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Effects of terbutaline on the fetal lamb during maternal oxytocin-induced uterine contractions*

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Terbutaline, a resorcinol derivative of isoprenaline, is primarily an adrenergic β_2 -receptor agonist [25]. Terbutaline has been demonstrated as being a potent inhibitor of myometrial contractility in vitro [1]. Recent clinical trials have confirmed the agent's tocolytic activity in both spontaneous and oxytocin-stimulated labor [2, 3, 15]. The investigations showed that terbutaline was well tolerated maternally despite a moderate tachycardia. Antepartum fetal heart rate monitoring and APGAR scores did not demonstrate any unusual or adverse effects on the fetus in human [2, 3, 15] or animal [6, 7] studies. However, presently there are no systematic clinical or other investigations showing the effect of varying maternal doses on the fetus and on uteroplacental circulation.

This study was undertaken to investigate dose-related effects of terbutaline on immature fetal lambs. The drug was infused into the maternal circulation in one phase and directly into the fetal circulation in another during oxytocin-induced labor. The fetal cardiovascular and acid-base status was monitored continuously.

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Curriculum vitae

JACQUES MILLIEZ was born in Paris, France, 1943. He graduated at the Faculty of Medicine of Paris in 1973. Intern des Hopitaux de Paris - 1967 - 1973. Research Fellow in Perinatal Medicine, Columbia University, New York, New York, 1976-1977. Assistant, full time, Département Ob/Gyn, Clinique Universitaire Baudelocque, Université René Descartes, Paris V, France 1977-1978. Assistant, full time, Faculty of Medicine of Sfax, Tunisia 1978-1979.

1 Materials and methods

Ten pregnant ewes and their fetuses (including two sets of twins) were prepared under spinal anesthesia as described previously [7]. Catheters were introduced into the fetal carotid artery and jugular vein and into the amniotic cavity at hysterotomy. The femoral artery and vein and main maternal uterine vein were also catheterized. An electromagnetic flow probe (Micron Instruments, Calif.) was placed around the uterine artery supplying the pregnant horn. A minimum period of three days was allowed

for postoperative recovery. Twenty-seven investigations making up this study were carried out from 3 to 14 days after surgery (125 to 143 days gestation). At least 24 hours were allowed to elapse between successive investigations of the same animal to ensure recovery of mother and fetus before the next one.

Terbutaline (Bricanyl®, Astra Pharmaceutical Products, Inc., Framingham, Mass.) was administered by continuous intravenous infusion to the ewe on four occasions when uterine contractions were not occurring and on eight occasions when uterine contractions were induced by a continuous infusion of oxytocin into a maternal vein. The amount of oxytocin required to induce regular uterine contractions like those of spontaneous labor in sheep ranged between 20–40 milliunits per minute. In sheep, uterine contractions during the first stage of labour occur 10–20 times each ten minutes with an intensity of at least 10 torr [26]. The oxytocin infusion was maintained throughout the study. After 20 minutes of well-established uterine contractions, terbutaline was infused into the maternal femoral vein at three sequential rates for 20 minutes each; at 0.2 $\mu\text{g/kg/min}$ (rate I); at 0.4 $\mu\text{g/kg/min}$ (rate II); and at 0.8 $\mu\text{g/kg/min}$ (rate III). When oxytocin infusion was not administered there were no uterine contractions; the ewes received no drugs other than terbutaline at the established sequential rates.

A bolus injection of 250 μg of terbutaline was given in eight separate investigations, four with oxytocin-induced contractions and the last four without.

In seven investigations terbutaline was infused directly into the fetal jugular vein at a rate of 0.4–10 $\mu\text{g/kg/min}$ for 20 minutes to examine fetal cardiovascular and acid-base responses. Fetal weight at the time of infusion was estimated according to gestational age [14, 19], and the fetus was sacrificed within 3 days of the final phase of the study.

Maternal and fetal blood pressures, heart rates, and intraamniotic pressure were monitored throughout the study and were recorded on a multi-channel polygraph. Uterine activity was expressed in Montevideo Units (MVU). Arterial blood samples were withdrawn at intervals from the ewe and

fetus simultaneously to measure pH, PO_2 and PCO_2 , using Radiometer microelectrodes. Base deficit was calculated according to the SIGGAARD-ANDERSEN nomogram. All results were analyzed by the Student "t" test and, when P values were less than 0.05, were considered statistically significant. Correlations were estimated by linear regression curves.

2 Results

2.1 Continuous maternal administration of terbutaline

The mean value ($\pm$ S.E.) for oxytocin-induced uterine activity prior to terbutaline infusions was 229 ± 17 MVU. Terbutaline given at rate I (0.2 $\mu\text{g/kg/min}$) reduced uterine activity to 140 ± 24 MVU (39% of the oxytocin-induced level); at rate II (0.4 $\mu\text{g/kg/min}$) to 117 ± 16 MVU (44%) and at rate III (0.8 $\mu\text{g/kg/min}$) to 21 ± 16 MVU (9%). Reduction in uterine activity during terbutaline infusion was statistically significant at all dose levels. Decreases in both the intensity and frequency of contractions were responsible.

Proportional changes in uterine blood flow during oxytocin and terbutaline infusions are illustrated in Fig. 1. For the eight experiments in which uterine activity was induced with oxytocin, the mean uterine blood flow had been reduced significantly ($P < 0.05$) to 75% of the pre-oxytocin value prior to terbutaline (baseline). Following infusion of the drug, uterine blood flow tended to increase above the baseline value, although the change was not significant. In the four experiments in which terbutaline alone was administered to the ewe, blood flow remained essentially unchanged at rates I and II, but fell to 76% of control with rate III. However, because the number of experiments was small, this change was not found to be statistically significant.

Maternal mean blood pressure showed no significant change during infusion of oxytocin and terbutaline alone (Fig. 1). The control value for mean arterial blood pressure was 86 ± 3 torr and remained essentially unaltered throughout the study with systolic blood pressure of 115 ± 2.6

Fig. 1. Percent change (mean $\pm$ S.E.) in uterine activity (MVU), and uterine blood flow (blood flow), and changes in maternal mean arterial blood pressure (MABP), and heart rate during the infusion of oxytocin and/or terbutaline (TRB) to the ewe.

torr for the control period, 121 ± 2 torr after oxytocin infusion and 128 ± 7.5 torr at the end of terbutaline administration. The corresponding values for diastolic blood pressure were 71 ± 5.1 , 72 ± 4.2 and 65 ± 3.8 torr respectively. The heart rate prior to oxytocin infusion was 91 ± 2.4 beats/min. With oxytocin infusion the rate rose to 102 ± 4.2 beats/min. Following terbutaline infusion heart rate increased, reaching a maximum of 158 ± 11 beats/min ($P < 0.01$) with rate III. The chronotropic effect of terbutaline, the increase in heart rate during the infusion, was similar in the animals not given oxytocin (Fig. 1).

Changes in arterial blood pressure and heart rate of the fetus before and at the end of continuous maternal infusion of terbutaline are seen in Tab. I. When oxytocin with terbutaline or terbutaline

alone was administered to the ewes, the fetuses showed no significant alteration of either blood pressure or heart rate.

Mean maternal pHa during the control period was 7.47 ± 0.006 ; PaO_2 , 91 ± 3.7 torr; PaCO_2 , 33 ± 1.9 torr, and base deficit, 0.7 ± 2.0 mEq/l. These values were maintained throughout the study. The pHa and PaO_2 in the fetus during terbutaline infusion are depicted in Fig. 2. Over-all mean control values for the acid-base state of the fetus prior to the infusion of terbutaline were pHa, 7.38 ± 0.017 ; PaO_2 , 25 ± 1.0 torr; PaCO_2 , 45 ± 1.5 torr and base deficit, 1.5 ± 0.8 mEq/L. These values did not change significantly during maternal infusion of combined oxytocin and terbutaline or terbutaline alone. At the end of the highest infusion rate of terbutaline, PaCO_2 was 51 ± 5.6 torr, and base

Tab. 1. Changes in fetal arterial blood pressure and heart rate following administration of terbutaline to the ewe.

	Oxytocin-Augmented Uterine Activity (N = 8)			Absence of Uterine Activity (N = 4)	
	Control	Oxytocin	End of terbutaline	Control	End of terbutaline
Systolic Blood Pressure (Torr)	66 ± 1.8	63 ± 1.6	64 ± 2.9	62 ± 1.9	62 ± 3.7
Diastolic Blood Pressure (Torr)	41 ± 2.4	43 ± 1.5	44 ± 2.4	39 ± 3.3	42 ± 3.7
Pulse Pressure (Torr)	23 ± 3.1	20 ± 2.6	18 ± 5.1	23 ± 1.9	20 ± 0.8
Heart Rate (beats/min)	160 ± 6.0	161 ± 6.0	169 ± 6.5	155 ± 3.4	160 ± 7.3

Fig. 2. Responses of fetal pHa (mean ± S.E.) and PaO₂ to maternally administered oxytocin and/or terbutaline.

deficit, 1.2 ± 0.68 mEq/L. Mean fetal hematocrit for the control period was $35 \pm 2.8\%$. This did not vary significantly during the course of the study.

2.2 Maternal bolus injection of terbutaline

Bolus intravenous injection of 250 μ g of terbutaline to the ewes with well established uterine contractions totally suppressed uterine activity within 30 seconds, and the suppression lasted an average of 9 minutes. Initially, uterine blood flow tended to decrease briefly, followed by a significant increase over the preinfusion value ($P < 0.02$). A typical recording of uterine blood flow, amniotic pressure, arterial pressure and heart rate of both ewe and fetus is shown in Fig. 3. In the animals with oxytocin-induced uterine contractions, blood flow remained essentially the

same following a bolus injection of terbutaline as in the absence of spontaneous uterine activity previously ($n = 4$). Bolus injection had a biphasic effect on maternal blood pressure; a fall in systolic from the control value of 118 ± 2.4 to 110 ± 2 torr ($P < 0.05$); and a fall in diastolic blood pressure from 98 ± 2.4 to 80 ± 3.1 torr ($P < 0.02$) in the first 15 seconds. This was followed by a rise in both systolic and diastolic pressures with a significant increase in pulse pressure from 20 ± 1 to 34 ± 6 torr ($P < 0.05$). Maternal heart rate rose from 110 ± 2.0 to 145 ± 2.8 beats/min ($P < 0.05$), with no evidence of cardiac arrhythmia. These elevated values lasted approximately nine minutes. Fetal blood pressure and heart rate were not affected by the maternal bolus injections. Fetal acid-base indices also remained unchanged after bolus injection, the initial pHa being 7.41 ± 0.01 ; PaO_2 , 23 ± 3 torr; and PaCO_2 , 46 ± 1.2 torr.

Fig. 3. A typical recording of uterine blood flow, intra-amniotic pressure, heart rate and arterial pressure of the ewe, and fetal heart rate following a maternal bolus intravenous injection of terbutaline (250 μ g). Uterine contractions had been induced by continuous infusion of oxytocin.

2.3 Continuous administration of terbutaline to fetus

In four immature fetuses (gestational ages 125–135 days) blood pressure and heart rate remained essentially unchanged when terbutaline ($0.4\text{--}0.8\text{ }\mu\text{g/kg/min}$) was infused directly. Heart rate was 165 ± 15 beats/min before the infusion and 164 ± 11 beats/min afterward. Mean arterial pressure was 51 ± 3 torr before infusion and 50 ± 4 torr after. In these fetuses, the dose necessary to alter the heart rate was $4\text{--}10\text{ }\mu\text{g/kg/min}$. In contrast, in three near-term fetuses (143 days gestation) receiving terbutaline with a rate of $0.4\text{ }\mu\text{g/kg/min}$, heart rate rose from 157 ± 7 to 210 ± 29 beats/min, but blood pressure remained unchanged: 52 ± 2 torr before and 51 ± 1 torr after infusion. Fetal acid-base state remained unchanged throughout.

3 Discussion

This study demonstrated that terbutaline given to the ewe is effective in suppressing oxytocin-augmented uterine contractions without reducing uterine blood flow or causing adverse effects in the fetus, thus confirming earlier clinical trials in man, and investigations in primates and sheep [2, 3, 6, 7, 15]. Terbutaline activity is related to a capacity to stimulate the myometrium β_2 adrenergic receptors. The most commonly used β_2 -selective adrenergic agonists, orciprenaline, ritodrine, salbutamol, fenoterol (Th 1165a) as well as terbutaline have all been shown to be capable of suppressing labor. The risk of maternal tachycardia, hypotension or respiratory depression limits the use of isoxsuprine and its derivatives, non-specific β -adrenergic agonists and other tocolytics (including diazoxide, alcohol, magnesium sulphate [12, 13, 18, 20, 24]. In contrast, this study shows that terbutaline does not have an adverse effect on blood pressure in the pregnant ewe. Tolerance is limited only by a consistent increase in heart rate. This same limitation has been reported for salbutamol [17], fenoterol [16] and ritodrine [18] in man. Tachycardia is an even greater problem with orciprenaline, which may induce maternal sinus arrhythmias [16]. In patients treated with terbutaline, maternal heart rates did not exceed 120

beats/min, and troublesome palpitations rarely occurred [2, 15].

Many tocolytic agents may also cause fetal hypotension, tachycardia and acidosis. Terbutaline administration into the maternal sheep circulation in this study, on the contrary, did not harm the fetus. When the drug was infused directly into the fetal circulation, the dose response pattern in the mature fetus ($0.4\text{ }\mu\text{g/kg/min}$) was comparable to that of the ewe ($0.2\text{--}0.8\text{ }\mu\text{g/kg/min}$). This suggests that if terbutaline does cross the sheep placenta, the amount reaching the fetus falls short of the amount required to produce a cardiovascular response. Immature fetuses (125–135 days of gestation) tolerated systemic administration of terbutaline without signs of distress. In these fetuses, the dose required to elicit a change in heart rate was 10–25 times greater ($4\text{--}10\text{ }\mu\text{g/kg/min}$) than the amount used in the mature fetus or the pregnant ewe to produce a comparable change in heart rate. This suggests an age-related response to terbutaline, perhaps due to the fact that vascular adrenergic β_2 -receptors are not yet fully developed. The increase in heart rate seen in mature fetuses may be in response to peripheral vasodilatation and not to a direct β_1 effect on the heart. This, in fact, has been shown in maternal tachycardia, which was not found to be affected by the administration of the β_1 blocker, practolol [2].

It has been well documented that active labor reduces uteroplacental blood flow. Spontaneous as well as oxytocin-induced and prostaglandin-induced uterine contractions decrease uterine blood flow in the sheep [11, 21], the dog [4], the monkey [23] and man [5].

It is suggested that the reduction takes place primarily in placental circulation as myometrial flow is maintained [10]. In the present study, oxytocin-induced uterine contractions significantly reduced uterine blood flow by a 25% average. Infusion of terbutaline (rate I and rate II) tended to increase uterine blood flow, but in the absence of uterine contractions, the over-all effects of terbutaline on the uterine circulation were not statistically significant. Similarly, fenoterol [10] and ritodrine [8] which increase cardiac output, fail to influence uteroplacental blood flow in the pregnant ewe. The increase in uterine blood flow

with terbutaline is likely to be caused by an attenuation of uterine contractions. On the other hand, terbutaline at a high infusion rate (rate III) tended to produce a fall in uterine blood flow both in oxytocin-induced labor and when there were no contractions. As no correlations were found between these changes in uterine blood flow and changes in systolic blood pressure ($r = 0.204$), diastolic blood pressure ($r = 0.570$), pulse pressure ($r = 0.313$) or uterine activity ($r = 0.104$), we feel that the reduction in blood flow is probably mediated by a direct pharmacological effect of terbutaline on the uterine vasculature. These conclusions were also recently hypothesized for ritodrine infusion in sheep [9]. Any increment in tocolytic effi-

acy could be offset by drastic reductions in the placental blood supply. It is noteworthy, on the other hand, that bolus injection of 250 μg of terbutaline caused a 25% increase in uterine blood flow as it also immediately suppressed all uterine contractions. The fetal condition remained unchanged.

The series of separate investigations making up this study indicate that terbutaline, administered to the pregnant ewe for short periods and at no greater rate than 0.2–0.4 $\mu\text{g}/\text{min}$, is a reliable and safe tocolytic agent which does not harm the fetus. Maternal and fetal effects of the drug when administration is prolonged remain to be determined.

Summary

The effect of terbutaline on the immature fetus, as well as on the uterine activity and blood flow, were investigated before and during oxytocin-induced uterine contractions in ten pregnant ewes prepared for chronic studies. The drug was administered either into the maternal or the fetal circulation. Terbutaline was infused into the maternal femoral vein for 20 minutes at three sequential rates (0.2, 0.4 and 0.8 $\mu\text{g}/\text{kg}/\text{min}$) in four experiments when uterine activity was absent, and in eight experiments in the presence of well-established uterine contractions. In addition, a bolus injection of the drug was given in eight separate experiments: four with oxytocin-induced contractions and four without. In seven experiments, terbutaline was infused directly into the fetal jugular vein. Maternal and fetal blood pressure, heart rates and intraamniotic pressure were monitored throughout the study. Arterial blood samples were withdrawn at intervals from ewe and fetus simultaneously to measure pH, PCO_2 and PO_2 .

Intravenous infusion of terbutaline to the mother at rates of 0.2–0.8 $\mu\text{g}/\text{kg}/\text{min}$ increased maternal heart rate in all experiments and suppressed uterine contractions which had been induced by oxytocin. The changes were dose-related. Low dose terbutaline had little effect on maternal blood pressure or uterine blood flow, but at a high infusion rate the drug produced a fall in uterine blood flow both in oxytocin-induced labor and when there were no contractions. The reduction in uterine blood flow did not correlate with alterations in systolic or diastolic blood pressure, pulse pressure or uterine activity. The reduction

in blood flow is therefore probably due to a direct effect of terbutaline on the uterine vasculature. Bolus injection of 250 μg terbutaline caused a 25% increase in uterine blood flow and also immediately suppressed all uterine contractions. Tolerance of the drug was limited only by a consistent increase in heart rate.

When terbutaline was infused directly into the immature fetus at rate of 0.4 to 0.8 $\mu\text{g}/\text{kg}/\text{min}$, fetal blood pressure and heart rate remained essentially unchanged. In order to produce significant increase in the fetal heart rate and fall in blood pressure, 4.0 to 10.0 $\mu\text{g}/\text{kg}/\text{min}$ was necessary. In contrast, the near term fetuses responded promptly to the drug, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ producing tachycardia, but not hypotension.

Although other tocolytic agents such as ritodrine, salbutamol and diazoxide also cause fetal hypotension, tachycardia and acidosis, this study demonstrated that low-dose, short-term administration of terbutaline infused into the maternal circulation caused no significant changes in fetal blood pressure, heart rate or blood pH and gases, nor did bolus injection change the fetal condition. It was concluded that terbutaline is a reliable and safe tocolytic agent which, if infused at no greater rate than 0.2–0.4 $\mu\text{g}/\text{kg}/\text{min}$ and for short periods (20 minutes) does not cause adverse effects in the fetus. At a high dosage (0.8 $\mu\text{g}/\text{kg}/\text{min}$) there was a fall in uterine blood flow which appear to be a direct effect on uterine vasculature. Maternal and fetal effects when administration is prolonged are still unknown.

Keywords: Beta mimetics, sheep fetus, terbutaline, tocolysis, toxicity.

Zusammenfassung

Der Einfluß von Terbutalin auf den Schaffsfeten bei oxytocininduzierten Uteruskontraktionen

Wir untersuchten die Wirkung von Terbutalin auf den unreifen Feten sowie auf die Wehentätigkeit und die Durch-

blutung an 10 schwangeren Mutterschafen. Das Pharmakon wurde entweder in den mütterlichen oder fetalen Kreislauf gegeben. In 4 Experimenten wurde Terbutalin 20 Minuten lang in aufsteigenden Dosen (0.2, 0.4 und

0.8 $\mu\text{g/kg/min}$) in die mütterliche Femoralvene infundiert, ohne daß Uteruskontraktionen vorhanden waren. Bei 8 Versuchsanordnungen wurde ebenso verfahren, wobei hier jedoch kräftige Uteruskontraktionen zu verzeichnen waren. Zusätzlich wurde in 8 Fällen das Medikament als Bolus injiziert: 4 Tiere hatten oxytocininduzierte Kontraktionen, die anderen 4 nicht. Bei 7 Experimenten wurde Terbutalin direkt in die fetale Jugularvene infundiert. Wie registrierten während der gesamten Versuchsdauer mütterlichen und fetalen Blutdruck, Herzfrequenz und intraamniotischen Druck. Außerdem wurde arterielles Blut in bestimmten Intervallen sowohl vom Muttertier wie auch vom Feten für die pH-, pCO_2 - und pO_2 -Messung entnommen.

Die intravenöse Gabe von Terbutalin in Mengen von 0.2–0.8 $\mu\text{g/kg/min}$ erzeugte in allen Versuchen einen Anstieg der mütterlichen Herzfrequenz und unterdrückte die Wehentätigkeit, die vorher durch Oxytocin induziert wurde. Die Veränderungen waren dosisabhängig: eine kleine Dosis zeigte einen geringen Effekt auf den mütterlichen Blutdruck oder die Uterusblutung, während bei hohen Dosen die Durchblutung des kontrahierenden wie auch des nicht kontrahierenden Uterus gesenkt wurde. Die Durchblutungs-minderung korrelierte nicht mit Veränderungen des systolischen bzw. diastolischen Blutdrucks, der Pulsqualität oder der Uterusaktivität, sondern ist wahrscheinlich auf einen direkten Einfluß des Terbutalins auf die Uterusgefäße zurückzuführen. Bolusinjektionen von 250 μg Terbutalin verursachten einen Anstieg

der Uterusdurchblutung um 25 Prozent und unterdrückten ebenfalls sofort die Wehentätigkeit. Die Dosis wurde lediglich limitiert durch einen stetigen Anstieg der Herzfrequenz.

Wenn Terbutalin direkt an den unreifen Fetus in Dosen von 0.4–0.8 $\mu\text{g/kg/min}$ verabreicht wurde, blieben fetaler Blutdruck und Herzfrequenz grundsätzlich unverändert. Um eine Wirkung auf diese Parameter hervorzurufen, waren Dosen von 4.0–10.0 $\mu\text{g/kg/min}$ notwendig. Im Gegensatz hierzu reagierten die Feten am Termin schon bei Dosen von 0.4 $\mu\text{g/kg/min}$ sofort mit einer Tachykardie, jedoch nicht mit einem Blutdruckabfall.

Während andere Tokolytika wie z.B. Ritodrin, Sulbutamol und Diazoxid eine fetale Hypotension, Tachykardie und Azidose hervorrufen, ergibt unsere Untersuchung, daß niedrig dosierte, kurzzeitige Verabreichung von Terbutalin in den mütterlichen Kreislauf keine signifikanten Veränderungen im fetalen Kreislauf hinsichtlich Blutdruck, Herzfrequenz und Blutgaswerten bewirkt. Auch nach Bolusinjektionen bleiben die fetalen Kreislaufparameter unverändert. Wir schließen daraus, daß Terbutalin ein wirksames und sicheres Tokolytikum ist, welches in Dosen von 0.2–0.4 $\mu\text{g/kg/min}$ über 20 Minuten appliziert keine unerwünschten Effekte beim Feten verursacht. Nach hohen Dosen (0.8 $\mu\text{g/kg/min}$) sank die Uterusdurchblutung, wahrscheinlich als Folge einer direkten Wirkung des Terbutalins auf die Uterusgefäße. Welche Effekte eine Gabe über einen längeren Zeitraum bewirkt, ist noch nicht bekannt.

Schlüsselwörter: Betamimetika, Schafsfetus, Terbutalin, Tokolyse, Toxizität.

Résumé

Les effets de la terbutaline sur le fœtus de mouton pendant les contractions utérines maternelles déclenchées par l'ocytocine

L'effet de la terbutaline sur le fœtus immature, ainsi que sur l'activité utérine et sur le flux sanguin, ont été étudiés avant et pendant les contractions utérines induites par l'ocytocine chez dix brebis gravides préparées en vue d'investigations chroniques. La drogue fut administrée soit dans la circulation maternelle, soit dans celle du fœtus. La terbutaline a été perfusée dans la veine fémorale maternelle pendant 20 minutes en trois doses séquentielles (de 0.2, 0.4 et 0.8 $\mu\text{g/kg/min}$) au cours de quatre expériences sans activité utérine et au cours de huit autres à activité utérine bien établie. En outre nous avons appliqué la drogue au cours de huit expériences individuelles: quatre avec des concentrations induites par l'ocytocine et quatre sans. Au cours de sept expériences, la terbutaline a été appliquée directement dans la veine jugulaire fœtale. La tension artérielle maternelle et fœtale, les fréquences cardiaques ainsi que les pressions intraamniotiques ont été enregistrées pendant l'expérience. Les pH, PCO_2 et PO_2 ont été mesurés à des intervalles réguliers sur des échantillons sanguins de la brebis et du fœtus.

L'administration par infusion de terbutaline à la mère à des doses de 0.2 à 0.8 $\mu\text{g/kg/min}$ augmente la fré-

quence cardiaque maternelle dans tous les cas et supprime les contractions utérines induites par l'ocytocine. Les modifications correspondent aux doses appliquées. Une faible dose de terbutaline n'avait qu'un effet faible sur la tension artérielle maternelle ou sur le flux sanguin utérin, par contre une perfusion hautement concentrée provoquait la chute du flux sanguin utérin aussi bien au cours du travail induit par l'ocytocine qu'en l'absence de contraction. La réduction de la perfusion utérine n'est pas en corrélation avec les perturbations de la pression sanguine systolique ou diastolique, avec le pouls ou l'activité utérine. Ainsi la réduction de la perfusion utérine semble-t-elle liée à un effet direct de la terbutaline sur la vascularisation utérine. Les injections isolées de 250 μg de terbutaline entraînaient une augmentation du flux sanguin utérin de 25% et supprimaient en même temps toute contraction utérine. La tolérance du médicament n'affectait qu'une importante augmentation de la fréquence cardiaque.

Lorsque la terbutaline était perfusée directement au fœtus immature à raison de 0.4 ou 0.8 $\mu\text{g/kg/min}$, la fréquence cardiaque et la tension artérielle fœtales demeuraient pratiquement inchangées. Seules des applications de 4.0 à 10.0 $\mu\text{g/kg/min}$ induisaient des augmentations significatives de la fréquence cardiaque et des chutes de pression sanguine. Curieusement les fœtus

proches du terme accusaient une réaction plus rapide à la drogue, 0.4 microg/kg/min produisant une tachycardie mais sans hypotension.

Alors que les autres agents tocolytiques tels la ritodrine, le salbutamol et le diazoxide entraînent également une hypotension foetale, une tachycardie et de l'acidose, cette étude montre qu'une dose faible et une courte durée de perfusion maternelle de terbutaline n'entraîne point de modifications significatives de la tension sanguine foetale, de la fréquence cardiaque ou du pH et des gaz du sang, pas plus que l'injection unique ne change les conditions foetales.

Mots-clés: Béta-mimétiques, foetus de mouton, terbutaline, tololyse, toxicité.

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