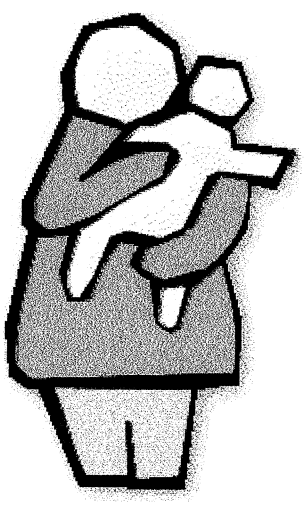
ACTUAL OPTIONS IN PREVENTION OF PRETERM LABOR



DEPARTMENT OF PREVENTIVE MEDICINE

APRIL - 2006

ELIN BERGH

ACTUAL OPTIONS IN PREVENTION OF PREMATURE LABOR

Preterm labor is labor occurring between 24th and 37th week of gestation. It is characterized by cervical effacement and/or dilatation, and increased uterine irritation. It is the leading cause of perinatal mortality and morbidity in the western world. In addition it is associated with massive neonatal and lifetime medical support costs.

It is important to discriminate between spontaneous preterm labor and iatrogenic/therapeutic preterm delivery. It is estimated that spontaneous preterm labor in otherwise uncomplicated singleton pregnancies accounts for about one third to one half of all preterm deliveries. Among premature newborns who survive, up to 5% have significant handicaps. Long-term sequelae include concentration problems in school, visual and hearing impairment, chronic lung disease, developmental delay, and cerebral palsy. The rate of preterm delivery has increased in recent years.

Risk factors (see table 1)

Specific maternal attributes increase risk of preterm delivery, though these factors need not be present for premature delivery to occur. The strength of the association of each identified risk factor has shown to vary. Women with a history of a previous preterm delivery are at highest risk of recurrence, estimated to be between 17 and 37 percent.
In most cases the precise causes of preterm labor are not known.

Although various risk scoring systems have been suggested, they have low positive predictive values, and are therefore of limited value in identifying women with a significant risk of preterm labour

TABLE 1

Risk Factors for Preterm Labor

- Previous preterm delivery
- Low socioeconomic status
- Non-white race
- Maternal age <18 years or >40 years
- Preterm premature rupture of the membranes
- Multiple gestation
- Maternal history of one or more spontaneous second-trimester abortions
- Maternal complications (medical or obstetric)
    - --Maternal behaviors
    - --Smoking
    - --Illicit drug use
    - --Alcohol use
    - --Lack of prenatal care
- Uterine causes
    - --Myomata (particularly submucosal or subplacental)
    - --Uterine septum
    - --Bicornuate uterus
    - --Cervical incompetence
    - --Exposure to diethylstilbestrol (DES)
- Infectious causes
    - --Chorioamnionitis
    - --Bacterial vaginosis
    - --Asymptomatic bacteriuria
    - --Acute pyelonephritis
    - --Cervical/vaginal colonization
- Fetal causes
    - --Intrauterine fetal death
    - --Intrauterine growth retardation
    - --Congenital anomalies
- Abnormal placentation
- Presence of a retained intrauterine device

Other ways of predicting preterm birth:

Cervical length

Clinical trials show that lesser cervical length means greater risk of preterm delivery. Before onset of labor, the cervix shortens and softens. Transvaginal ultrasound is used to detect these changes. The test should be performed at 24^{th}.-25^{th} week of gestation. A cervix length less than 2.5cm is indicative of preterm birth.

Fibronectin

Fetal fibronectin is an extracellular protein found in the fetal membranes, decidua and amniotic fluid. It functions as an adhesive between the developing embryo and the interior surface of the uterus. As the gestational sac implants, fetal fibronectin will normally appear in cervicovaginal fluid. The presence of fetal fibronectin in the cervix or vagina is infrequent after the 20th week (occurring in less than 10 percent of women) and rare after the 24th week. After the 24th week, the presence of fetal fibronectin may indicate detachment of the fetal membranes from the decidua.

Studies suggest that fetal fibronectin is a biochemical marker for labor. Some studies show that this is a more accurate indicator of preterm birth within seven days than both cervical dilatation and contraction frequency.

Many questions remain as to how to integrate the results of fetal fibronectin assays into clinical practise.

It is used some places today to predict preterm labor in high-risk women.

Home uterine activity monitoring

Home monitoring of uterine activity has been proposed as a diagnostic aid in reducing the incidence of preterm birth through early recognition of preterm contractions. Women who go on to deliver prematurely are more likely to exhibit increased uterine contractions 24 hours or more before the onset of delivery. A home monitor can identify these contractions

Whether there is significant evidence to warrant recommendation of routine or even selective use of home uterine activity monitoring in women at high risk for preterm labor and delivery remains a matter of controversy. Despite controversy over its efficacy, home uterine activity monitoring is currently licensed for the detection of preterm labor in women with a history of previous preterm deliveries some places.

Salivary estriol

There is evidence that measurements of salivary estriol may be predictive for onset of preterm labor. It may be used as a component of assessment of risk of preterm birth.

Primary, secondary and tertiary prevention

Most strategies used to prevent prematurity could be described as secondary or tertiary. Tertiary prevention has been directed at inhibiting the progress of labor with tocolytic drugs and treating PROM (premature rupture of membranes) with antibiotics. This is a short term measure as labor is already irreversible.

Primary prevention

Paediatricians and other health personnel can use primary preventive strategies to prevent behavioural characteristics that lead to prematurity.

Primary prevention would be to avoid pregnancy in adolescence, especially <16 years, avoidance of smoking and illicit drugs, avoidance of genital infections and good nutritional options.

Although this approach may be hard to accomplish, there are programs which have applied these strategies that have been effective.

The strategies include reproductive education in office and – clinic based settings in early teens and preteens years. In addition health personnel should participate in schoolbased educational programs.

Contraception

Reproductive education in early teen and preteen years. This should be offered in school and also clinics. All this to encourage use of contraception to prevent early, unwanted pregnancies.

The "morning-after-pill" is used after intercourse has taken place and before implantation has taken place. This pill is in some countries without prescription which makes it much easier to get for young people.

Smoking cessation programs

Cigarette smoking is known to have several adverse effects on pregnancy, one of them being its association with premature labor. Therefore, all patients who are smokers should ideally be offered information and access to as many smoking cessation programs as possible. While success rates for most programs seem to vary greatly, and success rates for quitting are known to be low, every attempt should be made and every patient must be fully informed. There are trials showing that more women manage to quit during pregnancy because they are highly motivated.

The possibilities of help with quitting are numerous these days and include: psycho-behavioral therapy and acupuncture.

Nutrition supplementation programs

Many have studied the effect of nutritional supplementation to prevent preterm birth. Most investigators reported no relationship between maternal nutritional status or interventions and duration of gestation.

Zinc, magnesium, and fish oil supplementations show promising results in reducing preterm birth, but the evidence is not strong. Calcium supplementation remains controversial, although one study showed significant reduction in preterm delivery in a subgroup of women at high risk of developing hypertension during pregnancy.

Increased iron intake is required during pregnancy because of the demand for iron from the developing baby and placenta as well as from the mother's own red blood cell expansion. Iron-deficiency anemia is one of the most common pregnancy complications. Iron deficiency has also been associated with low birth weight and preterm delivery.

Secondary prevention

Secondary strategies are to identify high-risk factors and trying to enhance the prenatal care. The secondary strategies include:

Treatment of bacterial vaginosis and UTI

Studies have confirmed that women who are found to be bacterial vaginosis positive during pregnancy have a significantly increased risk of delivering preterm over those with normal vaginal flora. Some studies implicate infection as a possible cause in up to 40% of the cases. The earlier in pregnancy at which this abnormal colonisation is detected, the greater is the risk of an adverse outcome

The normal type of vaginal flora of both pregnant and non-pregnant women is characterized by high concentrations of hydrogen-peroxide producing lactobacilli that by producing lactic acid, keep the pH of the vaginabelow 4.5, which discourages the growth of other organisms.. In bacterial vaginosis, the lactobacilli dominant vaginal flora is replaced by Gram negative anaerobic microorganisms, such as *Mobiluncus* and *Bacteroides* species, and microaerophilic organisms like *Gardnerella vaginalis.*. Factors responsible for the replacement of the lactobacilli dominant vaginal flora are unknown. It may be due to endocrine changes during pregnancy or antibiotics use.

Antibiotics should be used as early as possible in pregnancy. The problem is to decide who should receive the treatment. Today it is commonly given to women at high risk of preterm delivery and those in which vaginosis is diagnosed by culture of vaginal flora or clinical signs of vaginosis.

Consideration should be given to using a combination of different routes of administration of antibiotics. There is logic in using intravaginal antibiotics, because this is where the heavy load of microorganisms exists. If, however, some of these organisms have gained access to the decidua, then intra-vaginal antibiotics may not be of any benefit and systemic antibiotics may be necessary to eradicate those organisms which have already ascended into the upper genital tract. It seems that the best choice of antibiotics is metronidazole or erythromycin.

Also other infections like UTI of pregnant women should be treated and carefully followed up.

Cervical cerclage

Some of the preterm deliveries are thought to be due to incompetence of the cervix. The diagnosis of cervical incompetence is based on

- A history of recurrent abortions occurring after the 12th week of gestation, usually starting with painless leaking of amniotic fluid.
- The easy passage of a size 9 cervical dilator through the internal os of the cervix when the woman is not pregnant, and the absence of a "snap" on its withdrawal.
- The gradual dilatation of the internal cervical os to more than 3cm during pregnancy as detected by ultrasound or repeated vaginal examinations,

If cervical incompetence is diagnosed, cervical cerclage is applied. That means placing a soft unabsorbable suture around the cervix at the level of the internal cervical os. There are different techniques applied e.g. Mc.Donald and Shirodkar.
Also in subsequent pregnancies cervical cerclage should be applied to prevent preterm delivery.

Sometimes a rescue cerclage is applied between the 24th and 28th week of gestation, this is if specifically indicated. Amniocentesis improves the outcome of rescue cerclage.

Following cervical cerclage, 10% of women abort, 10% give birth prematurely and the remainder giver birth after the 36th week of pregnancy.
Cervical cerclage should not be made if the membranes have ruptured. If abortion becomes inevitable, the suture should be removed. In all other cases the suture is left until 7 days prior to term, at which time it is cut, and the woman may the be expected to give birth vaginally

Tertiary prevention

This is a short term measure as labor is already irreversible. It includes therapy with tocolytics and treatment of PROM to prevent infections.

Tocolytics

Tocolytic therapy may offer some short term benefit in the management of preterm labor. Once labor is established tocolytics can be administered to postpone delivery for at least 24 hours to allow for steroid-induced lung maturation to occur. This time can also permit mother to be transferred to hospital with neonatal intensive care facilities. No study has convincingly demonstrated an improvement in survival, long-term perinatal morbidity or mortality or neonatal outcome with the use of tocolytic therapy alone.

The women who are suitable to be treated with tocolytics are;

- The pregnancy is advanced to less than 35 weeks of gestation
- Preterm labor is confirmed
- The cervix is less than 5cm dilated
- The patient is not hypertensive, has no cardiac disease, is not diabetic, does not have abrupted placenta and is not infected.
- The fetus is alive and has no potentially lethal malformations that have been detected by US scanning.

-Calcium channel blockers

There are two types of calcium channels in the myometrial cell, the L type and the T type. Nifedipine binds to the inside of myometrial L type voltage dependent calcium channels causing them to remain closed, and hence inhibits contractility. However these channels are present in other smooth muscle cells. The T type channel is specific for myometrium . The drug mibefridal binds only T type channels and therefore inhibits myometrium specifically.

Trials show that nifedipine is more effective in postponing preterm delivery, leads to a better perinatal outcome and has lesser maternal side effects than beta-agonist ritodrine. Other advantages of nifepidine above ritrodine are easier administration (orally versus intravenously) and the fact that it is more safe in clinical practice.

-Prostaglandin inhibitors

Prostaglandins directly stimulate calcium channels on the myometrial cell membrane to open and allow an influx of extracellular calcium. They are produced from arachidonic acid by cyclooxygenases (COXs).

Indomethacin is a potent COX inhibitor and can therefore be used in the treatment of preterm labor. However, it inhibits both COX I and COX II and therefore poses a cardiovascular risk to the fetus and neonate. Trials of indomethacin versus ritodrine show that both treatments are equally effective in postponing delivery. There are fewer maternal side effects with indomethacin, but in 11% of trial participants oligohydramnios was noted. An increased rate of intraventricular haemorrhage and necrotising enterocolitis has been found in association with antenatal indomethacin use. There are also worries with regard to the effect of indomethacin on the ductus arteriosus and isolated reports of premature closure

-Magnesium sulphate

Magnesium sulphate inhibits voltage gated calcium channels from opening in response to action potentials. However, as a maintenance treatment, it does not appear to have any advantage over other treatments, and the problem of magnesium toxicity limit its use.

-Progesterone

Progesterone's mechanisms is inhibition of the oxytocin effect of prostaglandin F2a and stimulation of alpha-adrenergic receptors, thereby increasing the alpha-adrenergic tocolytic response. Natural progesterone appears to be free of any untoward teratogenic, metabolic, or hemodynamic effects.

Intramuscular injections are started at 12 to 16 weeks gestation and given until 37 weeks or delivery, whichever comes first.

The studies report different results. Some show significantly fewer women give birth before the 37^{th} week of gestation after taking progesterone. Some studies show the mean duration of pregnancy did not differ between those who took progesterone and those who don't.

Perhaps more importantly, treatment resulted in significant reductions in birth weight <2500 g, necrotizing enterocolitis, need for supplemental oxygen, and intraventricular hemorrhage

- Glyceryl trinitrate

Glyceryl trinitrate is a nitric oxide donor, causing smooth muscle contraction. It appears relatively safe and well tolerated. However it is relatively new and is yet to be assessed in trials.

Choice of tocolytics is difficult. And although tocolytics prolong pregnancy, they have not been shown to improve perinatal or neonatal outcomes and have adverse effects on women in preterm labor.

Tocolytic combinations do not work better than single agents and simply lead to multiplication of side effects.

Treatment of PROM with antibiotics

PROM frequently (50% of cases) predates preterm labor. It is also associated with chorioamnionitis. Prophylactic antibiotics should therefore be given. A combination of a penicillin or erythromycin and metronidazole is acceptable.

Summary

Unknown causes of preterm labor and difficulties in diagnosing it makes preventing preterm labor a difficult task.
Many measures have been tried with very different results.

Today the only measures that are really proven to prevent preterm labor are:

- treatment of vaginosis and other infections in pregnant women
- cervical cerclage in those with weakened cervix

By this means it is important to recognize infections of the mother and those who have a weakened cervix.

Primary prevention like education of teenagers is very hard to accomplish even though some studies show that they are successful.

Tertiary measures with tocolytics will help to postpone the labor for some hours or maximum days, but are not really preventing that the babies are born prematurely.

References

Iams JD, Johnson FF, Creasy RK. Prevention of preterm birth. Clin Obstet Gynecol. 1988 Sep;31(3):599-615.

Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Tocolytics for preterm labor: a systematic review. Obstet Gynecol. 1999 Nov;94(5 Pt 2):869-77

Owen, John MD a; Iams, Jay D.D. MD b; Hauth, John C. MD. Vaginal sonography and cervical incompetence. American Journal of Obstetrics & Gynecology. 188(2):586-596, February 2003.

Sarah Vause, Tracey Johnston. Management of preterm labour
Fetomaternal Medicine, St Mary's Hospital, Hathersage Road, Manchester M13 0JH, UK.
17 May 2000

McGregor JA, French JI, Lawellin D, Todd JK. Preterm birth and infection: pathogenic possibilities. Am J Reprod Immunol 1998;16:123-132.