

Combination therapy

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Objective Inhibiting preterm labour at extremely early gestations.

Design Observational study. Case reports.

Setting Perinatal Centre Lund University Hospital, South Sweden.

Population Twenty-five women (13 cases with intact membranes and 12 cases with ruptured) with threatened preterm labour and advanced cervical status before 26 completed weeks of gestation.

Methods A combination of different drugs was used. Atosiban, an oxytocin antagonist, was the first line drug and was given as an infusion for several days as required. Supportive therapy was also given to most women with subcutaneous injections of the β -receptor agonist terbutaline (0.25 mg up to six times a day); sulindac, a prostaglandin synthetase inhibitor (200 mg one to two times a day up to a week); and broad-spectrum antibiotics (metronidazole and cefuroxime intravenously for three days and thereafter oral therapy).

Main outcome measures Prolongation of pregnancy more than 48 hours or 7 days. Neonatal survival.

Results Prolongation of pregnancy for more than 48 hours to enable administration of corticosteroid therapy was obtained in all but three cases. Eight women were delivered after more than a week from admission. Three neonates died at birth due to obstetric complication or sepsis. The other neonates had normal pH in cord or venous blood at birth. No severe side effects were recorded and in no case did the treatment have to be discontinued due to side effects.

Conclusion The policy described here is not evidence based, relating only to clinical observations, and as such is of very limited value. However, it seems that with this combined approach to management, some days can be gained by achieving full effect of corticosteroid treatment and prolongation of the pregnancy, hopefully reducing time in the neonatal intensive care in these critical cases. No severe side effects were reported.

INTRODUCTION

The majority of neonatal deaths occur after birth in those born before 37 weeks of gestation. The neonatal mortality rate in Sweden is close to 50% at 23–24 weeks of gestation but falls abruptly to 10–20% at 25–26 weeks of gestation.¹ After 27 weeks of gestation, the neonatal mortality is <5% (Fig. 1). There has been a dramatic decrease in neonatal mortality during the last 20 years in Sweden. The neonatal mortality at 25 weeks of gestation has been reduced to one-third from 1985 to 2002. These are national figures and not results from selected perinatal centres. Concerns have been raised that the improved survival rate may result in an increased number of handicapped infants and the time spent in neonatal intensive care is an important factor for the outcome. There is a considerable risk of cerebral palsy, chronic pulmonary insufficiency and other handicaps. Survivors without these handicaps have an

increased risk, compared with infants born at term, of non-optimal performance in school, decreased ability for abstract thinking and mathematical skill. The prognosis for infants born after extreme preterm birth (<26 weeks) or with extremely low birthweight has been evaluated extensively in recent reviews.^{2–4}

REASONS FOR STOPPING PRETERM LABOUR

Optimal perinatal and neonatal management is a prerequisite for the reduction of the risks outlined above. Referral of the mother with preterm labour to a perinatal centre is essential because at very early gestations the neonate has a better outcome if the mother is delivered in a specialised centre.⁵ The first aim of pharmacological intervention is to inhibit preterm labour in order to make transport of the mother to such a unit possible. Maternal and fetal complications such as placental abruption, advanced labour or fetal hypoxia may impede a referral. It has been reported that 85–90% of all births before 28 completed weeks can occur in a regional perinatal centre.⁶

The second aim is to stop labour for at least 48 hours so that corticosteroid therapy can be administered. There is a non-significant reduction in respiratory distress syndrome

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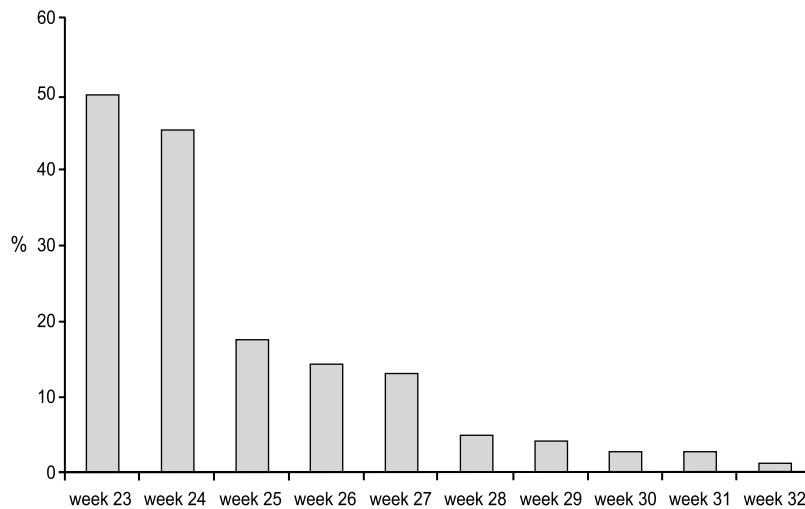


Fig. 1. Neonatal mortality (%) in Sweden 2001–2002.

if delivery occurs within 24 hours of the first injection of corticosteroid.⁷ So, it is of great importance to have access to a drug that will delay delivery for at least 48 hours.

The third aim is to prolong pregnancy, as every day gained is of importance at very early gestations. Between 23 and 26 weeks of gestation, the survival rate increases by about 3% per day⁵ and in Sweden (Fig. 1) that critical limit is between 24 and 25 weeks of gestation, when the survival rate increases considerably. We have tried by a number of means to give the mother the possibility of achieving this gestational age. The cerebral palsy rate also decreases sharply for every gestational week in this period.⁵ By prolonging pregnancy, it is also possible to reduce the period of neonatal intensive care with its inherent risks. In the neonatal ward of Lund University Hospital from 1999 to 2003, the time a newborn spent on a ventilator was an average of 23 days at week 23 but decreased to nine days at week 25.

In this paper, I present our experience with the aggressive treatment of preterm labour at very early gestations before 26 completed weeks. For over five years, we have been adopting a policy of combined treatment with different drugs and some clinical observations are outlined here.

WHICH TOCOLYTIC?

Myometrial contraction and relaxation result from the phosphorylation of myosin light chains regulated by intracellular calcium concentrations. There are uterorelaxant pathways mediated by agonists such as β -agonist drugs and nitric oxide (NO), or uterotonic pathways where inhibition of myometrial contraction is the result of an antagonistic action. Examples of such drugs are prostaglandin synthetase inhibitors, calcium channel blockers and oxytocin antagonists. Oxytocin antagonists have a twofold action by blocking the release of calcium from the intracellular

sarcoplasmic reticulum, but also by blocking the action of the second messenger diacylglycerol (DAG), which might promote cell contraction via intracellular prostaglandin synthesis from arachidonic acid by cyclooxygenase (COX) enzymes.⁸ One may speculate that attacking the contracting myometrial cell pharmacologically at more than one site might be more effective, even if a synergistic effect cannot be obtained. We have chosen to combine treatment with different drugs, including the oxytocin antagonist, atosiban, the β -receptor agonist, terbutaline and the prostaglandin synthetase inhibitor, sulindac.

Until the introduction of atosiban, β -agonists were commonly used for the inhibition of preterm labour. However, severe side effects, particularly pulmonary oedema, were not uncommon and have restricted the use of β -agonists, particularly for long term infusion. Risk factors for pulmonary oedema include infusion, for more than 24 hours, saline as a vehicle, infusion of more than 2 L, supine position and twin pregnancy.^{9,10} Infusions lasting more than 48 hours to ensure full corticosteroid administration carry a risk of severe side effects and may be unpleasant for the mother due to tachycardia and tremor. Such long infusions might be of importance for fetal outcome at these critical weeks. The large, multinational, randomised study comparing the effect of atosiban with β -agonists showed that discontinuation of therapy due to side effects was significantly more common during treatment with β -agonists than with atosiban.¹¹

Sulindac is an anti-inflammatory drug with an action similar to indomethacin. The first studies of fetal cardiac function and ductus arteriosus during indomethacin or sulindac therapy reported a reversible constricting effect of the fetal ductus arteriosus with indomethacin, but only a mild and transient constricting effect on the fetal ductus arteriosus with sulindac.^{12,13} Recent studies have suggested that sulindac may be comparable to indomethacin in these aspects.¹⁴

Table 1. Infusion with atosiban in 13 cases with intact membranes.

Case number	Gestational week at admission	Cervical dilation (cm)	Infusion time (hours)	Gestational age at delivery	Delay in days	Birthweight (g)	Mode of delivery	Cord pH	
								Artery	Vein
1	23 + 1	>5	46 + 63 + 12	25 + 1	14	1000	CS	7.23	7.32
2	23 + 2	3–4	44 + 24	27 + 6	34	1370	V	7.40	7.43
3	23 + 2	4–5	94	24 + 2	7	712	V	7.30	7.38
4	23 + 4	4–5	60	24 + 0	3	706	CS	NA	NA
5	23 + 4	4–5	66	24 + 0	3	590	CS	7.27	7.33
6	23 + 4	6	154	25 + 3	5	822	V	7.15	NA
7	23 + 5	9	180 + 43	25 + 0	12	835	V	7.14	NA
8	24 + 2	3–4	142 + 6	25 + 3	7	800	CS	7.36	NA
9	24 + 5	3	55	25 + 0	2	720	CS	7.32	NA
10	24 + 5	4–5	60 + 20	25 + 2	4	820	CS	7.34	NA
						958	CS	Tv I 7.31	
11	24 + 6	5	120	25 + 5	7	972	CS	Tv II 7.25	NA
12	25 + 2	3–4	17	25 + 3	1	834	V	7.28	NA
13	25 + 6	4–5	67	26 + 2	3	1010	V	7.33	7.38

All cases were also treated with antibiotics (metronidazole and cefuroxime intravenously) and intermittent doses of terbutaline 0.25 mg sc. Cases 4, 9, 12 and 13 with sulindac 200 mg orally.

NA = not available; CS = caesarean section; V = vaginal.

With atosiban, obstetricians now have the option of administering infusions for longer periods without severe side effects; therefore, the possibility of a more aggressive treatment policy has become possible. In our department, atosiban is the first drug of choice for the treatment of preterm labour. We have given atosiban continuously for up to a week, without reported side effects. In addition to atosiban infusion, the women have been given, in cases of recurring contractions, subcutaneous injections of terbutaline up to six times a day. The risk of severe side effects is much less after terbutaline injections intramuscularly compared with treatment by intravenous infusion, and only one case of pulmonary oedema (a twin pregnancy) has been reported so far after subcutaneous injections.¹⁵ Sulindac is administered orally 200–400 mg/day as required for up to seven days.

In addition to treatment with relaxant drugs, broad-spectrum antibiotics are given routinely for a week. The antibiotics chosen were metronidazole and cefuroxime, administered intravenously for three days followed by oral treatment. The rationale for this is that it is estimated that infection might trigger preterm labour in up to 40% of patients in these very early gestational weeks.¹⁶ In women with intact membranes, small randomised studies have shown a trend towards prolongation of pregnancy for seven days after prophylactic antibiotics,¹⁷ although the Oracle II study showed no prolongation of pregnancy or improvement in neonatal outcome compared with the placebo.¹⁸ The choice of drug has been criticised and treatment was often given late in pregnancy. The mean gestational age at entry to the study was 31+ weeks. Only 41.3% of the women received β -agonists and less than 10% were enrolled before 26 completed weeks. There is therefore uncertainty about the value of the Oracle II study when

evaluating the effect of antibiotics for prolonging pregnancy at very early gestations. In contrast, Oracle I showed significant prolongation of pregnancy and improvement in neonatal outcome in women with ruptured membranes in whom antibiotics were administered.¹⁹

CLINICAL OBSERVATIONS

The key case initiating our move to combination therapy was a woman at 23 + 5 weeks of gestation who was referred to us from another hospital (Table 1, case 7). The woman was in preterm labour and the cervix was dilated to 9 cm with bulging membranes.²⁰ She was given a continuous infusion of atosiban for 180 hours together with injections of terbutaline (0.25 mg subcutaneously, up to six times a day), sulindac (200 mg orally for six days) and broad-spectrum antibiotics. The contractions recurred, however, so another infusion treatment of atosiban, lasting 43 hours, was given. At 25 completed weeks, she delivered a male infant of 835 g with a cord artery pH of 7.14. The boy is healthy at two years of age.

Another 12 cases were given atosiban for up to 223 hours together with the supportive drugs (Table 1). They all were critical cases with preterm labour before 26 + 0 weeks of gestation. All had a cervical dilatation of 3 cm or more, effaced and with bulging membranes. The women would not have been eligible for a randomised study because delivery within a few hours after arrival to the hospital was anticipated. In all cases but one, the pregnancy was prolonged by two days or more so that corticosteroid therapy could take full effect. In one case, the pregnancy was prolonged by 34 days to 27 + 6 weeks of gestation. All the others were delivered at 26 + 2 weeks or earlier with a

Table 2. Infusion with atosiban in 12 cases with PPRM.

Case number	Gestational week at admission	Infusion time (hours)	Gestational age at delivery	Delay in days	Birthweight (g)	Mode of delivery	Cord pH	
							Artery	Vein
1	22 + 1	63	27 + 4	37	920–1126	CS	7.33– 7.35	7.33– 7.34
2	22 + 6	15	23 + 0	1	610	V	7.19	7.38
3	22 + 6	237	24 + 4	9	670 730	V	Neonatal death Neonatal death	
4	23 + 1	92	23 + 5	4	690	V	Intrapartum death	
5	23 + 3	108	26 + 1	17	790	CS	7.25	7.32
6	23 + 5	69	24 + 3	4	810	CS	NA	7.38
7	23 + 6	14	24 + 0	1	810	CS	7.30	NA
8	23 + 6	43 + 36	30 + 0	35	1600 1720	V	7.23 7.28	7.35 7.37
9	24 + 3	60	25 + 0	4	734	CS	NA	7.33
10	24 + 6	57	25 + 4		800	V	7.36	7.40
11	25 + 0	65	26 + 0	7	870	CS	7.23	NA
12	25 + 6	22	28 + 0	15	1158	V	7.40	7.43

All cases were also treated with antibiotics (metronidazole and cefuroxime intravenously) and intermittent doses of terbutaline 0.25 mg sc. Cases 1, 2, 3, 5, 7 and 11 with sulindac 200 mg orally.

NA = not available; CS = caesarean section; V = vaginal.

prolongation of 1–14 days, although most cases were delivered within one week. Eight women were delivered by caesarean section, either because of maternal indication (suspect abruption of placenta or chorioamnionitis) or fetal indication (breech presentation). pH levels in cord artery and vein at birth were obtained in most cases and showed normal results.

Women with ruptured membranes and threatened preterm labour before 26 weeks of gestation experienced more problems, even if they had less advanced labour than those with intact membranes (Table 2). In two cases, labour could not be stopped for more than 14 and 15 hours, respectively. In the other 10 cases, prolongation of pregnancy between 4 and 37 days was obtained. Caesarean section was performed in six cases due to the indications described above. pH values in cord artery and vein at birth were also satisfactory in this group of women. A woman with a twin pregnancy (case 3) was admitted with ruptured membranes and preterm labour at 22 + 6 weeks of gestation and was given atosiban continuously for 237 hours. On the ninth day of infusion at 24 + 4 weeks, the mother developed a high fever and signs of chorioamnionitis, and at birth the twins were in poor condition and in septic shock. They died soon after birth. One baby with a breech presentation died during delivery when the head was stuck in the cervix, which was not completely dilated. One woman with triplets and ruptured membranes at 22 + 1 weeks (case 1) had the pregnancy prolonged to 27 + 4 weeks and the neonates were in good condition at birth after a caesarean section.

No severe side effects were recorded with this policy of combination therapy and with very long atosiban infusion times. Maternal tachycardia and tremor were common after injections of terbutaline, but to a lesser extent than experienced during intravenous infusion.

CONCLUSION

The policy described here is not evidence based. It relates purely to clinical observations and as such is of very limited value. Unfortunately, it is probably impossible to perform randomised studies to evaluate this policy. Cases in the most critical weeks are few, even in perinatal centres, and to get a sufficient number of cases and randomise them between these different treatment arms seems impossible. From a clinical point of view, a limited period has been achieved in these cases of imminent preterm birth, which as far as we know could be beneficial for the baby. No severe maternal or fetal side effects have been recorded despite very long atosiban infusion times in combination with other drugs. One fetus died during delivery due to an obstetric complication and in the group with ruptured membranes a pair of twins died soon after birth from sepsis. The conditions of the other neonates at birth determined by pH levels in cord blood and vein blood were good. However, larger scale studies and long term follow up of the infants born in very early gestational weeks to mothers who have received tocolytic treatment similar to this seems mandatory.

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