

DELAYING AN UNTIMELY DELIVERY

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Preterm labour is defined as the onset of labour before 259 days of gestation or 37 completed weeks.

When diagnosing a case of preterm labour, problems arise because of the difficulty in defining established labour. Labour is usually heralded by the onset of regular uterine contractions which produce effective cervical dilatation. Premature births account for a large fraction of perinatal mortality and morbidity. Despite major advances in neonatal care, retention of the foetus in utero is preferred in most instances.

It is often difficult to determine if premature birth is imminent, and 50% or more of patients who present with regular contractions will respond to simple bed rest. If this fails, a tocolytic may be administered. The desire to prolong intrauterine development must be balanced against the risks of continuing the pregnancy, for both the mother and the foetus. One must also consider the risks of pharmacological intervention in the particular patient.

In general, the use of tocolytic agents is reserved for those pregnancies where the gestational age is greater than 20 and less than 34 weeks. At more advanced gestational ages definite evidence of foetal immaturity should be sought. When the decision to use a tocolytic agent is taken, therapeutic success is most likely if cervical dilatation is less than 4 cm and cervical effacement less than 80%. Opinion varies as to whether tocolysis should be attempted in the presence of ruptured membranes. In cases of P.R.O.M. (premature rupture of membranes) however, the greatest risk to the neonate is the prematurity rather than infection.

Definite contra-indications include eclampsia or severe pre-eclampsia, premature detachment of the placenta, foetal distress and overt chorioamnionitis.

Various drugs have been used in order to suppress uterine contractions including intravenous ethanol. However, since it was shown that uterine relaxation is a sympathetic β_2 receptor function, pharmacological manipulation of the synaptic junction has been successfully attempted.

β_2 Adrenergic Agonists

These agents are preferred for the treatment of premature labour. Currently, only ritodrine is approved for this purpose in the USA. Ritodrine hydrochloride is available in a solution (10mg/ml) for I.V. administration and in 10mg tablet preparations. Treatment is initiated by the intravenous infusion of a solution of ritodrine (0.3mg/ml) at the rate of 0.1mg per minute. If tolerated, the dose is gradually increased (0.05mg per min. every 10 mins.) to a maximum of 0.35mg per min. or until labour is controlled. Once contractions cease, the infusion is usually continued for 12 hours at the rate attained. Oral therapy is begun 30 minutes before termination of the infusion by the administration of 10mg every 2 hours for the first 24 hours, followed by 10mg to 20mg every 4 to 6 hours. The total daily dose should not exceed 120mg. A number of other selective β_2 adrenergic agonists have been used in preterm labour, and include salbutamol, terbutaline, fenoterol and orciprenaline.

No tissue in the body is either strictly β_1 to β_2 , but the relative receptor concentrations vary in the various organs. Selective beta-agonist therapy is therefore associated with both β_1 and β_2 side-effects, of which probably the most important are the cardiac side-effects. The pulse rate of the patient is the usual dose-limiting side-effect of treatment.

With β_2 -agonist use in preterm labour there is a consistent rise in cardiac output, which reaches its highest value at 40 minutes from the initiation of therapy (56% over the control). To this, one must remember that the cardiac output naturally rises in normal pregnancies, reaching the highest value by the first trimester. This rise is mostly due to a rise in the stroke volume as opposed to the increase in pulse rate mediated by β -agonists.

The systolic blood pressure rises by about 12% during treatment with β -agonists while the diastolic pressure is decreased by about 10%. The result is a raised pulse pressure while the mean arterial blood pressure remains stable.

There are a number of situations where it is **considered unwise** to use β -agonists in the management of preterm labour:

1. Hyperthyroidism is considered to be a hyper-beta-adrenergic activity state. Theoretically a patient with this disease could be pushed into thyroid storm.
2. The patient with insulin-dependent diabetes mellitus; the risks to the patient with non-insulin dependent diabetes mellitus are far less.

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3. The asthmatic who is already on β -agonists; because their beneficial bronchodilating effects they may be at risk of a paradoxical response from excess adrenergic stimulation.
4. The patient who has congenital or chronic heart disease.
5. The hypertensive patient.
6. Monoamine oxidase inhibitors will modify the dosage of β -agonists used for uterine relaxation.
7. Chronic medical disease may result in placental insufficiency thereby contra-indicating prolongation of the pregnancy.

Maternal Side Effects

Many patients experience nausea and vomiting which may be central or secondary to an effect on the gastrointestinal tract (decreased motility). Other phenomena reported are allergic dermatitis, effects on the bladder detrusor reflex, and thrombocytopenia secondary to the effect on platelet adenylate cyclase activity. With use, β -agonists cause a decrease in the number of β -adrenergic receptor sites leading to tachyphylaxis.

The most dramatic complications of β -agonist therapy in the suppression of preterm labour which have been reported are pulmonary oedema (even fatal and especially associated with the use of fenoterol) and hyperglycemia which may lead to diabetic ketoacidosis.

Pulmonary oedema has been reported from single case reports and were associated with sudden stopping of the drug postpartum without the appropriate weaning with concurrent use of corticosteroids. At least two maternal deaths have been reported. One had an underlying viral myocarditis and the other congenital Dardiomyopathy. Patients with pulmonary hypertension or obstruction to the left ventricular outflow, such as with hypertrophic subaortic stenosis, could be at particular risk as the cardiac output increases. The use

of electrocardiograms in pregnant women about to be embarked on β -agonist therapy is strongly recommended in an effort to identify those at risk. Furthermore, total fluid intake should be restricted to less than 2 litres over 24 hours as overhydration will increase the chances of pulmonary oedema.

β -agonists cause hyperglycaemia by phosphorylation of liver glycolytic enzymes and cause hyperinsulinaemia by a direct stimulation on the pancreatic islet cell. This can be enough to cause diabetic ketoacidosis in an insulin-dependent diabetic. The concurrent use of corticosteroids will exaggerate the hyperglycaemia in the diabetic. However, with careful blood glucose monitoring during I.V. ritodrine therapy and appropriate exogenous insulin, euglycaemia can be maintained.

Hypokalaemia has also been shown to occur due to a concomitant influx of potassium into the cell because of insulin-dependent glucose movement and as a direct effect on the $\text{Na}^+\text{-K}^+$ pump. Correction of the hypokalemia occurs rapidly on stopping the transfusion.

As a result of β_1 -stimulated lipolysis there is a mobilisation of free fatty acids in the blood and glycerol as well. These are metabolised to acetoacetic CoA, which in turn is converted to aceto-acetic acid, β -hydroxybutyric acid and acetone. The presence of these ketone bodies in the blood stream will lead to acidosis.

Foetal Side-effects

Foetal tachycardia, acidosis and hyperglycaemia also occur as a result of β -agonists. Changes in foetal heart rate are inconsistent, occur later and return sooner to baseline than those of the mother. Foetal pH may decrease as a result of transplacental passage of fixed organic acids. Foetal hyperglycaemia results from maternal hyperglycaemia and as a result of a direct effect on the foetal liver. β -

agonists also have a positive effect on lung maturation producing a synergistic action with corticosteroids, if these are employed.

In conclusions, it is important to remember that although β -agonists can delay delivery for at least 24 hours and slightly reduce the proportion of preterm deliveries, they do not reduce the incidence of low birthweight or perinatal mortality.

Other Tocolytic Agents

Magnesium sulphate in doses higher than those used to treat pre-eclampsia, and **ethanol** (a 10% solution at a rate of 7.5mg/hr for 25 hours and 1.5mg/hr for a maximum of another eight hours) are effective alternatives. Most of the expertise in the use of magnesium sulphate, as for its use in pre-eclampsia, is in North America. The side-effects of ethanol have made it obsolete with the availability of better drugs.

Calcium channel antagonists are known to relax the myometrium in vitro and to inhibit markedly the amplitude (but not the frequency) of oxytocin-induced contractions. One such agent, nifedipine, appears to be effective in delaying parturition by 4 to 27 days. However, the available data are limited and the potential usefulness of nifedipine or related agents cannot be estimated at this time.

Inhibitors of prostaglandin synthesis, such as indomethacin, can prolong gestation in both term and preterm pregnancies, but their use in the management of premature labour has been curtailed because of concern in their potential to cause adverse effects in the foetus. Of particular importance is the possibility of premature closure of the ductus arteriosus and the development of pulmonary hypertension. This class of drugs may be much less hazardous if employed for brief periods at earlier gestational ages when there is less possibility of premature closure of the ductus.

The latest innovative approach is an **oxytocin inhibitor** introduced by Dr Akerlund in a pilot study in November 1987. The preparation is an analogue of oxytocin which acts as a competitive inhibitor of the action of oxytocin on the uterus. The greatest advantage of this approach is the absence of side-effects and if proven to be equally effective as beta-agonists, would obviously make it the drug of choice.

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