Fetal Fibronectin in Clinical Practice Guideline

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Brief Summary of Document:	Fetal fibronectin in clinical practice
Scope	

To be read in conjunction with:	

Owning group	Obstetric Written Documentation Review Group

Reviews and updates		
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1	New guideline	14.9.2017

Glossary of terms

Term	Definition
PTL	Pre term labour
PRM	premature rupture of membranes

Keywords	Fetal fibronectin in clinical practice

CONTENTS

1. INTRODUCTION

Spontaneous preterm birth occurs in 7-11% of pregnancies before 37 weeks' gestation and in 3-4% of pregnancies before 34 weeks' gestation.

Births prior 34 weeks of gestation cause most of neonatal mortality and morbidity. Frequency of bronchopulmonary dysplasia, intraventricular haemorrhage, retrolental fibroplasia, neurodevelopmental problems, and cognitive difficulties increases with the grade of prematurity. Incidence of spontaneous preterm birth has not decrease in the last decade, but there is effective management to reduce the associated complications. Antenatal steroids significantly reduced morbidity and mortality. Timely institution of such treatment in clinical practice depends on accurate prediction of spontaneous preterm birth.

2. SCOPE

This guideline only refers to women in threatened PTL with intact membranes. It does not include guidelines for preterm labour with preterm, premature rupture of membranes (PPROM). For this, please refer to the Hywel Dda PPROM guideline.

3. AIMS OF GUIDELINE

The aim of this guideline is to aid diagnosis, investigation and management of threatened preterm labour (PTL).

4. RISK FACTORS ASSOCIATED WITH SPONTANEOUS PRE-TERM BIRTH

Although the absolute cause of spontaneous preterm birth is difficult to identify in most individual cases, risk factors have been identified and include black ethnicity, vaginal bleeding during pregnancy, low body mass index, anaemia, certain vaginal or urinary tract infections during pregnancy, preterm contractions, multifetal gestation, a short cervix during pregnancy, and a history of a prior spontaneous preterm birth (Table 1). However, approximately 50% of women who deliver preterm do not have identifiable risk factors

Table 1. The Relationship Between Maternal Characteristics and Spontaneous Preterm Birth in Singleton Gestations

Risk factor	Relative risk for spontaneous preterm birth < 37 weeks
Black ethnicity	1.5
Body mass index < 19.8	2.5
History of a previous spontaneous preterm birth	2.7
Preterm contractions	1.8
Vaginal bleeding	1.5
Cervical length ≤ 2.5 cm	3.5
Positive fetal fibronectin test	3.3

Approximately 80% of preterm births are considered to be spontaneous as a result of either preterm labour or preterm premature rupture of membranes. The remaining 20% are medically

indicated preterm births, usually because of preeclampsia, intrauterine growth restriction, or other indications. There appear to be 4 major pathways leading to preterm birth, and an understanding is paramount to predicting and ultimately preventing preterm birth.

The four pathways are

(1) premature activation of the fetal or maternal hypothalamic-pituitary-adrenal axis,

(2) decidual or systemic inflammation,

(3) decidual bleeding, and

(4) pathologic distension of the uterus.

All four of these processes lead to a final common pathway of preterm labour/preterm premature ruptured membranes and spontaneous preterm birth.

5. SCREENING TOOLS TO DETERMINE RISK FOR SPONTANEOUS PRE-TERM BIRTH

Two tools have shown high accuracy in predicting preterm birth - cervical length measurement by transvaginal ultrasound and fFN testing.

i) Cervical measurement

A cut-off of 15 mm for cervical length (three studies, 1266 women, rate of preterm birth within 48 h 7.1%) predicted 71.1% (95% CI, 59.5 – 80.9%) of preterm births at < 48 h with a specificity of 86.6% (95% CI, 84.6–88.5%).

In women with cervical length of ≤ 15mm, one study found 51% delivered within 7 days. However if the cervical length was ≥ 16mm, only 1% delivered within 7 days.

Administration of progesterone in women with a short (< 15 mm) cervix can decrease the likelihood of preterm birth at less than 34 weeks gestation by 45%

ii) Fetal fibronectin (fFN)

Most accurate prediction of spontaneous preterm birth gives cervicovaginal fFN test.

FFN is a glycoprotein found in amniotic fluid, placental tissue, and the extracellular substance of the decidua basalis next to the placental intervillous space. It is thought to be released through mechanical or inflammatory mediated damage to the membranes or placenta before birth.

In normal pregnancy fFN is present in the vagina up to the fusion of the chorionic membrane with the maternal decidua at approximately 20 – 22 weeks of gestation. After this time the level of fFN then falls to below 50ng/ml. After 22 weeks of gestation, a level above 30ng/ml is thought to result from inflammatory or mechanical insult to either the placenta or the fetal membranes indicating separation of the chorion and the deciduas, and imminent delivery. Concentrations ≥50ng/ml during 23 – 35 weeks of gestation have been shown to indicate a greater risk of preterm delivery. Meta-analysis suggests that fFN has a sensitivity of 77% and a specificity of 87% in predicting delivery within 7 days in symptomatic women.

fFN test can predict imminent birth among women with symptoms of threatened spontaneous preterm birth but before advanced cervical dilatation and then antenatal steroids, tocolytics, and in utero transfer may be used accordingly.

Antenatal steroids are most effective in the 2-7 days after they are given.

fFN test is most accurate in predicting spontaneous preterm birth within 7-10 days after testing among women with symptoms of threatened preterm birth before advanced cervical dilatation. After a positive test result 17 symptomatic women at 31 weeks gestation would need to be treated with antenatal steroids to prevent one case of RDS.

If steroids were to be used for all symptomatic women at this gestation without fFN testing then 109 women would be treated with antenatal steroids to prevent one case of RDS.

Table 2. Cervicovaginal Fetal Fibronectin Among Symptomatic Women and Number of Women Needed to Be Treated at 31 Weeks of Gestation With Antenatal Steroids to Prevent 1 Case of Neonatal Respiratory Distress Syndrome Associated With Spontaneous Preterm Birth Within 7-10 Days of Testing

Test result	Probability of spontaneous preterm birth within 7-10 days of testing (%)	Risk for respiratory distress syndrome at 32 weeks of gestation	Rate of respiratory distress syndrome at 32 weeks of gestation (%)	Number needed to treat
No testing	4.5	0.53	2.0	109
Test positive	20.6	0.53	11.0	17
Test negative	1.0	0.53	0.4	509

6. IMPACT OF FFN TESTING ON PRETERM BIRTH OUTCOMES

Recent data have shown that provider knowledge of fFN results is associated with a lower incidence of preterm birth prior to 37 weeks of gestation. Several studies have also demonstrated a cost savings when fFN testing was used to evaluate women with symptoms of preterm labour. One study from USA demonstrated 40% less admissions with symptoms of preterm labour.

Different studies demonstrated similarly high negative predictive value of fFN test. Honest and colleagues found that in women symptomatic for preterm labour, a positive test was associated with a 20.6% risk for delivery within 7-10 days of testing, whereas a negative test was associated with a 1% risk for delivery in this interval of time.

A more recent meta-analysis- confirmed these findings: a positive test was associated with a 25.9% risk for delivery within the following week, whereas a negative test was associated with a 2.4% risk for delivery within the following week.

Thus, the primary benefit of fFN testing appears to be in its negative predictive value, its ability to identify patients who will not deliver within the following week and in whom interventions and hospitalization may be avoided.

FBS may not be appropriate when

- Fetal heart pathological
- Suspicious EFM pattern – consider instrumental delivery or emergency Caesarean Section

7. INITIAL ASSESSMENT

All women with suspected PTL should be assessed on labour ward.

A full history should be taken, including details on

- previous obstetric history
- previous medical history
- history of present pregnancy to date including gestational age from agreed EDD
- the start and timing of contractions
- any vaginal loss of blood or fluid
- urinary and bowel symptoms
- symptoms of systemic illness
- history of recent sexual intercourse

Obstetric examination should include

- abdominal palpation to determine the lie and presentation of the fetus
- symphysial-fundal height
- abdominal ultrasound examination *by a trained operator* to assess fetal viability, presentation, estimate fetal weight, measure the liquor volume and placental site
- any evidence of uterine, suprapubic or renal angle tenderness
- any palpable uterine contractions

Vaginal examination should then be performed

- pass a sterile speculum
- look for a pool of liquor, vaginal blood and cervical dilatation
- if appropriate a fibronectin swab should then be taken (see below)
- take swabs from the vaginal fornix (HVS), low vagina (LVS) and endocervical canal (Chlamydia) for infection screen
- if membranes are intact a gentle sterile digital examination can be performed to assess cervical effacement and dilation OR
- transvaginal ultrasound for cervical length if skilled operator available
- digital examination should be avoided if premature rupture of membranes is suspected

Investigations

- maternal pulse, BP, temperature and respiratory rate
- CTG (continuous ≥ 26 weeks)
- urine dipstick and MSU
- blood for FBC, CRP, G&S (and blood cultures, if temperature above 37.5^{o}

8. FETAL FIBRONECTIN ANALYSIS

Analysis to measure the fFN concentration in a swab taken of the cervicovaginal secretions is done using the automated Rapid fFN 10Q Analyzer, Hologic. The Fetal Fibronectin Test is an *in vitro* diagnostic test that uses a single-use, disposable cassette analyzed on the automated Rapid fFN 10Q Analyzer, to measure the fFN. The machine gives a result within 10 minutes of the swab being tested. The result is exact quantitative level of fFN and is marked as either Positive, Negative or Invalid.

Women transferred from another hospital via *in utero* transfer should have a fFN swab performed if they fulfil the criteria for testing and provided they have not had a fFN swab performed at their referral hospital. NOTE: If the woman has had a digital vaginal examination in the last 24 hours at the referring hospital, the fFN test may show a false positive result and be invalid. Testing for fFN

should be delayed until 24 hours after the digital vaginal examination. Transvaginal ultrasound can be used as an alternative method of predicting the risk of preterm labour, if a skilled practitioner is available.

Criteria for testing (all 3 conditions must apply):

- Women with signs and symptoms of PTL between 22 and 35 weeks of gestation
- Intact membranes
- Cervical dilatation < 3cm

Contraindications (do not test- test is not valid)

- Ruptured membranes
- Placenta praevia
- Placental abruption
- Moderate or gross vaginal bleeding
- Within 24 hours of sexual intercourse
- Within 24 hours after vaginal examination
- Cervical cerclage (especially within 4 weeks of cerclage placement)

All these situations can increase the false positive result (see later).

Avoid contaminating the cervicovaginal secretions with lubricants, soap, disinfectants, creams or jelly.

Use water to lubricate the speculum

Taking a fFN swab

The sample should be collected **before** digital examination is carried out. You will need:

- Sterile speculum
- Fibronectin swab
- Buffer solution
- Rapid fFN 10Q Analyzer, Hologic

  - Only use water to lubricate the sterile speculum (no cream or KY jelly)
  - Place the sterile Fibronectin swab provided in the fibronectin kits in the posterior fornix of the vagina for 10 seconds and rotate it
  - Remove swab and immerse it into the buffer solution for 10 – 15 seconds and remove it
  - Set up Rapid fFN 10Q Analyzer for the patient
  - Insert Rapid fFN Cassette into machine
  - Using a 1ml syringe pipette 200µl from the sample collected in the buffer solution into the well of the Rapid fFN Cassette
  - Complete the log book beside the machine with patient name, hospital number, date and your name
  - A result will be printed in 10 minutes
  - Get 2 copies of the machine print out and place one in woman's notes and the second in the log book next to the machine beside the patient name.

9. NEGATIVE FFN RESULT

It is reasonable to **withhold tocolysis and steroids if the fFN swab is negative**. Instead, the woman should be **observed on the labour ward for four hours** until the results of other investigations have been obtained.

- Analgesia should be prescribed as required.

- Inform and discuss with the woman and her partner, that her risk of delivering in the next 10 days is 1%.
- Educate on signs and symptoms of PTL.
- Discharge home if clinically well.
- Arrange antenatal follow up within 2 weeks with the woman's consultant

For women transferred from another hospital via *in utero* transfer who do not have fFN testing available at their referring hospital and who subsequently has a negative fFN test:

- discuss the case with the on call consultant obstetrician and consultant neonatologist
- consider transfer back to the referring hospital or discharge home depending on the clinical situation
- inform on call obstetrician from the referring hospital
- All relevant staff must attend appropriate training in performing Fetal Blood Sampling techniques and be familiar with and competent in maintaining the gas analyser

10. POSITIVE FFN RESULT

A symptomatic woman with a positive swab has an increased chance of delivering her baby preterm. Inform on call Consultant immediately.

- offer antenatal corticosteroids according to protocol below
- offer tocolysis according to protocol
- inform NNU and neonatal sister in charge

The neonatal SpR or consultant should counsel the woman and partner appropriately.

If there is no NNU cot available then in utero transfer should be considered. See Wales guidelines for in utero transfer.

11. INVALID RESULT

An invalid result means that either too little or too much buffer solution has been added to the cassette. The analysis can be repeated using the same buffer solution and a second cassette making sure that the person running the test is familiar with the Rapid fFN 10Q Analyzer. If the test is again invalid, then transvaginal ultrasound assessment of cervical length should be used as an alternative if there is a trained practitioner available (see below). If this is unavailable, the woman should be managed according to clinical judgement. Discuss with the on call consultant.

12. WHAT IS THE EFFECT OF DIGITAL VAGINAL EXAMINATION AND CERVICAL CERCLAGE ON FFN RESULTS?

The presence of a cervical cerclage or performing a digital vaginal examination before fFN testing increases the false positive rate, but does not reduce the negative predictive value of a test.

13. FURTHER MANAGEMENT

If there is evidence of ruptured membranes, follow the Hywel Dda PROM guideline.

If the cervix is ≥3cm dilated

- offer antenatal corticosteroids according to protocol below
- consider tocolysis according to protocol
- inform NNU and neonatal sister in charge

The neonatal SpR or consultant should counsel the woman and partner appropriately.

If there is no NNU cot available then in utero transfer should be considered. See Wales guidelines for in utero transfer.

Transvaginal ultrasound assessment of cervical length can be used to aid management if:

- fFN testing is contraindicated (eg digital vaginal examination done within 24 hours)
- fFN test result is invalid
- fFN test is negative but persistent uterine contractions still raise concerns that the woman is in PTL

A transvaginal scan should be performed by trained person. Women who have a cervical length at presentation of >15mm, consideration should be given to withholding steroids and to discharge from hospital.

For a woman transferred from another hospital via *in utero* transfer in whom fFN testing is contra-indicated and who subsequently has a cervical length > 15mm:

- discuss the case with the on call obstetrician and neonatologist
- consider transfer back to the referring hospital or discharge home depending on the clinical situation
- inform the referring hospital on call obstetrician

Antenatal Corticosteroids

- Antenatal corticosteroids should be offered to all women in PTL from 24+0 to 34+0 gestation in established preterm labour and in those with threatened PTL who have a positive fFN swab or a short cervix on ultrasound (≤15mm).

- If the pregnancy is less than 24 weeks of gestation, the decision for administration of maternal corticosteroids should be made after discussion with the consultant obstetrician on call and in conjunction with the neonatal team.

- From 34 to 36 weeks, there is some evidence of benefit and these cases should be discussed with the consultant obstetrician on call.

The regimen is 2 doses of betamethasone 12mg intramuscularly 24 hours apart.
The foetal half life of betamethasone is 12 hours. Accelerated courses (2 doses 12 hours apart) have not been shown to be of greater benefit and may increase side effects.
Contraindications

- Active tuberculosis

Caution

- Systemic maternal sepsis. In the presence of definite evidence of chorioamnionitis, the administration of betamethasone should first be discussed with the on call consultant and its relative merits and potential adverse effects discussed.
- In Gestational diabetes or type1/2 diabetes steroids can exacerbate hyperglycaemia and the course of steroids may need to be given in conjunction with extra doses of insulin (see Hywel Dda guideline on Management of diabetes in pregnancy).

Repeat courses of corticosteroids
If repeat courses of corticosteroids are being considered, consultant opinion must be sought. There is some evidence to support repeating corticosteroids if the first course is given very early in pregnancy. There is, however, mounting evidence that repeated courses can be harmful, associated with decreased birth weight and head size, sepsis and neonatal death.

14. AUDITABLE STANDARDS

1. No of women fFN positive who deliver in the next 7 days
2. No of women fFN negative who deliver in the next 7 days
3. No of women with cervical length ≤ 15mm on transvaginal ultrasound who deliver in the next 7 days
4. No of women with cervical length > 15mm on transvaginal ultrasound who deliver in the next 7 days
5. No of *in utero* transfers with fFN negative and do not deliver in the next 7 days
6. No of *in utero* transfers with cervical length > 15mm on transvaginal ultrasound and do not deliver in the next 7 day

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