J. Perinat. Med.
10 (1982) 119

Ritodrine concentrations in maternal and fetal serum and amniotic fluid

M. van Lierde, K. Thomas

Physiology of Human Reproduction Research Unit,
Department of Obstetrics and Gynecology, University of Louvain, Brussels

1 Introduction

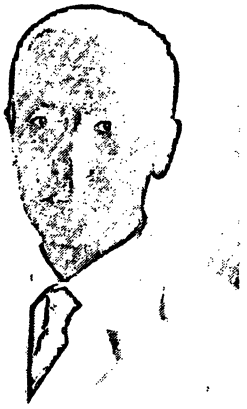
Ritodrine hydrochloride is a beta-sympathomimetic drug, with predominantly beta 2-effects, which is effective in the treatment of premature labor [6]. The compound may be administered intravenously, intramusculary or orally. It is inactivated by glucuronide and sulphate conjugation and excreted in the urine.

The placental transfer of ritodrine was initially suspected on clinical grounds, namely the increase in fetal heart rate associated with ritodrine infusion [1]. Using radioactively labelled drug, KLEINHOUT and VETH [5] demonstrated placental transfer in the sheep. In this model, fetal blood levels of radioactivity never exceeded 20% of those present in the ewe. These results are in accordance with similar investigations undertaken by COSMI [2]. However, data from studies using radiolabelled drug give no indication of the ratio between unaltered ritodrine and its conjugates. WEIDINGER [8] and WIEST [9] published results of diaplacental passage, using tritium-tagged fenoterol in legal abortions.

The development of radioimmunoassay for ritodrine [3, 7] permitted measurement of active drug without the inactive conjugates. In a study using the radioimmunoassay technique in pregnant women, GANDAR et al. [3] confirmed the placental transfer of ritodrine itself in humans.

The present study reports data on ritodrine concentrations in maternal and fetal serum and amniotic fluid, measured by radio-immunoassay. Samples were taken from eight patients undergoing elective cesarian section following intravenous infusion of ritodrine.

Curriculum vitae



MICHEL VAN LIERDE *was born in 1945 in Belgium. After obtaining his degree in Doctor of Medicine in 1970 from the Catholic University of Louvain (Belgium), he successively worked as assistant (1970–1972) and as "Chef de Clinique" (1973–1974) in the Department of Obstetrics and Gynecology under Prof.* R. GANDAR *and* R. RENAUD, *at the University Hospital of Strasbourg (France). From 1975 until 1977 he was attached to the University Hospital of Butare (Republic of Rwanda in Central Africa) in the programme for University Technical Cooperation, simultaneously he held the post of secretary of the faculty. Since 1977, he is in the Department of Obstetrics and Gynecology and the Physiology of Human Reproduction Research Unit (Prof.* K. THOMAS*) at the University of Louvain in Brussels. "Resident" until 1979, date when he was appointed "Chef de Clinique Adjoint". Fields of interest: Perinatology, beta-mimetics, and physio-pathology of the feto-placental unit.*

2 Materials and methods

2.1 Radioimmunoassay of ritodrine

Unlabelled ritodrine hydrochloride of pharmaceutical grade, tritiumlabelled ritodrine hydrochloride and anti-ritodrine serum were supplied by DUPHAR B. V., Weesp, The Netherlands.

0300-5577/82/0010-0119$02.00

The anti-ritodrine antiserum was tested for immunological cross reactions with: Isoxsuprine, fenoterol, salbutamol, terbutaline, hLH, hFSH, hCG, hCGα, hCGβ and relaxin. The only cross-reaction was with fenoterol, but even this was slight and not significant. Progesterone, 17β-estradiol, adrenalin, noradrenalin, albumin and prostaglandins E_2 and $F_2\alpha$ showed no interference with the assay procedure, details of which are published elsewhere [7].

2.2 Volunteers

Eight healthy, pregnant, women between 37 and 41 weeks of gestation and not in labor, who were to undergo elective cesarian section, agreed to participate after being fully informed on the aim of the study and the possible effects of ritodrine infusion. The indications for cesarian section were: Iterative (n = 4), pathological pelvis (n = 3) and a breech presentation (n = 1). The clinical, hormonal and echographical investigations gave no abnormal results or contra-indication to the administration of beta-mimetics.

2.3 Procedure

The patients were placed in the left lateral position and ritodrine infusion was started (Fig. 1). The infusion was controlled by means of a drop-by-drop regulation pump. The dose was 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the first 30 minutes, to assess maternal cardiovascular adaptation, and then 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 90 minutes (Total dose 420 $\mu g \cdot kg^{-1}$). Every 30 minutes maternal heart rate and blood pressure were measured, and a blood sample drawn from a

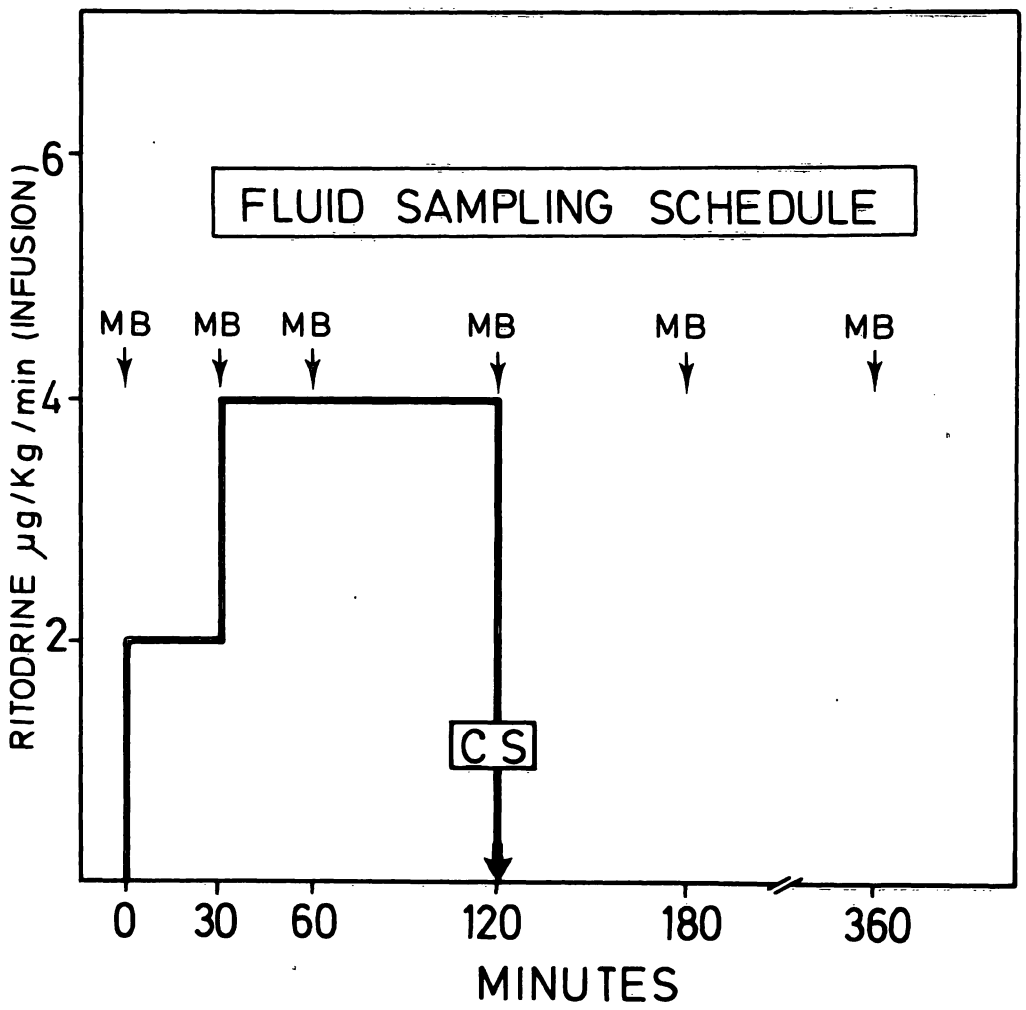


Fig. 1. Schedule of biological fluid sampling. MB = maternal peripheral blood sampling CS = time of cesarian section and uterine vein, umbilical artery and vein blood sampling, and amniotic fluid sampling.

peripheral vein for ritodrine assay. Surgical procedures started with patients in the half left lateral decubitus position. After anesthesia was established, the following procedures were carried out in rapid succession: ritodrine infusion stopped, peripheral blood sampling, laparotomy, uterine vein blood sampling, amniotic fluid sampling by amniocentesis, hysterotomy, fetal extraction, umbilical artery and vein blood sampling, child placed under pediatric care. All cesarian sections were performed by the same operator. One and four hours after anesthesia was established, maternal blood samples were drawn for ritodrine assay.

3 Results

3.1 Newborns

Tab. I shows the data for the newborn babies. All the children's weights fell within the 10° to 90° percentiles for gestational age. One baby had a one minute APGAR score less than 7 and another acidosis (pH < 7.15) related to maternal "hypoxic-hypercapnic" status during tracheal intubation. The course during the neonatal period was normal for all babies.

3.2 Ritodrine concentrations

Fig. 2 shows the development of the maternal ritodrine levels during the infusion and after its discontinuation. Tab. II shows simultaneous ritodrine concentrations in the maternal compartment (peripheral and uterine veins) and the fetal compartment (umbilical artery and vein, amniotic fluid) at the moment of cesarian section, i.e., after 2 hours infusion.

Tab. I. Parameters of the newborn.

Case	Birth weight	APGAR score		Umbilical artery		Weeks of gestational age	
N°	(g)	1'	5'	pH	Base-excess	Ame-nor-rhea	Du-bo-witz
1	2800	8	10	7.26	-13	37	37
2	2700	9	9	7.25	ND	38	38
3	3350	9	9	7.28	- 9	37	38
4	3100	9	9	7.32	- 5	39	38
5	3250	8	9	7.12	-12	41	40
6	3225	7	9	7.20	- 8	40	39
7	2950	10	10	7.28	- 6	40	38
8	3625	5	7	7.19	-11	40	40

4 Discussion

Our results, with respect to peripheral maternal blood, appear to agree with those of other authors. GANDAR et al. [3] infused six non-pregnant women with 150 $\mu g \cdot min^{-1}$ for 60 minutes and obtained serum ritodrine concentrations of 28.9 ± 2.5 ng/ml (mean ± SEM) at 20 minutes and 41.0 ± 1.9 ng/ml at 50 minutes.

Tab. II. Concentrations of ritodrine (ng/ml) in maternal and fetal compartments at the time of cesarian section.

Case	Maternal Compartment			Fetal Compartment			
	Peripheral vein	Uterine vein	Uterine vein/ peripheral vein ratio	Amniotic fluid	Umbilical artery	Umbilical vein	Umbilical vein/ maternal vein ratio
1	59	44	0.74	24	17	33	0.55
2	53	38	0.71	3	13	15	0.29
3	26	25	0.96	7	18	8	0.32
4	55	50	0.91	18	9	10	0.18
5	58	ND	–	6	14	15	0.26
6	61	42	0.68	26	24	25	0.41
7	62	22	0.35	19	12	7	0.12
8	60	42	0.70	19	20	20	0.34
Mean ± SD	54.2 ± 11.8	37.5 ± 10.3	0.72 ± 0.19	15.2 ± 8.7	15.8 ± 4.8	16.6 ± 8.9	0.30 ± 0.13

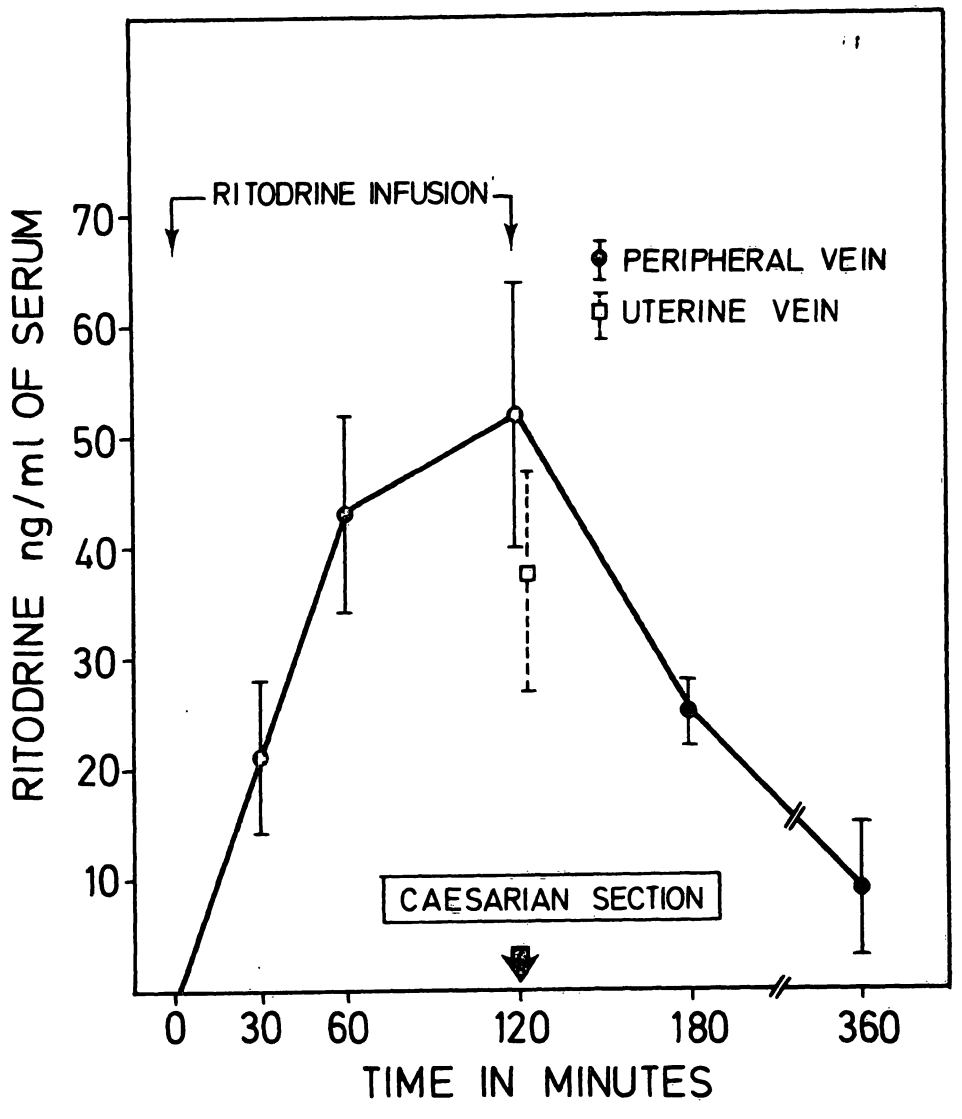


Fig. 2. Ritodrine concentrations (ng/ml) in maternal serum during and after ritodrine infusion.

Comparison of concentrations, after 2 hours infusion, between the peripheral venous blood and uterine venous blood, showed a significant difference ($p < 0.02$, paired-t test). The mean concentrations were, respectively 54.2 ± 11.8 ng/ml and 37.5 ± 10.3 ng/ml. This difference probably reflects the trans-placental passage.

In the fetal circulation, ritodrine levels in blood from the umbilical vein and artery did not differ significantly. The respective mean concentrations were 16.6 ± 8.9 ng/ml and 15.8 ± 4.8 ng/ml.

The mean ratio of fetal vein and peripheral maternal vein serum ritodrine concentrations was 0.30 ± 0.13 (mean ± SD). This is at variance with the results from GANDAR et al. [3] who found a mean ratio of 0.64 ± 0.25 (mean ± SD). However, comparison of results is hampered by the lack of standardization in the latter study. INGEMARSSON et al. [4] studied the concentrations of terbutaline in plasma after bolus intravenous administration of 250 μg during the second stage of labor. The found of mean ratio for mixed cord blood: Maternal vein blood of 0.36 ± 0.15 (mean ± SD). Finally, the similarity between mean concentrations in amniotic fluid (15.2 ± 8.7 ng/ml), umbilical arterial blood (15.8 ± 4.8 ng/ml) and umbilical venous blood (16.6 ± 8.9 ng/ml) is striking. **In as far as the ritodrine in the amniotic fluid originates in the fetal urine, these results suggest that the fetus does not conjugate this drug.**

Summary

Ritodrine hydrochloride concentrations were measured by radioimmunoassay in maternal and fetal sera and amniotic fluid from eight, pregnant, volunteers.
Each patient agreed to have 420 $\mu g \cdot kg^{-1}$ of ritodrine infused intra-venously over two hours prior to elective cesarian section. During infusion a blood sample was taken every 30 minutes from a maternal peripheral vein. Once anasthesia was established the infusion was discontinued. During surgery, samples were drawn from maternal peripheral vein, uterine vein, umbilical artery and vein, and amniotic fluid. All the children delivered were healthy and had a normal course during the neonatal period.
Ritodrine concentrations in maternal and fetal compartments at the time of cesarian section were 54.2 ± 11.8 ng/ml (mean ± S.D.) in maternal peripheral vein, 37.5 ± 10.3 ng/ml in uterine vein, 15.8 ± 4.8 ng/ml in umbilical artery, 16.6 ± 8.9 ng/ml in umbilical vein, and 15.2 ± 8.7 ng/ml in amniotic fluid. There was a statistically significant difference ($p < 0.02$, paired-t test) between the mean ritodrine concentrations in sera from the maternal peripheral vein and uterine vein. This difference probably reflects transplacental passsage. The mean ratio of fetal vein and peripheral maternal vein serum ritodrine concentrations was 0.30 ± 0.13 (mean ± SD).
The similarity between mean ritodrine concentrations in amniotic fluid, and sera from umbilical arterial and venous blood was striking. These results suggest that the fetus does not conjugate the drug.

Keywords: Amniotic fluid, betamimetic drug, fetus, placental transfer, radioimmunoassay, ritodrine hydrochloride.

Zusammenfassung

Ritodrine-Werte im mütterlichen und fetalem Serum und im Fruchtwasser
Durch ein radioimmunologisches Verfahren wurde der Ritodrinegehalt bei der Mutter und auch beim Feten bestimmt.
Acht freiwilligen Patientinnen wurde vor geplanter, termingerechter Sectio eine zwei Stunden dauernde Infusion 420 $\mu g \cdot kg^{-1}$ Ritodrine verabreicht.
Nach allmählichem Anstieg der mütterlichen Blutkonzentration von Ritodrine während der Infusion ergaben sich zum Zeitpunkt der Sectio folgende Werte: Im peripheren Venenblut der Mutter 54,2 ± 11,8 ng/ml; im Plexus venosus uteri 37,5 ± 10,3 ng/ml; für den Nabelstrang 15,8 ± 4,8 ng/ml im arteriellen und 16,6 ± 8,9 ng/ml in venösen Blut, sowie 15,2 ± 8,7 ng/ml im Fruchtwasser.
Diese Ergebnisse lassen auf einen statistisch signifikanten Konzentrationsunterschied zwischen dem mütterlichen Blutkreislauf und Plexus venosus uteri ($p < 0.02$) schließen. Dieser Unterschied spiegelt sehr wahrscheinlich den transplazentaren Übergang des Ritodrine wider.
Das Verhältnis der Durchschnittswerte in Nabelstrangvene und mütterlichem Blut beträgt 0,30 ± 0.13.
Schließlich wurde Ritodrine auch im Fruchtwasser nachgewiesen. Hier entspricht der Mittelwert dem des fetalen Blutes, was vermuten läßt, daß der Fetus die Substanz nicht abbaut.

Schlüsselwörter: Betamimetika, Fetus, Fruchtwasser, Radioimmunoassay, Ritodrine hydrochloride, transplazentarer Übergang.

Résumé

Concentrations de ritodrine dans le serum foetal et maternel et dans le liquide amniotique
Les concentrations de ritodrine ont été mesurées par technique radioimmunologique dans le serum maternel et dans le liquide amniotique chez 8 volontaires enceintes. Chaque patiente a reçu 420 $\mu g \cdot kg^{-1}$ de ritodrine en perfusion I.V. pendant 2 heures avant une césarienne élective. Au cours de la perfusion, un prélèvement sanguin a été pratiqué toutes les 30 minutes. A l'induction de la narcose, la perfusion a été stoppée et au cours de l'intervention, les prélèvements suivants ont été réalisés pour dosage de ritodrine: veine périphérique maternelle, veine utérine, artère ombilicale, veine ombilicale, liquide amniotique. Tous les enfants sont nés dans de bonnes conditions cliniques et biochimiques et ont présenté une évolution néonatale normale.
Les concentration de ritodrine dans les compartiments maternel et foetal au moment de la césarienne étaient les suivantes: 54,2 ± 11,8 ng/ml (moyenne ± D.S.) dans la veine périphérique maternelle, 37,5 ± 10,3 ng/ml dans la veine utérine, 15,8 ± 4,8 ng/ml dans l'artère ombilicale, 16,6 ± 8,9 ng/ml dans la veine ombilicale, et 15,2 ± 8,7 ng/ml dans le liquide amniotique.
Il existe une différence statistiquement significative ($p < 0,02$) entre la concentration moyenne de ritodrine dans la veine périphérique et dans la veine utérine. Cette différence reflète probablement le passage transplacentaire. Le rapport moyen veine ombilicale/veine périphérique maternelle dans la concentration de ritodrine est de 0,30 ± 0,13 (moyenne ± D.S.).
La similitude entre les concentrations de ritodrine dans le liquide amniotique, l'artère ombilicale et la veine ombilicale est étonnante. Ces résultats suggèrent que le foetus ne conjugue pas la substance.

Mots-clés: Béta-mimétique, foetus, liquide amniotique, radioimmunoassay, ritodrine hydrochloride, transfert placentaire.

Acknowledgement: This work was supported by a grant from the "Oeuvre Nationale de l'Enfance", (O.N.E.), Belgium.

Bibliography

[1] BARDEN, T. P.: Effect of ritodrine on human uterine motility and cardiovascular response in term labor and the early post-partum state. Amer. J. Obstet. Gynec. 112 (1972) 645

[2] COSMI, E. V.: Effects of beta-stimulants on maternal and fetal cardiovascular function and acid-base status, and on fetal breathing. In: BOMPIANI, A. et al., (Eds.): Recent advances on beta-mimetic drugs in obstetrics. Societa' Editrice Universo, Roma 1975

[3] GANDAR, R., L. DE ZOETEN, J. VAN DER SCHOOT: Serum level of ritodrine in man. Eur. J. Clin. Pharmacol. 17 (1980) 117

[4] INGEMARSSON, I., M. WESTGREN, C. LINDBERG, B. AHREN, I. LUNDQUIST, C. CARLSSON: Single injection of terbutaline in term labor: Placental transfer and effects on maternal and fetal carbohydrate metabolism. Amer. J. Obstet Gynec. 139 (1981) 697

[5] KLEINHOUT, J., A. F. L. VETH: Placental transfer of ritodrine and its effects on the fetal cardiovascular system. In: ESKES, T. K. A. B. et al. (Eds.): Aspects of obstetrics today. Excerpta Medica, Amsterdam 1975

[6] MERKATZ, I. R., J. B. PETER, T. P. BARDEN: Ritodrine hydrochloride A beta-mimetic agent for use in preterm labour. II. Evidence of efficacy. Obstet. and Gynec. 56 (1980) 7

[7] THOMAS, K., L. VAN KRIEKEN, M. VAN LIERDE: Characterization of ritodrine radioimmunoassay: Standard curves, cross reactions and serum levels. Gynecol. Obstet. Invest. (In press)

[8] WEIDINGER, H., W. WIEST, B. ZSOLNAI, J. SOMOGYI: Diaplazentare Passage von Partusisten. In: DUDENHAUSEN, J. W., E. SCHMIDT (Eds): Perinatale Medizin. Bd. VI. Thieme, Stuttgart 1975

[9] WIEST, W., H. WEIDINGER, B. ZSOLNAI, J. SOMOGYI, K. ROMINGER: Diaplacental transfer on partusisten in humans. In: WEIDINGER, H., (Ed.): Labour inhibition: beta-mimetic drugs in obstetrics. Fischer, Stuttgart–New York 1977

Received October 29, 1981. Accepted January 21, 1982.

M. van Lierde, M.D.
Physiology of Human Reproduction Research Unit
Department of Obstetrics and Gynecology
University of Louvain, UCL 5330
Av. E. Mounier 53
1200 Brussels – Belgium