

## PRELIMINARY STUDY OF RITODRINE—A UTERINE RELAXANT TO PREVENT PREMATURITY

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### Introduction

Prevention of prematurity is one of the most important avenues for lowering the perinatal mortality. Sixty-two per cent of perinatal deaths at K.E.M. Hospital are due to prematurity. Of 581 cases of prematurity studies during one year, no definite cause could be established in 73% of the cases. An effective drug to arrest premature labour and prolong the pregnancy is being searched for, particularly in the last three decades.

The present study deals with Ritodrine, a para-aminoephedrine group of drug having a specific action on the B—adrenergic nerve fibres of the uterus causing a decrease in the excitability and contractability of the uterine musculature. The effectiveness of this drug in the prevention of premature birth in two groups of cases has been studied.

The first group comprises of cases where premature labour has already set in and the second group comprises of

cases where there have been histories of two or more consecutive second trimester abortions or premature deliveries. The drug was given prophylactically to prevent premature labour in the latter group.

### Material and Methods

The first phase of the study was to assess the effectiveness of the drug on the uterine contractions in patients at or near term and to study the side effects, such as variations in maternal heart rate, blood pressure as well as foetal heart rate, etc. Twenty cases were given Ritodrine intravenously, 25 mgs. in 500 cc of 5% glucose at the rate of 15 to 30 drops per minute. The maternal heart rate and blood pressure as well as the foetal heart rate variations were recorded. The intensity, duration and frequency of uterine contractions were also recorded.

In the second phase, the efficacy of Ritodrine was evaluated in the two groups mentioned above.

*Group I*—Twenty-eight cases, where onset of premature labour had occurred were selected for this trial and put on parenteral therapy. After the active uterine contractions subsided, the patients were given intramuscular injections of 10 mgs. of Ritodrine 8 hourly. After 3 to 4 days of this therapy, patients

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were put on oral treatment, 10 mgs. 3 to 4 times a day. Patients with leaking membranes and cervical dilatation of more than 4 cms. were excluded from this study.

*Group II*—Eighty patients with history of two or more consecutive second trimester abortions and/or premature births were selected. Twenty-one patients had associated incompetent os for which tightening was done in 15 cases. Laboratory investigations such as haemogram, glucose tolerance curve (GTC), blood urea nitrogen and NPN, SGOT and SGPT (liver function tests) and creatinin clearance tests were carried out in the first 30 cases. In the latter half of the trial, serial urinary oestrogen estimations as well as urine cultures were done.

#### Results

Eighteen of the 20 patients who were given Ritodrine intravenously in Phase I study had cessation of uterine contractions within 10 to 45 minutes. There were marginal variations in the maternal heart rate and blood pressure. The foetal heart rate increased by 10 to 30 beats per minute but settled down within an hour or two in 80% of these cases.

In Phase II, in Group I, there were 28 cases where premature labour had already set in. Of 28 patients in this group, uterine contractions gradually decreased and ceased in 24 of them. The results are as shown below in Table No. I.

TABLE I  
*Outcome of Pregnancy*

Outcome of Pregnancy	No. of cases
Full term live births	15
Over 37 weeks gestation	4
Between 32 to 36 weeks gestation	2
Premature delivery	5
Abortions	2

Of the 7 cases of premature delivery and abortion, in 3 cases the uterine contractions had stopped but restarted within one to two weeks and the patients delivered prematurely. Of these, one baby could be salvaged, while 2 had neonatal deaths. In the remaining four cases, the drug did not act at all and the patients delivered. Two of them aborted, while 2 had premature delivery. One case had macerated foetus, one had mild antepartum haemorrhage, while 2 women were suffering from severe toxemia. From this we may conclude that these 4 cases were wrongly selected for trial of this drug.

In Group II, of 80 cases put on prophylactic Ritodrine tablets, treatment had to be discontinued in 4 cases as patients complained of considerable palpitation and giddiness. Eight more cases were lost to follow up. The outcome of remaining 68 cases is as follows (Table II):

TABLE II  
*Outcome of Pregnancy*

Outcome of Pregnancy	No. of cases
Full term live births	37
Over 37 weeks gestation	16
Between 30 to 36 weeks	4
Premature delivery	7
Abortion	4

Of the 68 cases mentioned above, 21 had associated incompetent Os. Fifteen of these had the operation of tightening of Os done during pregnancy and 6 of them were given conservative treatment of complete bed rest as well as Ritodrine. Three of the 6 cases treated conservatively delivered prematurely. The cases treated on oral tablets were given additional parenteral treatment when there were signs of uterine hyperactivity.

In the 30 cases where haemogram,

glucose tolerance, liver functions and kidney functions were studied, before and after the drug, no significant alterations were observed. Of 15 cases where serial urinary oestrogens were done, all showed normal increase of urinary oestrogens in pregnancy. Of 12 cases where urine cultures were done, all were negative.

#### Discussion

The onset of labour is a complex biological phenomenon controlled by multiple regulatory mechanisms which are only

with the success rate of 68%. The mode of action of this drug is not exactly known, though it is presumed to be an ADH inhibitor blocking oxytocin release.

Orciprenaline (Baillie 1970), mesuprine (Bardon 1971) and isoxsuprine (Hendricks *et al* 1961) are other beta-mimetic drugs which have been tried for arrest of premature labour with varying results.

The comparative results with the use of these drugs by various workers are shown in Table III.

TABLE III  
Comparative Effectiveness of Different Drugs (used i.v.)

Drugs	No. of cases	Successful cases	Failed	% Success
Orciprenaline	30	21	9	70
Alcohol	25	17	8	68
Mesuprine	17	9	8	52.9
Isoxsuprine	9	6	3	66.6
Ritodrine (present series)	19*	14	5	73.7

\* Only cases treated primarily with i.v. drip are included for the comparison.

partly known. All these regulatory mechanisms have their effect on the myometrial cells and are initiated through changes in extracellular ionic equilibrium. These changes are propagated through adrenergic transmitters, alpha receptors stimulating the contractions, and betareceptors inhibiting them.

Thus, in order to arrest uterine contractions beta-mimetic drugs would be useful. However, most of these drugs also have an effect on the cardiovascular system and are therefore of limited use. Ritodrine Hydrochloride, also a beta-mimetic compound, has a selective inhibiting action on the myometrium, with minimal cardiovascular effects.

Fuchs *et al* (1967) used ethanol intravenously to stop uterine contractions,

Ritrodine has been tried by various workers and Table IV shown the effectiveness of intravenous Ritodrine.

#### Summary and Conclusions

1. Ritodrine Hydrochloride, a beta-mimetic drug was tried on 108 cases.
2. No adverse effects of maternal heart rate and blood pressure as well as foetal heart rate were found.
3. The drug did not cause any significant variations in haemogram, glucose tolerance, liver function and kidney function tests.
4. Giddiness and palpitation required withdrawal of the drug in 4 cases.
5. The efficacy of the drug was found to be 70% in cases where premature onset of labour had already taken place.

TABLE IV  
Comparative Effectiveness of Intravenous Ritodrine Drip

Author	No. of cases	Successful	Per cent
Flynn	64	42	65.6
Sivasamboo	32	-	84.2 (33-35 weeks) 64.3 (upto 33 weeks)
Decolle and Vokaer	40	24	60
Present series	19	14	73.7

The cases on prophylactic treatment had 80% foetal salvage rate.

6. A double blind study of this drug is necessary and has been started in order to establish its effectiveness.

7. The cases with incompetent Os do not benefit by conservative treatment of bed rest and Ritodrine alone.

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