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),