

analysis of a total of 9 studies. There was no difference in the risk of preterm delivery in either group (OR 0.93, 95% CI 0.75, 1.08) or risk of delivery before 34 weeks gestation (OR 0.98, 95% CI 0.74, 1.19).

Conclusion:

The routine use of HUAM is not beneficial.

6. Future possibilities:

Electromyographic signals obtained from the uterus recorded on the lower abdominal wall by a newer technique under development and assessment may be helpful in the future.²⁷³

Collascope, a tool measuring auto fluorescence from the cervix reflecting collagen content, has been shown to predict labor in animal experiments. This may prove to be a useful tool in the future.²⁷³

Conclusions for early diagnosis:

Several methods have been employed for early diagnosis of preterm births. A combination of history, physical examination, biochemical tools and sonography may provide a better prediction. Diagnostic tools available to date have moderate predictive accuracy. Further research is needed.

B. Treatment:

It is not always possible to distinguish between preterm labor and preterm contractions. Allowing time may provide a clearer picture in some situations. The mainstay of management of threatened preterm labor has 3 objectives: 1) to prevent contractions, 2) to control contractions to allow maximum time to birth and 3) to improve fetal maturation before delivery. Gestational age also plays a vital role in decision making as a number of therapies given to the mother directed at the fetus can cause side effects and pose risks to the mother.

1. Bed rest:

Bedrest in hospital or at home is a very widely prescribed intervention for pregnancy complications. There is an increased risk of venous thrombosis, stress to the mother and cost to the health care system.

Gulmezoglu et al²⁷⁸ reviewed one study comparing bed rest versus ambulatory management in women suspected to have impaired fetal growth for the Cochrane Collaboration. There was no difference in the fetal growth parameters (RR 0.43, 95% CI 0.15, 1.27). The evidence was not strong in support of bed rest.

Goldenberg et al²⁷⁹ reviewed the use of bedrest for various obstetric conditions and found no evidence to support its efficacy. The authors concluded that there is insufficient evidence from either randomized controlled or observational studies to support bedrest to reduce preterm/LBW births.

Crowther et al²⁸⁰ reviewed 6 randomized controlled studies assessing the impact of bed rest for multiple pregnancy for the Cochrane Collaboration. There was no difference in the risk of preterm birth (RR 1.06, 95% CI 0.92, 1.20),

delivery before 34 weeks (RR 1.29, 0.87, 1.89) and LBW (RR 0.92, 0.83, 1.01) between bed rest and control groups.

Conclusion:

Any advantage of bed rest may lie in the degree of supervision but there is little evidence of improvement in uteroplacental blood flow. Currently there is no evidence to support routine use of bedrest for threatened preterm/LBW births.

2. Hydration:

Hydration with either oral fluids or intravenous fluids is a common practice for a mother admitted with a diagnosis of threatened preterm labor.

Biological Plausibility:

The biological mechanism is not clear but animal experiments have shown the following effects of hydration:

- Inhibition of antidiuretic hormone secretion following hydration and
- Plasma volume expansion.

Mothers admitted with preterm labor are often observed to be hypovolemic.

Excessive hydration may be counterproductive as subsequent use of beta mimetics for tocolysis may cause pulmonary edema.²⁸¹

Epidemiological evidence:

Ramsay et al²⁴⁵ reviewed two studies assessing the effect of hydration on preterm labor. In both studies no difference was observed between the groups receiving hydration with intravenous therapy compared to the bedrest only group.

Hearne et al²⁸¹ found no beneficial effect of hydration in four studies reviewed.

3. Sedation:

Ramsay et al²⁴⁵ reviewed the only study that randomized women in preterm labor to sedation and hydration compared to bedrest alone. There was no difference in cessation of contractions or preterm birth among the groups.

4. Tocolytics:

The use of tocolytics is widespread for women presenting with threatened preterm labor. Various tocolytic agents have been used.

Mechanism of action:

Different tocolytics have different mechanisms of action.²⁸¹

- Betamimetics: Act on β_2 receptors in the uterus and increase cyclic adenosine monophosphate in smooth muscles leading to a reduction in free calcium and thus inhibiting uterine contractions.
- Magnesium sulphate: Magnesium acts as a competitive antagonist to calcium entry into the myocyte and decreases myometrial contractility.

- Calcium channel blockers: Inhibit the influx of calcium ions through the muscle membrane and inhibit contractions.
- Prostaglandin synthetase inhibitors: Inhibit cyclooxygenase and decrease prostaglandin synthetase. This inhibits the conversion of free arachidonic acid to prostaglandins, which are mediators of uterine contractions.
- Nitroglycerin: It is a potent smooth muscle relaxant and relaxes the uterus.
- Oxytocin antagonists: Inhibit oxytocin, which is believed to stimulate uterine contractions.

Epidemiological evidence:

Several studies have evaluated the efficacy and safety of various tocolytic agents either with controls or with another tocolytic. The most important advantage gained by tocolytics is delay in delivery for at least 48 hours. This allows for administration and effectiveness of corticosteroids to promote fetal lung maturation.²⁸¹

Gyetvai et al²⁸² reviewed 17 randomized controlled studies of tocolytic agents vs. placebo or no treatment for women in preterm labor. Tocolytics (any) decreased the likelihood of delivery within 24 hours (OR 0.47, 95% CI 0.29, 0.77), within 48 hours (OR 0.57, 95% CI 0.38, 0.83) and within 7 days (OR 0.60, 95% CI 0.38, 0.95). Stratified analysis of various tocolytics showed a significant delay in delivery for at least 48 hours with betamimetics, indomethacin and atosiban. There was a significant increase in the maternal side effects such as palpitations, nausea, tremor, chorioamnionitis, hyperglycemia and hypokalemia. The benefits of prolonging the interval time between onset of threatened preterm labor and delivery were not translated into advantages during the perinatal period for the neonate.

Hearne et al²⁸¹ reviewed various studies on tocolytics. The studies reviewed compared placebo with tocolytic or one tocolytic with another. In 4 studies reviewed they found betamimetics to be effective in delaying delivery for more than 48 hours. Three studies on Magnesium Sulphate were also found to be efficacious but there was an increased risk of neonatal adverse effects. Two studies on calcium channel blockers revealed the effectiveness in postponing the delivery. Indomethacin was the most commonly used prostaglandin synthetase inhibitor for the purpose of tocolysis. It was effective in delaying the delivery but was associated with increased risk of closure of the ductus arteriosus in neonates. Ketorolac and Sulindac are other tocolytics not adequately examined in human studies. Nitroglycerin has not been tested in controlled human experiments. Two studies on Atosiban were reviewed which revealed similar efficacy as other tocolytics with fewer side effects. The studies lack power.

Moutquin et al²⁸³ performed a randomized controlled trial of atosiban and ritodrine for treatment of preterm labor. In a study involving 247 women Atosiban was as effective as Ritodrine in preventing preterm labor. Atosiban was well tolerated compared to ritodrine by mother and fetus.

Fisk et al²⁸⁴ performed a randomized controlled trial of Atosiban and Terbutaline in the treatment of preterm labor. Atosiban was shown to have similar efficacy as Terbutaline with a superior safety profile.

After successful tocolysis maintenance therapy may be needed. Sanchez-Ramos et al²⁸⁵ reviewed 12 randomized controlled trials. Meta-analysis of these studies revealed that maintenance tocolytic therapy was not associated with reduction in the rates of preterm labor or preterm delivery with pooled OR 0.95 (95% CI 0.77, 1.17).

Humphrey et al²⁸⁶ performed a randomized controlled trial of Sulindac for post tocolytic maintenance therapy. Sulindac was not effective in reducing the incidence of preterm labor after tocolysis.

Conclusion:

Tocolytics are effective in reducing the rate of delivery within 48 hours. This allows the administration of corticosteroids to the mother in an attempt to improve fetal lung maturity. The use of glucocorticoids in conjunction with tocolytics can be beneficial to the fetus. However, tocolytics have not reduced the risk of preterm/LBW births or improved neonatal outcomes. In addition, tocolytics are associated with maternal side effects. Further research of adequate power is needed to establish the safety profile of newer agents and their effect on neonatal outcomes.^{281;282;287}

5. Antibiotics:

The use of antibiotics is reviewed in the section on infections.

6. Cervical cerclage:

Cervical incompetence is a cause of preterm labor and preterm prelabor rupture of the membranes. With the advent of ultrasonography and measurement of cervical length prophylactic cerclage have been attempted in certain cases. A suture is placed around the cervix in an attempt to mechanically block the progress of labor.

Rust et al²⁸⁸ randomized 55 patients to the cerclage group, and 58 patients to the no cerclage group. Cerclage did not affect perinatal outcome. Readmission for preterm labor and infection were associated with early gestational age. The authors suggested that the cervical changes represent a severe pathophysiologic process probably not modifiable by cerclage.

Althuisius et al²⁸⁹ randomized 19 women with cervical length < 25 mm to the cerclage group and 16 to the bed rest group. Preterm delivery before 34 weeks was observed in 7 women in the bed rest group compared to none in the cerclage group ($p = 0.002$).

Conclusion:

Cervical cerclage can lead to adverse outcomes for fetus and mother. The results of the studies attempting cervical cerclage to mothers at high risk of preterm labor vary. Cerclage for women with short cervical length is not proven to be effective. Further research is needed.

7. Calcium channel blockers:

Calcium channel blockers have been attempted to improve blood flow to the fetus. Gulmezoglu et al²⁹⁰ reviewed one study assessing the efficacy of calcium channel blockers in fetus with restricted growth in utero. There was an increase in the mean birth weight in the treatment group compared to the placebo group (3291g vs 3011g, $p = 0.0024$). There was no difference in the rates of preterm birth (RR 0.55, 95% CI 0.22, 1.36). The evidence is insufficient to suggest the use of calcium channel blockers for improvement of the fetal growth.

8. Betamimetics:

Betamimetics may promote fetal growth by decreasing vascular resistance and increasing nutrient transfer across placenta. Gulmezoglu et al²⁹¹ reviewed 2 studies assessing effects of betamimetics for suspected impaired fetal growth for the Cochrane Collaboration. There was no difference in the risk of LBW (RR 1.17, 95% CI 0.75, 1.83). Further research is needed.

9. Antiplatelet agents:

Preeclampsia is an important cause of fetal growth restriction. Platelet aggregation is increased in women with preeclampsia. Antiplatelet agents have been used to reduce platelet aggregation. Knight et al²⁹² reviewed 42 randomized controlled studies of antiplatelet agents for pregnant women at risk of developing preeclampsia. The risk of preterm births was reduced in women who received antiplatelet agents (RR 0.92, 95% CI 0.88, 0.97). There was no reduction in the risk for SGA births (RR 0.92, 95% CI 0.84, 1.01).

Antiplatelet agents have shown benefit for mother and infant. Mothers at risk of developing preeclampsia may have potential benefit. It is not clear when this therapy should be started. Further research is required.

Conclusions for treatment:

Various measures have been attempted in the treatment of threatened preterm labor and IUGR in order to prevent delivery or enhance fetal growth. Bedrest and hydration are not shown to be effective strategies. Tocolytics are effective in prolonging the interval time to allow for administration of glucocorticoids to enhance fetal lung maturation. However, this has not resulted in any benefit to the fetus with respect to preterm/LBW births. Tocolytics are also associated with maternal side effects. Further research is needed to establish safety and efficacy of newer tocolytics. Prophylactic cervical cerclage needs to be evaluated in future studies. Measures to improve fetal growth by administration of calcium channel blockers and betamimetics have not shown benefit. Administration of antiplatelet agents to women at high risk of developing preeclampsia is effective, though the effect is very small and a large number of women are required to be treated. Further research is needed to identify high-risk women and the time of administration.

Another issue deserves attention in targeting treatments. Out of all preterm deliveries 20 - 25% of the births are induced for maternal or fetal reasons, and 25 – 40% occur following preterm prelabor rupture of the

membranes when any form of preventive measures are not indicated. Of the remaining 30 – 40% of idiopathic labors nearly half occur after 34 weeks gestation when treatment with tocolytics are not indicated. This leaves only 15 – 20% of all preterm births where any preventative measures may be beneficial.²⁴⁵

C. Multicomponent preterm birth prevention programs:

Multi-component programs aimed at prevention of preterm birth are undertaken in various settings. The following presents certain preterm birth prevention programs that have evaluated the impact of more than one component for prevention of preterm birth.

Armson et al²⁹³ evaluated a population-based preterm birth prevention program in Nova Scotia, Canada. The program was implemented between 1995-97 (n=24,572) and the results were compared with a historic cohort from 1993-95 (n=26,582). The program consisted of assessment of the risk of preterm birth based on a previously developed tool. Women were classified into high risk and low risk groups. The low risk group had risk assessment, review of warning signs for preterm labor and cervical examination at 20 - 24 weeks and 28 - 32 weeks and educational material was provided at 20 - 24 weeks. The high risk group received educational material, an educational session with the project coordinator, modified bedrest at home, weekly prenatal visits between 24 - 34 weeks, weekly cervical examination between 24 - 34 weeks, uterine activity monitoring by self palpation, and weekly telephone contact with the project coordinator. There was no difference in the overall rates of preterm births during the intervention period compared to the historical cohort period (RR 1.10, 95% CI 0.97, 1.23).

A multicenter randomized controlled study was performed in the US for prevention of preterm births in a low income population.²⁹⁴ Pregnant women at high risk for preterm labor were randomized to intervention and control groups. The women in the intervention group (n=1,200) received instructions from specially trained staff regarding early signs of labor, notification of medical staff regarding signs of labor, weekly pelvic examination from 20 - 24 weeks onwards, early and frequent observation of uterine activity for brief periods of 1 - 3 hours and prompt and aggressive tocolysis for all women with labor. The control group (n=1,195) received routine obstetric care. There was no difference in the observed preterm birth rates (16.2 vs 15.4% for < 37 weeks gestational age).

Hobel et al²⁹⁵ randomized clinics in Los Angeles, US to experimental (n=1,774) and control groups (n=880). The control group received standard antenatal care, which included clinic visits at 4-week intervals up to 30 weeks gestation, at 2-week intervals from 30 - 35 weeks gestation and at weekly intervals through to delivery. No education for warning signs of preterm labor was provided. The high-risk women, identified based on a scoring system, from experimental group clinics were offered a number of interventions, which included 2 weekly clinic visits and 3 classes regarding preterm birth prevention. In addition they were also randomized to one of four secondary interventions (bedrest, social support, progesterone or placebo). The preterm birth rate in the control group was 9.1% and 7.4% in the experimental group. The authors