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Fetal Fibronectin

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1. What is Fetal Fibronectin?

Fetal Fibronectin (FFN) is a glycoprotein produced by the chorionic membranes and is localized to the decidua basalis adjacent to the intervillous space. Its primary purpose appears to be that of an adhesion molecule (tissue glue) which helps bind the chorionic membranes to the underlying maternal decidua. Although it can normally be found in cervical-vaginal secretions until 22 weeks gestation, it is virtually never found in the window between 24 and 34 weeks gestation unless the cervix has undergone premature effacement and dilatation, usually in association with symptomatic uterine contractions. There is a strong association between the expression of FFN in cervical-vaginal secretions and preterm labour.

2. Summary of the Literature

Numerous trials have shown both an association between the presence of fetal fibronectin and preterm birth as well as a decrease in the risk of preterm birth when the test results for this protein are negative[3-6]. In a meta-analysis of 27 studies using delivery at <34 weeks gestation as the outcome, a positive fetal fibronectin test predicted likelihood of preterm birth at 61% with a negative test predicting the likelihood of continuation of the pregnancy beyond 34 weeks at 83%[9]. When individual risk factors for preterm birth were analyzed, the highest association with preterm birth followed a positive fibronectin test result, then a cervical length <25 mm., and then a history of preterm birth. The greatest usefulness of this test, however, appears to be in patients with symptomatic preterm labour and for whom the negative predictive value of the test ranges from 69 to 92% using 37 weeks of gestation as the outcome. Even more important, particularly when a decision to arrange a maternal transfer must be made within a short period of time**, a negative fetal fibronectin test confers a more than 95% likelihood of remaining undelivered for the 14 days following a negative test result.**[4,11,12]

In the past two years alone, there have been nine papers/posters presented at the Annual Meeting of the Society of Obstetrician/Gynecologists of Canada supporting the usefulness of fetal fibronectin testing, both in the tertiary care institutions where it reduces unnecessary maternal interventions and facilitates reverse transfer of patients, but also in primary care centers where point of care testing has been a useful adjunct in reducing the number of expensive maternal transfers. These abstracts involve an entire cross section of Canada from Nova Scotia in the East to Vancouver in the West. An as-yet-unpublished study from BC Women's Hospital confirms the highly reassuring negative predictive value of the test for symptomatic patients. A large Australian study using nine referral hospitals over an 18 month period and its tertiary care referral hospital was able to show a significant cost reduction by avoiding unnecessary maternal transfer.[2] In British Columbia, point of care testing costs less than $100 per patient. Each maternal transport, on the other hand, costs approximately $10,000 in terms of air transport, road transport, and specialized personnel, not to mention considerable safety issues when transfers need to be done in inclement conditions. Other issues to consider are the emotional

Fetal Fibronectin *cont. from page 1*

wellbeing of the mother displaced from her family/usual surroundings and the financial burden of finding domicile close to a tertiary centre, sometimes for weeks at a time.

One of the critical issues for British Columbia is that if point of care testing or biochemical laboratory testing for fetal fibronectin is undertaken, the additional cost of testing must be undertaken by the individual laboratory without accruing any of the benefit of the reduced utilization cost of maternal transport. Maternal transport costs rest currently under a different Ministry of Health budget and, unless some steps are taken at the Ministry level to ensure appropriate laboratory provision of such tests at peripheral sites, significant economic impact will not be realized. The negative impact of unnecessarily transferring a mother from her local community as well as subjecting her to possible multiple unnecessary interventions (tocolysis therapy, steroids, prolonged bed rest in hospital) cannot be underestimated in the face of an assay that has repeatedly shown its usefulness in this context in both Canada and abroad.

3. BCRCP Recommendation on FFN Testing

The BCRCP is presently advocating that peripheral centers gain access to this important laboratory adjunct and is making inroads to see that peripheral laboratory sites will be compensated for adding this testing scheme to their diagnostic armamentarium.

4. How is specimen collection done?

Fetal fibronectin specimens are collected during speculum examinations with a special FFN testing swab. The speculum exam should occur *before vaginal ultrasound*, *before digital examination* and *without the use of lubricants* as all of these can alter the predictability of the test. If vaginal ultrasound or digital exam has been performed on the patient, then it is advisable to wait 24 hours before obtaining the FFN specimen. As the protein is found in high concentration in amniotic fluid, the test is only advised in patients with symptomatic preterm labour (low abdominal pain and/or cramps, low backache, pelvic pressure, regular uterine contractions) *WITHOUT RUPTURED MEMBRANES.*

A rapid FFN testing device is available to facilities and allows FFN results within one hour of testing depending on the laboratory protocol. Results are reported as positive ($\geq$ 50 ng/ml) or negative ($<$ 50 ng/ml).

There are several potential confounding factors that can decrease the accuracy of the FFN test. A false – positive test may result from: 1) digital examination prior to the speculum exam, 2) more than a minimal amount of blood in the specimen as FFN is in plasma, 3) the presence of amniotic fluid (which contains FFN) in the specimen, or 4) the patient having had intercourse within the previous 24 hours (FFN can be found in seminal fluid). False – negative tests may be caused by the use of lubricants on the speculum.

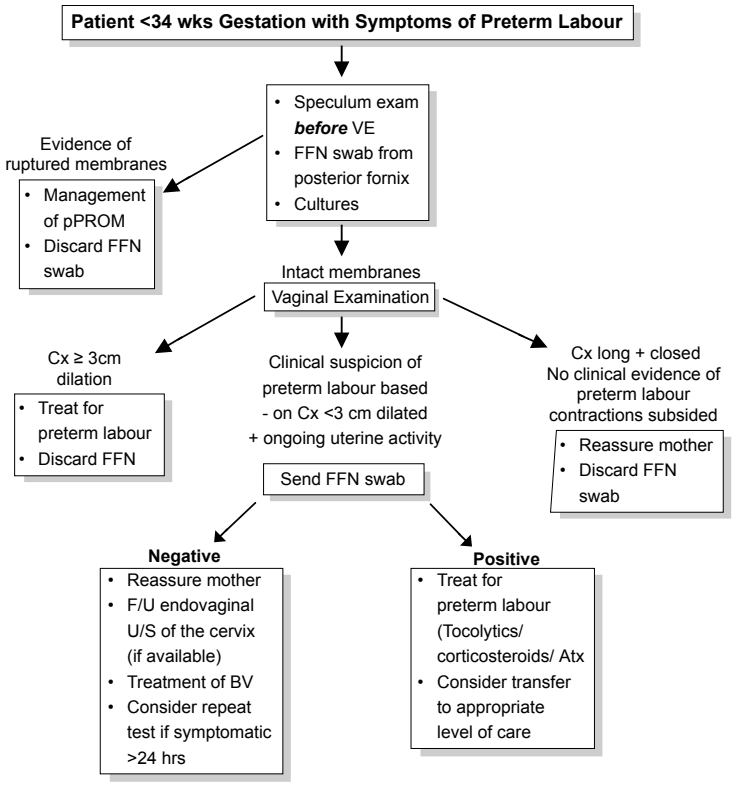
5. What should I do if the FFN comes back positive?

A positive test in association with symptoms of preterm labour and cervical change suggests a high enough risk of preterm delivery that the woman should be treated and transferred to an appropriate facility to care for a neonate of the expected gestational age. If the woman is in an urban tertiary centre, then management plans including consideration of tocolytics, administration of corticosteroids, etc. may be undertaken.

6. What should I do if the FFN comes back negative?

A negative test provides greater than 95% probability that the woman will not deliver within the next 14 days. Consideration should be given to having her stay in her community and treatment with tocolytic therapy and corticosteroids would not be justified. The patient should be educated about preterm labour symptoms and advised to avoid activities that aggravate her symptoms. She should receive close follow-up care including vaginal cultures for bacterial vaginosis (BV). Oral treatment with metronidazole should be provided if cultures are positive for BV. If accessible, an endovaginal ultrasound for cervical length should be obtained as part of follow-up. Cervical length greater than 2.5 cm is further reassurance that the patient will not deliver preterm. The data demonstrate that a negative predictive value of the test decreases with time and reevaluation should be considered if the patient continues to have symptoms suggestive of preterm labour[16].

Fetal Fibronectin Flow Chart



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