sulprostone group, while multiparae aborted in 10.60±6.67 hours and in 9.83±6.46 hours respectively (Table 5).

The main induction/abortion time (i.e., the time between the beginning of the treatment and the abortion) failed to show remarkable differences between the drugs (Table 5).

Patients' parity strongly affected the induction/abortion time (Table 5) as well as the amount of drug required to accomplish the abortion (Tables 6, 7).

Uterine motility

Gemeprost, vaginally administered, gave rise to an increase of the uterine tone with a time interval between the admini-

Table 4. – *Findings 24 hours after the beginning of the treatment with Gemeprost or Sulprostone.*

	Gemeprost	Sulprostone
No.	40	40
Complete abortions	33	34
- Primigravidae	13/19 (75.0%)	12/16 (75.0%)
- Multiparae	20/21 (91.6%)	22/24 (91.6%)
Failures	7 (17.5%)	6 (15.0%)
- Primigravidae	6 (85.7%)	4 (66.7%)
- Multiparae	1 (14.3%)	2 (33.3%)
Incomplete abortions	5 (71.4%)	3 (50.0%)
- Primigravidae	2 (40.0%)	0 ———
- Multiparae	3 (60.0%)	3 (100%)

Table 5. – *Mean induction/abortion time (hours).*

	Gemeprost	Sulprostone	P
Total	12.92±6.95	11.88±6.80	NS
Primigravidae	16.50±6.05(*)	15.65±5.98(**)	NS
Multiparae	10.60±6.67(*)	9.83±5.46(**)	NS

(*) $p<0.1$
(**) $p<0.1$

Table 6. – *Mean number of Gemeprost suppositories administered to each patient (1 suppository = 1 mg Gemeprost).*

		Range	Mean±SD
Primigravidae	(19)	1 - 5	4.73±0.65(*)
Multiparae	(21)	1 - 5	3.47±1.43(*)

(*) $p<0.1$

Table 7. – *Mean number of sulprostone ampoules administered to each patient (1 ampoule = 250 mcg).*

		Range	Mean±SD
Primigravidae	(16)	1 - 4	3.75±0.57(*)
Multiparae	(24)	1 - 4	2.66±1.23(*)

(*) $p<0.01$

stration and the response of 25 - 50 minutes (mean ± SD = 36.75 ± 8.25) (Table 8). The highest intensity of uterine contractions was nearly 70 minutes after administration, and it lasted almost 80 minutes (Fig. 1a).

The response was more gradual, and markedly prolonged than by Sulprostone i.m., with an elevation from the base line slightly delayed and weaker at the outset.

One hundred and twenty minutes later, although the increase of the tone persisted, uterine contractions similar to the physiological labour were observed. This uterine activity lasted during the entire administration of vaginal suppositories, up to the abortion.

The increase of the uterine tone induced by Sulprostone intramuscularly administered, was faster. It happened 10 - 30 minutes after drug administration (mean ± SD = 18.32 ± 5.71) (Table 8) (Fig. 1b).

The uterine response persisted for about 60 minutes, with small and frequent contractions. The immediate response resembled an uterine contracture; the hypertonic uterus reached its maximal response, and slowly returned to its natural tone.

A short or prolonged uterine hypertonia reappeared with every administration, delaying the uterine activity which was never similar to physiological labour, either for hypertone with frequent contractures or for strong tachysystolic activity.

The increase of the uterine tone, a characteristic feature of PGE analogues, appeared with both drugs, while the strength of isolated contractions increased during the descenting phase of hypertone, thus miming the physiological labour.

Table 8. – *Time interval between drugs administration and the beginning of the uterine response (minutes).*

	Range	Mean ± SD
Gemeprost	25 - 50	36.75 ± 8.25
Sulprostone	10 - 30	18.32 ± 5.71

Table 9. – *Side effects.*

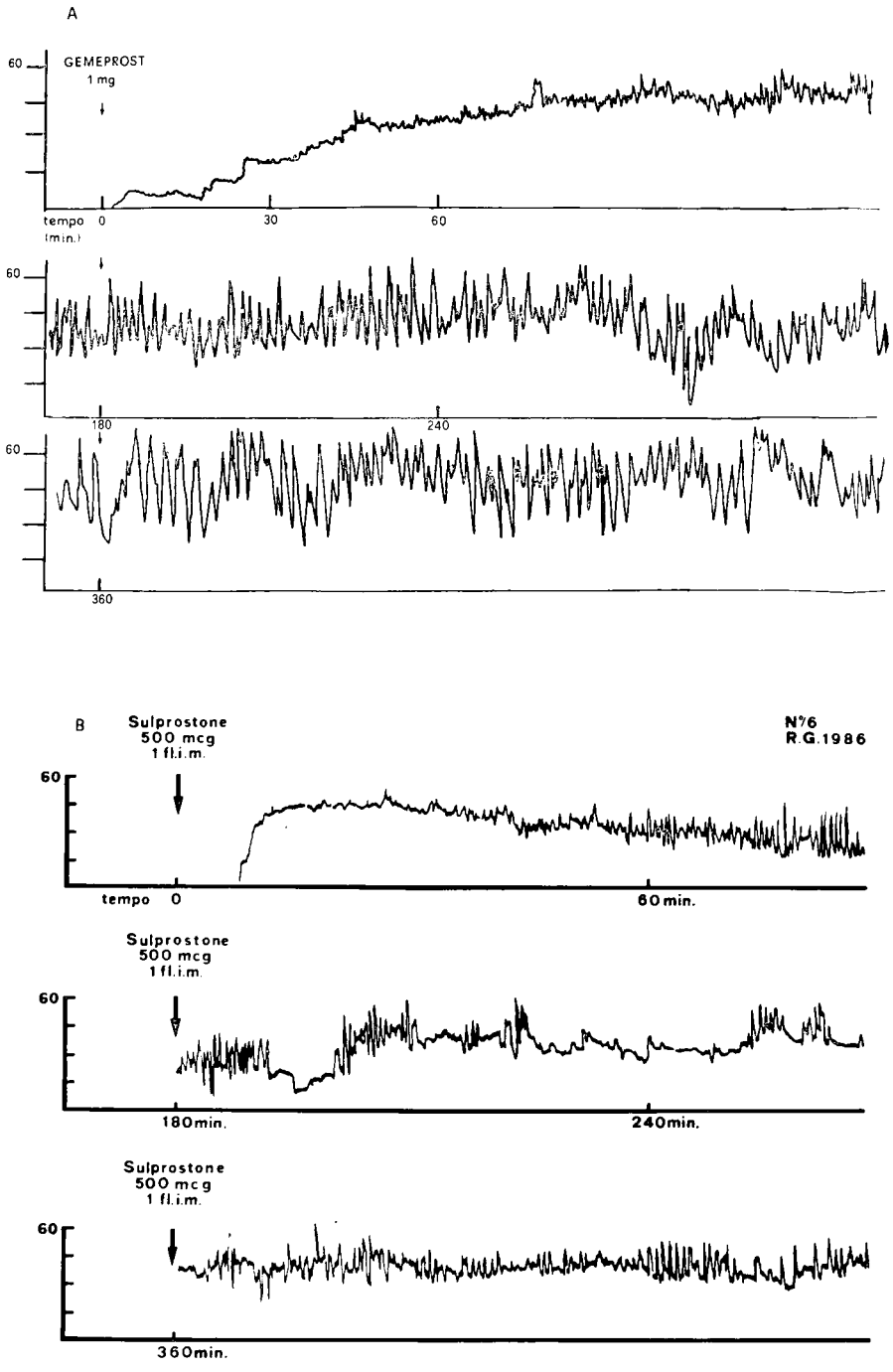
	Gemeprost	Sulprostone
Total	9 (22.5%)	16 (40.0%)
Abdominal pain	5 (55.5%)	12 (75.0%)
Diarrhoea	2 (22.2%)	8 (50.0%)
Sickness	3 (33.3%)	5 (31.2%)
Nausea	3 (33.3%)	8 (50.0%)
Headache	4 (44.4%)	3 (18.7%)
Hypertension	–	1 (6.2%)
Shivers	2 (22.2%)	2 (12.5%)
Dizziness	1 (11.1%)	–
Hyperpyrexia	1 (11.1%)	2 (12.5%)
Facial flush	1 (11.1%)	–

Morphological observations

The examination of cervical biopsies performed at the beginning of the treatment, before Sulprostone or Gemeprost administration, showed that the human cervix is made up mainly by fibrous tissue, constituted by closely connected collagen fibres immersed in a poor amorphous basic substance. There are usually fibroblasts, and a few granulocytes and monocytes. Muscular tissue is scant.

In the biopsies performed 3 hours after the beginning of the treatment there were already considerable modifications of cervical histological characteristics with stromal oedema and an initial leukocytic infiltration. Electron microscope examination showed a break-down of some collagen fibres which were messed up and dispersed in the basic substance.

Light microscope examination, 6 hours after drug administration showed a large submucousal oedema, an increase of extracellular basic sustance, blood vessel dilatation, with leukocytes, monocytes, lymphocytes and plasmocytes diapedesis and infiltration (Fig. 2a).


A
60
GEMEPROST
1 mg
tempo
(min.)
0
30
60
60
180
240
60
360
B
Sulprostone
500 mcg
1 fl.i.m.
N°6
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60
tempo 0
60 min.
Sulprostone
500 mcg
1 fl.i.m.
60
180min.
240min.
Sulprostone
500 mcg
1 fl.i.m.
60
360min.

Fig. 1 *a-b*.

Table 10. – *Ultrastructural and morphometric characteristics of the uterine cervical tissue after treatment with Gemeprost or Sulprostone.*

	Gemeprost	Sulprostone
Diameter of capillary vessels	+++	+++
Number of fibroblasts	+	+
Number of ribosomes in fibroblasts	+++	++
Number of leukocytes	+++	+++
Break-down of collagen fibres	+++	+++
Basic substance	++	++

(+) Slight increase
(++) Mild increase
(+++) High increase

Ultrastructurally, a complete dissociation of collagen fibres with loss of cross linkages and a marked increase of basic substance constituent were observed.

Fibroblasts, filled with vesicles closely crowded to plasma membrane, contained a lot of ribosomes and a large rough endoplasmic reticulum, but only a few lysosomes and a small Golgi complex (Fig. 2b).

Side effects

Side effects occurred in 16 Sulprostone (40%) and in 9 Gemeprost (22.5%) treated patients (Table 9).

More frequent was the abdominal pain; hypertension, shivers, dizziness, vomiting, diarrhoea, nausea, headache, facial flush, hyperpyrexia were present too.

DISCUSSION

Before prostaglandins discovery, mid-pregnancy terminations were performed by various methods such as hysterotomia and administration of urea or hypertonic saline solutions in the amniotic cavity [2].

These methods were responsible for side effects so strong that PGs quickly became the elective drugs for mid-pregnancy termination [2].

Natural $PGF2^{d}$ and PGE2 were administered intravenously or intracavitarily, often causing side effects such as nausea, vomiting, pyrexia, phlebitis and, in some cases, bradycardia and hypotension. The recently introduced PGE analogues (Gemeprost, PGE1 analogue and Sulprostone, PGE2 analogue) administred in different ways made mid-pregnancy termination easier. Indeed, these drugs, administered intravenously or intramuscularly and locally by gel or vaginal suppositories, have remarkable advantages compared to intra-uterine administration. Accidental injection into the bloodstream is mainly avoided, the uterine selectivity of PGs analogues minimizes the risks of heavy systemic side effects and the availability of different formulations makes administration by the patients themselves and by trained nurses easier.

In the present study Sulprostone, intramuscularly administered, produced a success rate of 85%, while Gemeprost, vaginally administered, provided a percentage of complete abortion of 82.5%.

These results, showing the remarkable efficacy of both drugs, were obtained starting from similar objective conditions, except for a prevalence of primigravidae in the Gemeprost group, which could explain the slightly lower success rate in this group.

It must be stressed that the patients considered had normally evolving, not interrupted pregnancies. Indeed, to determine fetal expulsion in the internal abortion is easier, because natural processes that cause cervical ripening and fetal expulsion are already activated.

Previously published data about mid - pregnancy termination by Sulprostone intramuscular administration showed a success rate similar to the findings ot this study.

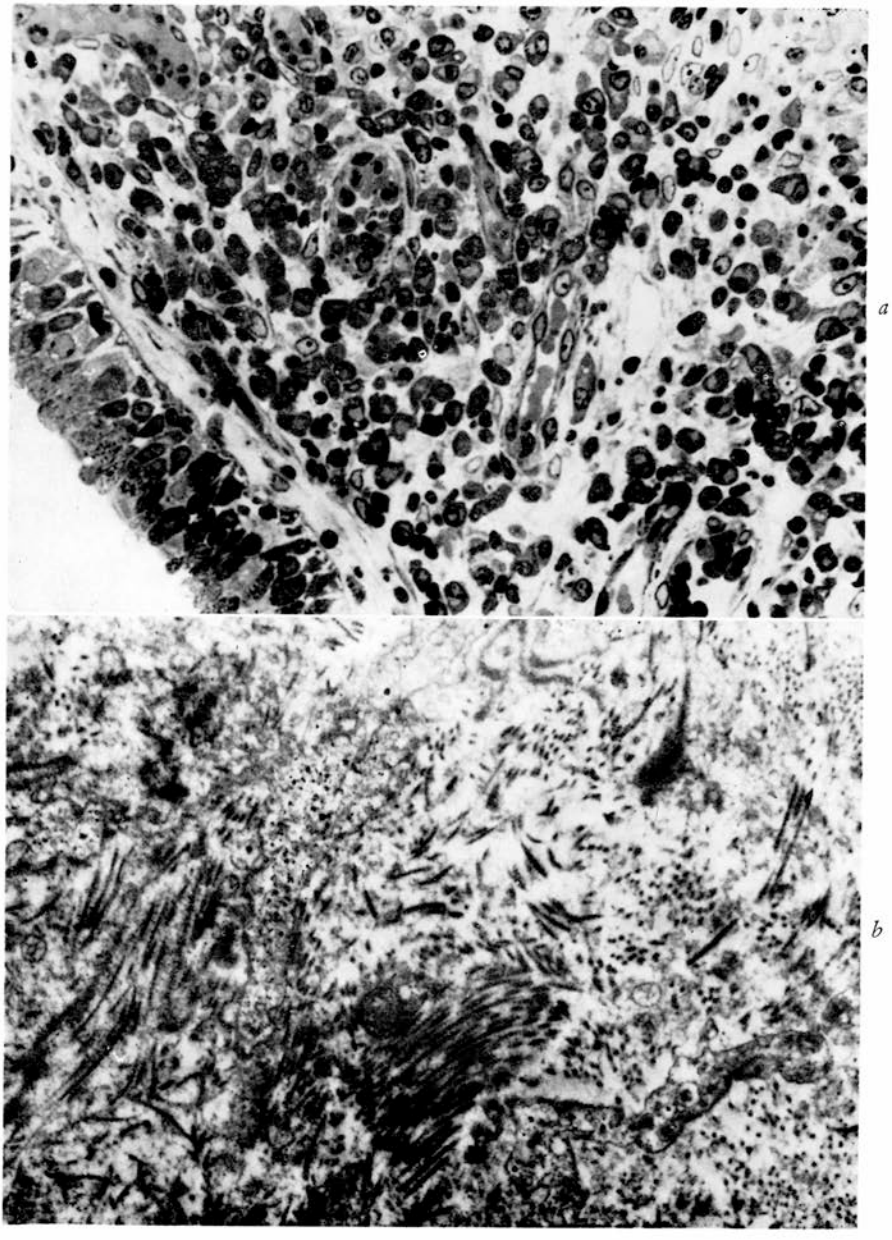

Fig. 2 *a-b*.

Some Authors ([5]) observed 90% of complete abortion after Sulprostone 500 mcg was administered every 4 hours, with a mean induction/abortion time of 19.2 hours in primigravidae and of 17 hours in multiparae. Vomiting occurred in 20% of cases, while diarrhoea only in 5%.

Others observed ([6]) a global rate of complete abortion of about 33% and 91%, 12 hours and 24 hours later respectively, with a mean induction/abortion time of 14.1 h.

Primigravidae experienced a complete abortion in the mean time of 16.1 hours, multiparae in 12.8 hours. Vomiting occurred in 54.4%, diarrhoea in 36.8% and abdominal pain in 33.3%.

Moreover, others ([7]) observed a global rate of complete abortion of 96.9% in interrupted pregnancies after repeated administrations of Sulprostone 500 mcg i.m., with a mean induction/abortion time of 8.9 ± 1.1 hours.

Side effects were pelvic pain, nausea, vomiting and diarrhoea. Vomiting occurred in 50% of examined patients. All the previously mentioned studies were carried out in interrupted pregnancies.

Gemeprost, 1 mg every 3 hours, administered to women with internal abortion, missed abortion or trophoblastic molar degeneration ([8]), caused expulsion of the conceptus in 95.8% within a mean of 8 hours and 4 minutes.

Side effects occurred in 37.5% of patients; diarrhoea (25%) and vomiting were most frequent (20.8%). In some patients headache and, in one case hand itching occurred.

In the present study side effects were more frequent and marked in the Sulprostone group than in the Gemeprost group (40% vs. 22.5%).

This findings probably arises from the intramuscular administration which has more marked systemic effects than the vaginal route. Moreover 1 mg of Gemeprost intravaginally administered (1 suppository) could be considered equivalent to half of Sulprostone ampole (250 mcg) ([9]).

Others have reported a rate of side effects after Gemeprost treatment varying from 20 to 40%. These data are partially equivalent to those obtained in the present study.

Comparing the effects of Gemeprost and Sulprostone on uterine contractility, we observed that after an hypertonic period in both groups, contractions caused by Gemeprost administration were similar to physiological labour, while Sulprostone caused hypertone of higher degree.

Christensen ([9]) stated that the activity of 1 mg Gemeprost intravaginally administered, could be considered equivalent to Sulprostone 250 mcg i.m. He obtained better results using 500 mcg Sulprostone i.m.

Others ([10]), have shown higher activity of Gemeprost, but it must be pointed out that these Authors administered only 300 mcg Sulprostone.

The ultrastructural and morphological observations of cervical biopsy specimens, from both groups of patients failed to show significant differences 3 and 6 hours after administration, probably because, as Christensen and Bygdeman ([11]) stated, these drugs increase the biosynthesis of a still unknown metabolite of arachidonic acid. Therefore, the effects of PGE analogues on the cervical tissue in mid-pregnancy are not directly caused by the drugs themselves but could be indirectedly due to the above-mentioned compounds ([11]).

Although the pharmacological effects of both drugs were difficult to compare, we conclude that there are not significant differences in the characteristics and progression of cervical ripening. Moreover, the clinical results were similar in both groups. Uterine contractility seemed similar to physiological labour only in the Gemeprost treated women.

Worthy of mention is the rate of side effects which, although lower than after PGF2a administration, was higher in the Sulprostone treated group.

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