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Preterm Birth

Definition

The World Health Organisation (WHO) definition of spontaneous preterm labour is labour resulting in birth before 37 completed weeks (259 days) of gestational age.[1]

Epidemiology

- Preterm birth accounts for 6-10% of all births and is a major contributing factor to neonatal and infant morbidity and mortality. The incidence of spontaneous preterm birth is rising, even in women who are considered to be low risk. This is confounded by the current lack of successful preventative measures. [3]

- Approximately half a million babies are born prematurely in the UK annually.[2]

- The UK has one of the highest rates of premature births in Europe.[2]

Risk Factors

Obtaining an accurate history is the first step of identifying a high risk woman.[3]

- Previous pre-term birth[3]
- Previous second trimester loss[3]
- Smoker[4]
- Socio-economic status (increased risk in lower social class)[4]
- Ethnicity (increased risk in Black and Asian mothers)[4]
- BMI (increased risk with low BMI i.e. <18)[4]
- Multiple pregnancy or higher order births[4]
- Age[3] (increased risk at extreme ends of reproductive age)
- Assisted conception e.g. IVF
- Previous surgery on the cervix (cone biopsy, forced dilatation of cervical canal)

Composite risk scores (which incorporated history, socio-economic status and lifestyle choices) have not found to be as useful as initially hoped. Outcomes have not improved because of the low sensitivity and lack of efficacy of the interventions. [3]
However, risk scores alongside **predictors**, for example fetal fibronectin, Actim Partus and cervical length (to be discussed), improve the sensitivity of identifying pre term birth, especially in women who are symptomatic. [3]

Asymptomatic women, who are considered to be at high risk of preterm birth, are monitored antenatally in a Preterm Labour Surveillance Clinic.

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Aetiology

SPONTANEOUS (70%)	IATROGENIC (30%)
Infection	Hypertension
Spontaneous rupture of membranes	Diabetes
Idiopathic contractions	Intrauterine growth restriction
Multiple pregnancy	
Cervical dysfunction	
Antepartum haemorrhage	
Stress	
Malnutrition	

70% of the causes of preterm labour are of a spontaneous cause, and it is these that are of importance as they could potentially be predicted and subsequently prevented.
There is much ambiguity about the aetiology of preterm birth, however ultimately; it is early maturation of the normal physiological process. This is namely cervical ripening, decidual membrane activation and uterine contractions. What causes this to occur early in some women, and not in others, is unclear and warrants the need for an accurate predictive test. [3]

Clinical Features

The following are the signs and symptoms of a women presenting with threatened preterm labour. Unfortunately, they are poor indicators of which women will actually give birth and those whose symptoms resolve and continue their pregnancy.[5]

- Pressure in pelvis
- Pre-menstrual like cramping
- Increased vaginal discharge
- PROM
- Contractions

Differential Diagnosis

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It is necessary to determine whether the mother is in actual pre-term labour or threatened preterm labour.

Investigations

There are two different settings in which investigation for pre-term labour is necessary:

1) Asymptomatic, high risk women in pre-term labour clinic
2) Symptomatic woman presenting to delivery suite at less than 37 weeks gestation.

There has been research into which predictive tests and investigations obtain the greatest predictive power. The existing techniques currently used are ultrasound cervical length measurement, Actim Partus and fetal fibronectin in the cervico-vaginal secretions.

Cervical length:
The role of the cervix is to provide mechanical strength and prevent ascending infection. The diagnosis and risk of preterm birth can be assisted through measurement of the length of the cervix. This is best achieved using transvaginal ultrasonography. This enables clinicians to examine the condition of the cervical canal in patients with contractions in order to determine who is at high risk of delivering.

Daskalakis et al conducted a prospective cohort study in Athens 2005. 172 singleton pregnancies symptomatic of preterm labour were given transvaginal ultrasonographic cervical measurement and followed up through their pregnancy. The primary outcome measure of the study was delivery before 34 weeks. The results showed that the positive predictive value (PPV) increased from 43.1% and 45.3% in those women whose cervical length was <35 mm on admission to 64% and 68.2% in those whose cervical length was <25 mm, in nulliparous and multiparous, respectively.
The shorter the cervical length, the greater the positive predictive value. i.e a shorter cervical length is a strong predictor preterm birth.

This fits with the converse results that the greater the cervical length, the higher the negative predictive value (NPV). A cervical length of 30mm and above has a NPV of 100% - this test will not misclassify a healthy woman at risk of preterm birth with a cervix at these lengths.
Therefore a long cervix (>30mm) can eliminate someone from being at risk of premature labour.

Fetal Fibronectin (fFN):
fFN is a glycoprotein found in the amniotic fluid, placental tissue and the extracellular component of the decidua basalis. It is produced by fetal cells and as it is found between the chorion and the decidua it can be regarded as an adhesive that binds the fetal sac to the uterine lining. If fFN is found to be present in the cervico-vaginal secretions, this can suggest that a pathological process has resulted in premature disruption of the chorio-decidual junction.[5]

Qualitative fFN testing uses a threshold of 50ng/mL and has a NPV of ~ 99% for predicting delivery at 7 days in symptomatic women.[5] This means fFN testing reliably predicts the women who won't deliver. This can lead to

targeted management and cost saving implications by reducing admissions and administering unnecessary treatment. However, fFN testing has a modest PPV of 20%, which means that many women are over-treated. A recent study by Abbott et al, April 2012 investigated whether using quantitative concentration levels of fFN improved the PPV of the test. This was a prospective observational cohort of 300 symptomatic women and the subjects were categorized into the following fFN concentrations: 0-9 ng/mL, 10-49 ng/mL, 50-199 ng/mL, 200-499 ng/mL, > 500 ng/mL. Their results showed that the rate of preterm birth is strongly associated with fFN concentration; the rate increased from 1.5% in the lowest concentration category to 75% in the highest.[5]

Changing the threshold from the conventional 50 ng/mL to 200 ng/mL led to a 2-fold increase in the PPV (31.8% to 61.1%) for the prediction of delivery at <34 weeks' gestation with minimal effect on the NPV (96.8% to 95.8%). The relative risk increased from 5.6 to 51.3 from the lowest to highest concentrations. [5]

These results have management implications as this could enable clinicians to tailor decisions and treat patients on an individual basis. Knowledge of fFN levels in symptomatic women may be used to support early discharge, allow steroid use to be more appropriate and targeted and make informed decisions on tailored in-utero transfers. Quantitative fFN levels can also be used in the antenatal setting as a monitoring tool through pregnancy progression.

Actim Partus:

Actim Partus test is another cervico-vaginal dipstick test for detecting the presence of phosphorylated IGFBP-1 (insulin-like growth factor binding protein) in cervical excretions. During the events preceding labour, fetal membranes start to detach from the decidua and (pIGFBP-1) leaks into cervical secretions. Therefore, its presence at less than 37 weeks gestation suggests preterm birth.[6] Paternosta et al 2007 performed a study of 108 symptomatic women and found that having a positive fetal fibronectin test increased the risk of preterm birth 6 fold.[7] Actim Partus is a cheap and quick test to perform, it gives a result in less than 5 minutes and costs £7-£10 per test in comparison to £50 for fetal fibronectin.[7]

Khambay et al 2012 have performed a pilot study in a London high risk surveillance clinic to compare the effectiveness of fFN to Actim Partus in asymptomatic women. Despite being a small pilot study it showed significantly better predictive power in favour of fFN. Sensitivity, specificity, PPV and NPV were consistently and considerably superior in comparison to Actim Partus. It appears this should be the test of choice in asymptomatic women. [6]

Management

A diagnosis of preterm labour leads to admittance to delivery suite. The hospital will then make sure that NICU is informed and there is adequate space for the premature baby.

Steroids

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The mother will be administered with antenatal steroids as these are associated with a significant reduction in rates of neonatal death, respiratory distress syndrome, intraventricular haemorrhage and are safe for the mother. 2 doses of 12mg Betamethasone are given IM, 24 hours apart if the women are between 24^{+0} and 34^{+6} weeks gestation. [8]

Tocolysis[9]

Those in current use include beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donors and oxytocin receptor antagonists. Ritrodine (beta agonist) and atosiban (oxytocin antagonist), nifedipine (Ca^{2+} channel blocker) are the most commonly used in the UK.

There is no evidence that tocolysis improves outcome therefore it is reasonable not to use them. The evidence shows that they are effective at reducing preterm birth for up to 7 days. Those who would benefit most are those who need to complete a dose of steroids, in utero transfer to a hospital with NICU, or those in very preterm labour.

Contraindications = any pregnancy complications eg chromosomal abnormality, intrauterine infection, placental abruption, severe pre-eclampsia, advanced cervical dilatation, fetal compromise, placental insufficiency.

Relative contraindications = mild haemorrhage due to placenta praevia, non-reassuring CTG, fetal growth restriction., multiple pregnancy, gestation less than 24 weeks. Although 24 weeks is seen as the age of viability, many centres will take babies born at less than 24 weeks on a case by case basis.

Adverse effects = palpitations, tremor, headache, N+V, chest pain, dyspnea. [9]

Cervical Cerclage:

Cervical cerclage first performed in 1902 in women with mid trimester miscarriages and spontaneous preterm births. Recent evidence suggest cerclage may provide a degree of structural support to a 'weak' cervix, its role in maintaining the cervical length and the endocervical mucus plug as a mechanical barrier to ascending infection may be more important.(10)

1) History-indicated cerclage

Insertion of a cerclage as a result of factors in a woman's obstetric or gynaecological history which increase the risk of spontaneous second-trimester loss or preterm delivery. Normally inserted electively at 12–14 weeks of gestation.

2.Ultrasound-indicated cerclage

Insertion of a cerclage as a therapeutic measure in cases of cervical length shortening seen on transvaginal ultrasound. Sonographic assessment of the cervix is usually performed between 14 and 24 weeks of gestation.

3)Rescue cerclage

Insertion of cerclage as a salvage measure in the case of premature cervical dilatation with exposed fetal membranes in the vagina.

4)Transvaginal cerclage (McDonald)

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A transvaginal purse-string suture placed at the cervicovaginal junction, without bladder mobilisation.

5)High transvaginal cerclage (Shirodkar)

A transvaginal purse-string suture placed following bladder mobilisation, to allow insertion above the level of the cardinal ligaments.

6)Transabdominal cerclage

A suture performed via a laparotomy or laparoscopy, placing the suture at the cervicoisthmic junction.

7)Occlusion cerclage

Occlusion of the external os by placement of continuous non-absorbable suture. The theory behind the potential benefit of occlusion cerclage is retention of the mucus plug

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