Part 3: Secondary prevention

Secondary prevention for preterm/LBW/SGA/IUGR births involves early detection and treatment to delay the onset of labor. Most of the following represents methods of early diagnosis and treatment of preterm labor. Detection of IUGR by ultrasonography is incontrovertible. The measures to reduce IUGR are mentioned briefly.

A. Early diagnosis:

1. Education:

Educating pregnant women regarding early recognition of preterm labor is proposed as a strategy for early detection and appropriate medical attention. These programs are inexpensive as they can be provided to pregnant women during routine clinical visits so even a small gain could be advantageous.

Hueston et al[263] performed a meta-analysis of 6 studies reporting on the efficacy of preterm birth prevention educational programs for high-risk women. There was no difference in the risk of preterm delivery rates (RR 1.08, 95% CI 0.92, 1.27) or LBW (RR 0.99, 95% CI 0.88, 1.11). There was increased diagnosis of preterm labor (RR 1.71, 95% CI 1.41, 2.08). There were several limitations of this analysis. The studies were aimed at high-risk women, in some of whom it may not be possible to prevent preterm labor by educational interventions. The authors suggested that low risk women are likely to have idiopathic preterm labor and programs may be of more benefit in that population. The possibility that subjects in the control group may have received components of the interventions can not be ruled out.

Currently, there is no evidence to suggest that educational programs directed towards high risk women prevent preterm births.

2. Clinical markers:

a. Risk factors:

Attempts to identify preterm births based on clinical scoring systems have yielded poor results. Creasy et al[264] reported a scoring system based on risk factors in maternal medical and social history. The positive predictive value of this scoring system was 38%. Further studies using this scoring system have yielded poor results.

b. Cervical changes:

Prior to the onset of labor certain changes occur in the cervix of the uterus. Papiernik et al[265] evaluated 8,303 pregnancies by serial weekly observations of cervical changes. Cervical changes were observed 3 – 4 weeks prior to the onset of labor. Cervical dilatation of more than 1 cm was associated with 2 – 3 fold increase in the risk for preterm labor. The false positive values were not reported which makes it difficult to assess the findings.

Mortensen et al[266] examined cervical changes at 24, 28 and 32 weeks. In the low risk group (no associated risk factors) the positive predictive value for preterm births was 4% and in the high-risk group it was 25 – 30%.

Cervical changes observed prior to the onset of preterm labor are not highly predictive for preterm labor. In addition, they require frequent antenatal visits and examinations.

3. Biochemical markers:

a. Fetal fibronectin:

Fibronectin is a glycoprotein found in malignant tissues, fetal tissues, the placenta and amniotic fluid. It is produced by the chorion. Disruption of the choriodecidual surface leads to its release in cervical and vaginal secretions. It is present in the secretions from the vagina up to 21 weeks of gestation. The appearance of fetal fibronectin after 21 weeks has been shown to be associated with preterm labor. The presence of a minimal amount of blood in the sample, recent intercourse or digital examination can result in a false positive test. A careful collection of specimen by speculum examination is necessary.[267] Fibronectin assessment has been performed in women with or without symptoms of preterm labor.

Andersen et al[267] reviewed five studies reporting use of fetal fibronectin for the diagnosis of women with symptoms of labor. Three studies reported on prediction of labor within the next 14 days and all 5 studies reported predictive values for preterm labor before 37 weeks. In the three studies reporting the predictive values for delivery within the next 14 days, sensitivity ranged from 69 – 83%, specificity ranged from 79 – 83%, positive predictive value ranged from 17 – 41% and negative predictive value ranged from 95 – 99%. The relative risk ranged from 7.4 – 20.4. The results for the predictive values for labor before 37 weeks were a sensitivity range of 41 – 82%, specificity range of 81 – 96%, positive predictive value range of 45 – 83% and negative predictive value range of 76 – 92%. The ORs ranged from 2.5 – 9.1. The CI for OR in all studies was above one indicating usefulness of the test. Fetal fibronectin is a valuable tool in predicting women unlikely to give birth within 7 – 14 days of the test. The authors suggested an approach for pregnancy management based on fetal fibronectin results.

Andersen et al[267] reviewed 8 double blind studies reporting on the risk of preterm delivery in women without symptoms of labor. The study with largest sample size was from the US “National Institute of Child Health and Human Development Network - Maternal Fetal Medicine Unit - Preterm Prediction Study” in which 2,929 women were assessed for fibronectin levels biweekly from 22 – 24 weeks gestation. The relative risk of preterm delivery between 24 – 31 weeks if a woman was found to be positive for fetal fibronectin at 24 weeks was 21 (95% CI 14.3, 31.4). The test was found to be more predictive for early preterm (< 28 weeks) delivery. The predictive values for labor before 37 weeks from another 7 studies were sensitivity range of 18 – 93%, specificity range of 52 –

96%, positive predictive value range of 15 – 64% and negative predictive value range of 79 – 97%. The relative risk ranged from 1.0 to 7.6.

A subgroup analysis of the "Preterm Prediction Study" and another study by Wennerholm et al[268] revealed significant positive predictive values for fetal fibronectin assessed at 28 weeks in multiple pregnancies, which were at high risk for preterm labor.

Combinations of factors such as history of previous preterm birth, short cervix on ultrasound scan and fetal fibronectin were analyzed from the "Preterm Prediction Study".[269] For example, a woman with a previous history of a preterm birth with a normal cervical length had a risk of 7% for preterm birth if the fibronectin was negative, a risk similar to the normal population. A combination of fetal fibronectin with other tests may provide better predictive accuracy.

Conclusion:

The absence of fetal fibronectin is a strong indicator of women not having preterm labor in the next 7 – 14 days. Presence of fetal fibronectin in cervical-vaginal secretions is a moderate predictor for preterm labor within next 14 days. Presence of fetal fibronectin is a good marker for preterm labor at 24 - 28 weeks. A rapid test kit has been developed.

b. Estriol:

The level of estrogen increases prior to parturition. It is possible to detect rising levels of estrogen in maternal saliva. McGregor et al[270] noted a rise in salivary estriol levels 3 weeks prior to delivery in a prospective study. A threshold of 2.3 ng/dl had a sensitivity of 71% and a specificity of 77% for prediction of preterm labor. The same group of investigators [271;272] reported that serial salivary estriol predicts preterm birth 91% of the time. The relative risks for preterm delivery in women with estriol level $\geq$ 2.1 ng/dl was 3.4 to 4.0 for low risk, moderate risk and high risk for preterm labor.

Hayashi et al[273] reviewed the studies on salivary estriol in singleton and multiple pregnancies. The use of salivary estriol was moderately predictive for preterm labor in women with symptoms in both singleton and multiple pregnancies.

c. Corticotrophin releasing hormone (CRH):

CRH is presumed to play a role in the initiation of parturition and is increased before labor. Various authors have explored its association with prediction of labor. Ramsay et al reviewed the studies reporting on CRH for prediction of preterm labor.[245] Three studies found a positive association and one study found no association. Leung et al[274] using a cutoff value of 1.9 multiples of the median found a sensitivity of 73%, a specificity of 78%, a positive predictive value of 4% and a negative predictive value of 100% for preterm labor.

Further research is needed to establish the exact role of CRH in early detection of preterm labor.

d. Metalloproteinases (MMP):

The breakdown of the chorioamniotic membrane results in a release of metalloproteinases in the amniotic fluid and blood. Presence of MMP-2 and MMP-9 have been investigated for the correlation with preterm labor. The predictive power of MMP is limited.[274]

e. Cytokines:

Infection is one of the preceding events for preterm labor. Elevated levels of cytokines such as interleukins, ferritin and lactoferrin in various body fluids have been tested for their association with preterm labor.[274] All hospitals dealing with deliveries and birth may not have the capacity to assess levels of cytokines, which has prevented its widespread use. In addition, there have been inconsistencies in the results among various studies. Further research is needed.

f. Others:

Alpha- fetoprotein, human chorionic gonadotrophins, human placental lactogen, C - reactive protein, collagenases and cervical granulocyte elastase activity[274] have been studied for the prediction of preterm labor. Limited availability of these tests and lack of confirmation in other studies have precluded the results from being widely used.

4. Ultrasound markers:

Ultrasonography is used for assessment of the fetal well being and changes in the maternal lower genital tract. In addition, it is useful for identification of any previously unrecognized malformations. With labor, changes in the cervix start at the internal os. The cervical canal shortens as labor advances and at the same time the internal os opens. This process continues distally until the external cervical os joins the internal os and completes the effacement.[275] Investigators have attempted to predict preterm labor based on cervical changes on ultrasonography.

Colombo et al[275] reviewed the studies of a predictive association of cervical length with preterm labor. The "Preterm Prediction Study"[269] evaluated the cervical length of 2,531 women at 24 and 28 weeks gestation. The risk for preterm birth increased at a cervical length < 30 mm. Women with a cervical length of 30 mm or less at 24 weeks gestation had an increased risk of preterm labor (RR 6.19, 95% CI 3.84, 9.97) compared to women with a cervical length of 40 mm.

Taipale et al[276] evaluated 3,694 women between 18 – 22 weeks' gestation for cervical length and dilatation of the internal os. Women with a cervical length of $\leq$ 29 mm had an increased risk of preterm birth (RR 8, 95% CI 3, 19). Dilatation of the internal os of > 5 mm in addition to a cervical length $\leq$ 29 mm was associated with a significantly increased risk (RR 28, 95% CI 12, 67) for preterm birth before 35 weeks gestation. The sensitivity of this finding was only 29%. The presence of cervical funneling had a negative predictive value of 97%, which may be an important finding in the clinical context.

Colombo et al[275] reviewed 2 studies evaluating cervical length in women with symptoms suggestive of preterm labor. Cervical length > 30 mm was

associated with a low risk of preterm labor. Presence of cervical funneling was associated with 100% chance of preterm labor.

Colombo et al[275] reviewed 2 studies of women with multiple gestation and cervical length for prediction of preterm labor. The data from both studies suggested that the use of cervical length for the prediction of preterm labor is beneficial to restrict use of intervention. Further research is needed.

Cervical length has also been assessed for the prediction of preterm labor in conjunction with other markers (fetal fibronectin and history of previous preterm birth) as mentioned previously.

Conclusion:

The risk of spontaneous preterm birth seems to increase as the cervical length is reduced. Cervical length < 30 mm and funneling of the cervix have been shown to be associated with preterm birth. The measurement of cervical length as a screening tool is not justified. The finding of short cervix should be considered in the context of history, physical examination and biochemical markers.[275] It is still debated, however, whether the use of ultrasound has reduced the incidence of preterm births.[245]

5. Home uterine activity monitoring (HUAM):

Uterine activity is reported intermittently throughout pregnancy and it is increased in the third trimester. The monitoring of uterine activity has been proposed to predict preterm labor.[277]

Biological Plausibility:

Before labor (term or preterm) a pregnant woman experiences increased frequency of uterine contractions. Investigators have utilized an arbitrary cut-off of 4 - 6 contractions per hour as predictive of preterm labor. There is no recognizable consistent pattern of the uterine contractions and progression of preterm labor.[277]

Epidemiological evidence:

Devoe et al[277] reviewed 6 published meta-analyses or reviews of the major trials on HUAM. These reviews were reported between 1991 and 1995. These meta-analyses included 5 – 7 studies. The results or conclusions differed depending upon the primary objective of the review and the studies included. All the individual studies included in those meta-analyses lacked power. Two larger studies were published after these reviews. The intervention group in the studies received monitoring of uterine activity 1 – 3 times per day. Some trials had a component of home visits by a nurse, which made it difficult to assess which component was effective. HUAM was associated with increased frequency of referral for threatened preterm labor. The criteria for the diagnosis of preterm labor varied between the studies.

All the meta-analyses or reviews were performed before the publication of major randomized controlled studies. Devoe et al[277] included the latest randomized controlled studies in their assessment and performed another meta-

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 al[278] 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 al[279] 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 al[280] 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 al[245] 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 al[281] found no beneficial effect of hydration in four studies reviewed.

3. Sedation:

Ramsay et al[245] 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 al[282] 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, 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 al[281] 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 al[283] 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 al[284] 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 al[285] 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 al[286] 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 al[288] 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 al[289] 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 al[290] 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 al[291] 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 al[292] 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 al[293] 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 al[295] 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

indicated that low sensitivity and poor predictive power with more than 60% of preterm births occurring in women who were classified as low risk may be the reason for the failure.

Scott et al[296] conducted a multi-phased evaluation of a community-wide preterm birth prevention program (Perinatal Partnership Program of South Eastern Ontario). The program consisted of visits by public health nurses to all prenatal caregivers to stress the importance of teaching all women the signs of preterm labor. The caregivers were also provided with evidence-based guidelines for the use of tocolytics and corticosteroids for treatment of women with preterm labor. The evaluation included pre/post surveys of caregivers (n=107), pre/post surveys of postpartum women (n=102/100) and pre/post hospital chart review of administration of drugs and gestational age (n=38/40). There was significant increase in women's knowledge about preterm labor ($p < 0.001$) and their knowledge of the action to be taken ($p < 0.02$) in the event of signs and symptoms of preterm labor among women interviewed after the implementation of the program. Chart review to ascertain the use of tocolytics and corticosteroids did not show any difference in their usage before and after the implementation of the program. There was no difference in the gestational ages of the infants born to women who experienced preterm birth. The authors concluded that the lack of difference in the results could be attributed to a failure in the "React" (presentation at the hospital at the earliest signs of labor) or "Respond" (appropriate administration of tocolytics and glucocorticoids) components of the program.

Conclusion:

Multi-component preterm birth prevention programs are based on interventions that promote detection of the early signs of preterm labour, encourage the woman to seek medical attention, and promote the administration of a variety of medical interventions to reduce the risk of the initiation of labour. These programs are usually directed towards pregnant women classified as high risk. These programs have failed to reduce the rate of preterm births. One possible explanation for the failure may be that most of the interventions tested in these programs have not been shown to be effective in preventing preterm birth when used as a single intervention. Failure on the part of health care professionals to adhere to modalities considered to be effective needs further exploration.

Concerns about the safety of tocolytics on maternal health have prompted some tertiary care centres to reduce or no longer use currently available tocolytics and engage in studies to examine the impact of newer tocolytics on maternal and fetal outcomes. Therefore, until safe interventions are available that prevent initiation of an impending preterm birth or arrest a preterm labour in the early stages, preterm birth prevention programs, as they are presently conceptualized, are unlikely to reach their goal. However, it is still important to implement and evaluate strategies that help all women recognize the signs of early preterm labour and respond by seeking urgent medical attention so that

proper evaluation and management including glucocorticoids, which improve neonatal outcomes, can be administered as soon as possible.