Obstetric Guideline 2A

PRETERM LABOUR

This guideline has been divided into two parts. Part A addresses general preterm labour management, and Part B addresses specific management issues of the mother/fetus and newborn near the threshold of neonatal viability (22-25 completed weeks).

1. DEFINITION

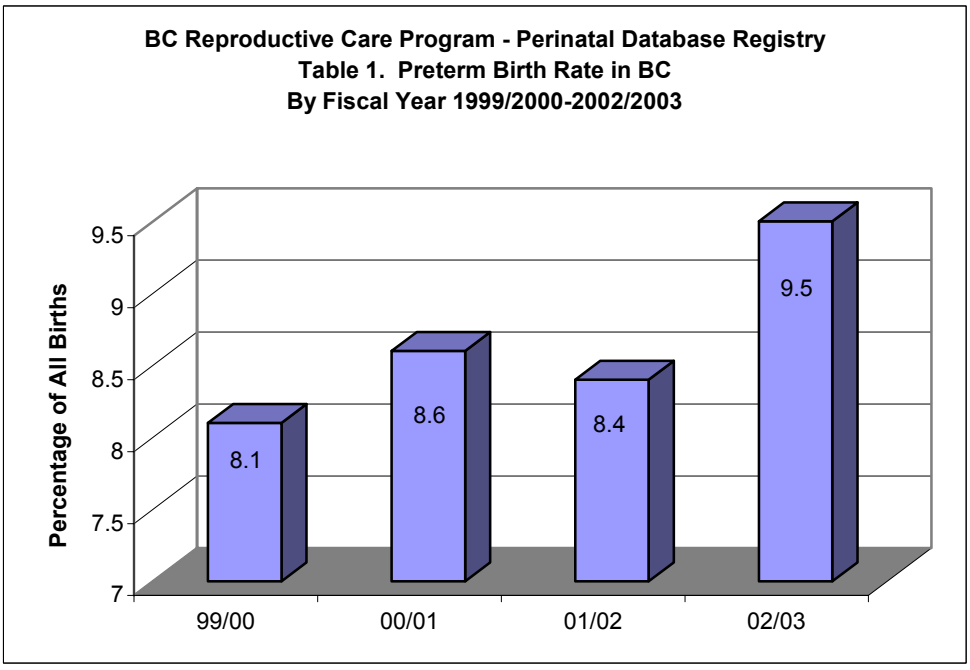
Demonstrated progressive dilatation of the cervix with uterine contractions between 20 and 36 completed weeks gestation, e.g. 36 completed weeks includes the time span from 36^0 to 36^6.

Preterm: 33-36 weeks
Moderately Preterm: 28-32 weeks
Extremely Preterm: 20-27 weeks

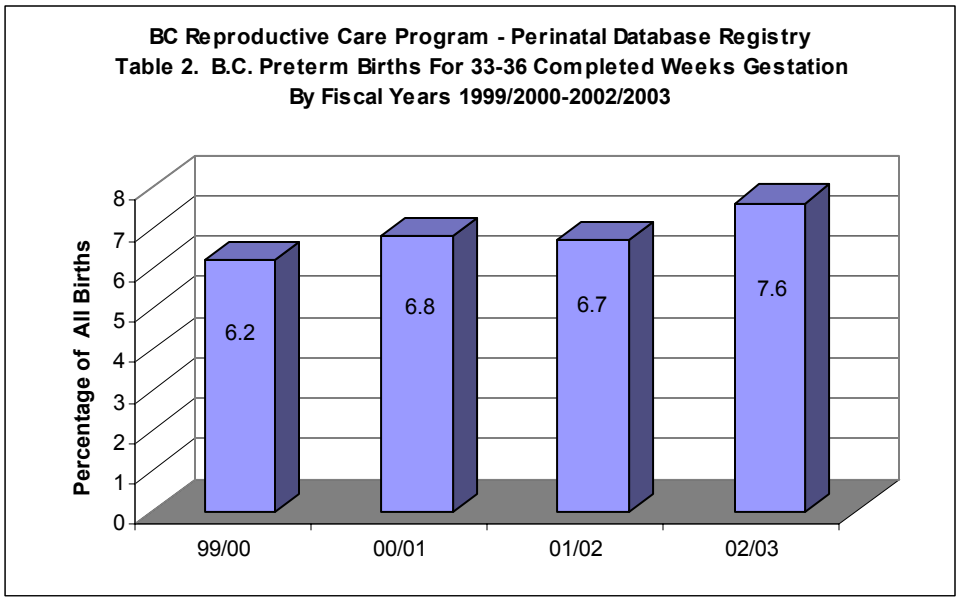
2. DEMOGRAPHICS OF PRETERM BIRTH IN BRITISH COLUMBIA

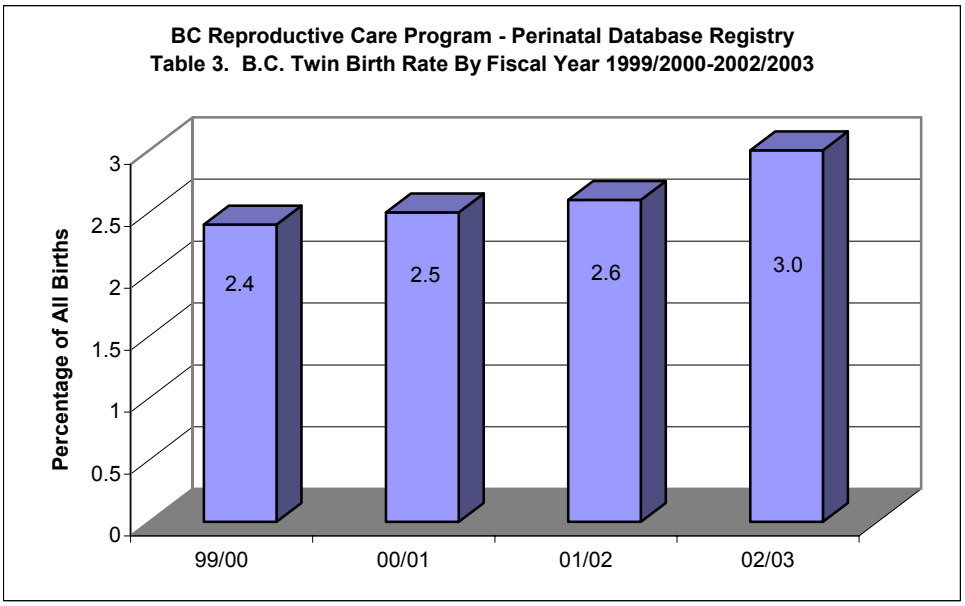
Preterm labour and delivery is the major cause of neonatal morbidity and mortality in reproductive care. According to Statistics Canada, the rate of preterm birth in Canada has risen from 6.6% in 1991 to 7.6% in 2000. In British Columbia from April 1, 1999 to March 31, 2003, the preterm birth rate has risen from 8.1% to 9.5%[1] (see Table 1).

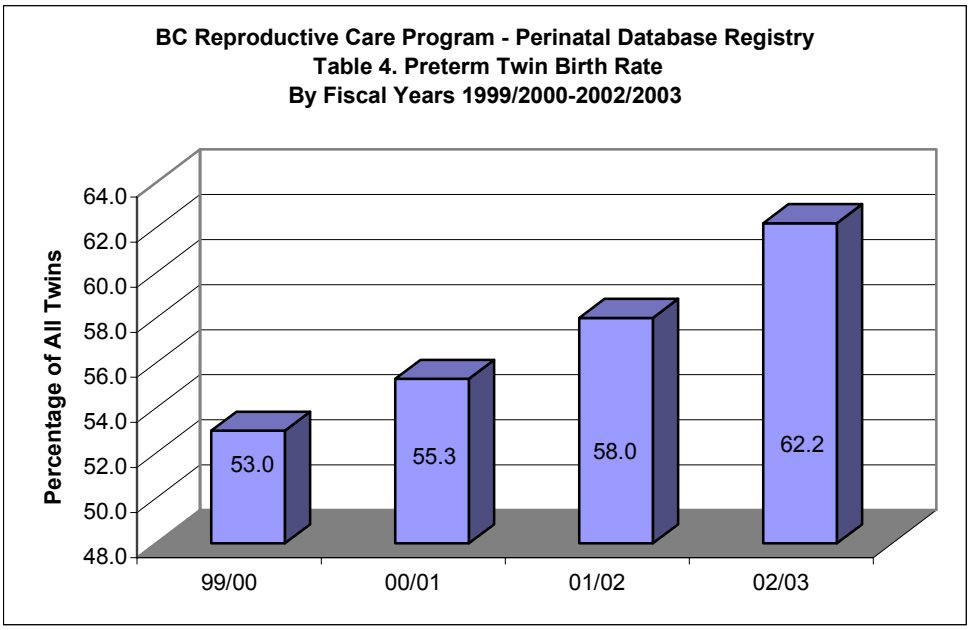
Note: The source of all tables in this guideline is the BCRCP Perinatal Database Registry. (1999/2000 data excludes 3 facilities with > 500 births, therefore captures 89% of provincial births for that year.)



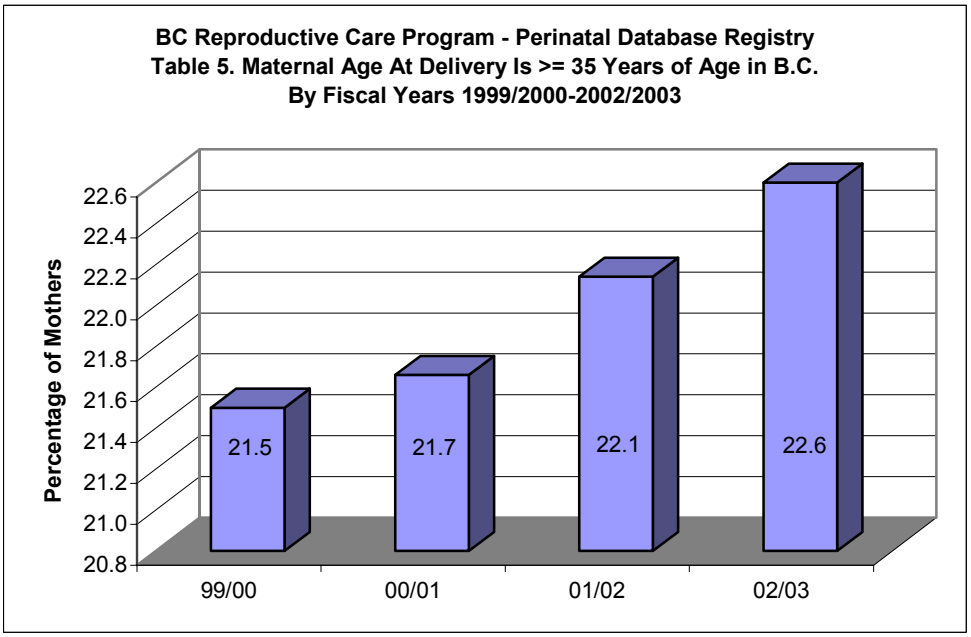
The greatest change in the preterm birth rate in B.C. is in the 33-36 week gestational age group. Over this 4 year period, the preterm birth rate in this group has increased from 6.2 to 7.6 per 100 live births (see Table 2). Also during this 4 year period, there was an increase in the percentage of twin pregnancies and in the percentage of twins delivering preterm (see Tables 3 & 4).







Advanced maternal age is associated with a higher incidence of preterm birth.[10] During the period 1999 – 2003, there was an increase in the percentage of mothers aged ≥ 35 years in B.C. (Table5).



Increases in multiple pregnancy rates and maternal age are factors associated with the increase in preterm birth rates in B.C. for 1999/2000 to 2002/2003.

Much is still unknown about the underlying mechanism of preterm and term birth.[2] There is evidence supporting the effectiveness of population-based prevention programs that provide education about the early identification of preterm labour or preterm rupture of membranes (PROM) to all women and their care providers, combined with supportive hospital policies.[3] Clinical trials however, have not been able to demonstrate a reduction in preterm births from the following prevention strategies: home uterine activity monitoring, frequent digital cervical exams, bed rest for twin pregnancies, tocolytics, and education about the signs of preterm labour among women with identifiable risk factors.[4]

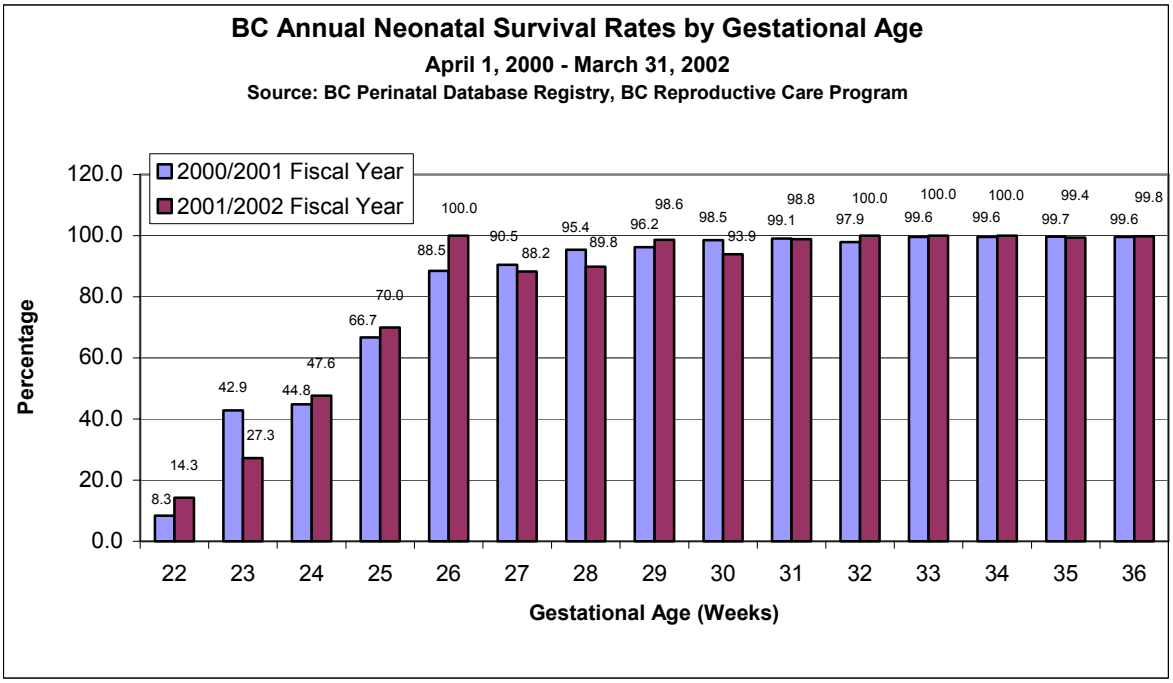
This guideline discusses two advances in the use of screening tools to predict preterm birth - the use of ultrasound cervical assessment and the fetal fibronectin (fFN) test. Despite the advent of sophisticated antenatal screening tests, most of the advances in this area have occurred in neonatal care of the premature infant. Maternal stabilization and consideration of transport so that delivery of premature infants occurs in the appropriate setting is inherent to achieving optimal neonatal outcomes.

3. NEONATAL SURVIVAL AND OUTCOMES

Neonatal survival is critically dependent on the maturity of an infant and progressively increases with gestational age. Each day critically impacts on maturity and consequently survival, particularly in the extremely low gestation infant.[5,6]

The British Columbia Neonatal Survival Rates by Gestational Age are presented in Table 6 for the period April 1, 2000 - March 31, 2002. It includes infants who die < 28 days, regardless of place of death. This data has not been corrected for lethal congenital anomalies. After 32 weeks gestation, the survival rate for each week of gestation is 99% - 100%.

Table 6.



With the greatest change in the preterm birth rate in the 33-36 gestational age group, it's important to consider the outcomes in this particular group. An examination of data from the **BCRCP Perinatal Database Registry** indicates that about 25% of 33-36 week infants have a diagnosis of neonatal respiratory disease. While the percentage has not changed over the past 4 years, the incidence of infants at 33-36 weeks with respiratory problems is increasing due to the increased rate of preterm birth in this gestational age group.

While neonatal survival is important, long-term outcome is more critical to the individual and family. With appropriate antenatal and intrapartum care of the pregnant woman, and appropriate newborn care immediately at and following birth, opportunities for the newborn are improved. It's important to remember that the more preterm the newborn, the higher the risk for adverse outcomes.[7,8,9] When caring for a pregnant woman in preterm labour, it is critical that consideration be given to the most appropriate place for her to deliver where both she and her anticipated neonate can receive the care they need.

4. RISK FACTORS

4.I PAST HISTORY

- Previous preterm birth

Table 7: Risk of Preterm Birth in Subsequent Birth(s)
From: Creasy, R. & Resnik, R. (1999). Maternal-Fetal Medicine, 4th Edition

First Birth	Second Birth	Subsequent PTB%
Not Preterm		4.4%
Preterm		17.2%
Not Preterm	Not Preterm	2.6%
Preterm	Not Preterm	5.7%
Preterm	Preterm	28.4%

- Second trimester losses
- Habitual abortions
- Uterine anomalies
- Conization of cervix

4.2 ANTEPARTUM

- Twins, triplets (51% & 91% chance of preterm delivery respectively)[10]
- Preterm rupture of membranes
- Polyhydramnios
- Antepartum hemorrhage
- Intra-abdominal surgery
- Urinary tract infection
- Tobacco or cocaine use
- Serious maternal infection
- Physical/emotional trauma

5. APPROACHES TO ANTENATAL CARE

5.1 POPULATION BASED STRATEGIES

Up to 50% of preterm births are potentially preventable.[11] In some jurisdictions, population-based strategies that provide information to all women have been shown to be effective in reducing the rate of preterm birth.[12] Population-based strategies include:

- Preconception preparation: nutritional status, avoidance of smoking and drugs
- Supportive environment
- Providing the woman with an increased role in her own prenatal care including ongoing support, time to answer questions, and information on avoidance of risk factors
- Prenatal education at 18-20 weeks for all women in the recognition of early symptoms of preterm labour such as low abdominal pain, low backache, pelvic pressure, increased vaginal discharge, bleeding, spotting or show
- Treatment of symptomatic vaginal infections before 32 weeks, e.g. bacterial vaginosis[13]

5.2 WOMEN WITH PREVIOUS PRETERM BIRTH

- In women with previous preterm birth there is evidence that screening for the presence of bacterial vaginosis may reduce the likelihood of preterm labour, prelabour rupture of membranes (ROM) and low birth weight[14,15]
- In the very rare occasion of women with a history of cervical insufficiency, cervical cerclage has been effective

5.3 WOMEN WITH RISK FACTORS FOR PRETERM LABOUR[27]

Research supports prenatal assessment of cervical length by transvaginal ultrasound for women identified to be at increased risk of preterm birth. Cervical length is inversely related to preterm birth risk in asymptomatic women, and the positive predictive value of a short cervix ($\leq$ 15 mm) is much greater for extreme prematurity ($\leq$ 28 weeks). Transvaginal ultrasound measurement of the cervix has a high negative predictive value if the length is greater than 3 cm after 24 weeks. Although transvaginal ultrasound assessment of cervical length can predict increased risk of preterm birth, there is no evidence that this information can be used to improve outcomes. There is no evidence to support routine prenatal transvaginal ultrasound assessment of cervical length in the absence of risk factors.

5.4 WOMEN WITH MULTIPLE PREGNANCY

There is no evidence supporting the use of routine hospitalization for bed rest to prevent preterm birth in women with multiple pregnancy. Until further evidence is available to the contrary, the policy cannot be recommended for routine clinical practice. [31]

6. DIAGNOSIS

6.1 SUGGESTIVE EARLY SYMPTOMS

- Low abdominal pain and/or cramps and/or pelvic pressure
- Low backache
- Increased vaginal discharge
- Bleeding/spotting/show

6.2 DEFINITIVE SIGNS

- Regular uterine activity accompanied by cervical effacement and dilatation

7. ASSESSMENT OF PRETERM LABOUR

7.1 GENERAL

- Accuracy of gestational age
- Uterine contractions: intensity, frequency, duration
- Maternal vital signs
- Fetal heart rate assessment
- Sterile speculum examination to obtain sample for fetal fibronectin test, determine status of membranes, and to obtain vaginal cultures including GBS. A digital exam should not be done until after the speculum exam has ruled out ROM.
- Cervical Assessment: Transvaginal cervical measurement is superior to the digital examination of the cervix in predicting preterm birth. [28,29] The difficulty of estimating cervical length digitally may be decreased in later gestation or if the cervix is dilated and effaced. Digital and transvaginal ultrasound examination may be complementary in the accurate assessment of cervical length, effacement, consistency, and dilation. For possible preterm labour with intact membranes beyond 34 weeks, management choices are unlikely to be altered by cervical measurement and decisions can be based on digital exam.[27]
- CBC/urinalysis
- Consider ultrasound if gestational age, placental site, or fetal presentation is unknown

7.2 FETAL FIBRONECTIN TEST

A. Fetal Fibronectin

Fetal Fibronectin 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.

B. Summary of the Literature on Fetal Fibronectin

Numerous trials have shown both an association between the presence of fFN and preterm birth as well as a decrease in the risk of preterm birth when the test results for this protein are negative.[36-39] In a meta-analysis of 27 studies using delivery at <34 weeks gestation as the outcome, a positive fFN 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%.[40] When individual risk factors for preterm birth were analyzed, the highest association with preterm birth followed a positive fFN 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 fFN test confers a more than 95% likelihood of remaining undelivered for the 14 days following a negative test result**.[37,41,42]

In the past two years alone, there have been nine papers/posters presented at the Annual Meeting of the Society of Obstetricians & Gynecologists of Canada supporting the usefulness of fFN 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.[43] 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 occur under inclement conditions. Other issues to consider are the emotional 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.

C. 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. The anticipated benefits of using the fFN test include:

- Decrease in hospital admissions, length of hospital stay, and assessment time in community – based hospitals throughout B.C. for suspicious preterm labour
- Decrease in hospital admissions, length of stay, assessment time and air and road ambulance transports from rural B.C. into Level III facilities in Victoria and Vancouver
- More appropriate identification of patients who needs corticosteroid and tocolytic treatment
- Decrease in the use of tocolytics in the woman who is not at risk for preterm delivery

- Reduced stress and anxiety for the pregnant mother and her family due to reassurance and absence of unnecessary transfer out of her home community

D. Indications for fFN Testing

- 24 to 34 completed weeks
- Threatened preterm labour (regular uterine contractions >6 per hour and/or pelvic pressure)
- Intact amniotic membranes
- Cx $\leq$ 3 cm dilatation
- Established fetal wellbeing

E. Contraindications for fFN Testing

- EGA < 24 weeks or > 34 completed weeks
- Preterm PROM
- Cx > 3 cm dilatation
- Cervical cerclage
- Active vaginal bleeding
- Vaginal exam or sexual intercourse in the past 24 hours

F. Specimen Collection

The fFN specimen should only be collected using the ADEZA Fetal Fibronectin Kit (see Appendix A). The equipment required includes the swab, collection tube, tube cap, test cartridge and an instrument based system to perform the fFN testing. Fetal fibronectin specimens are collected during speculum examinations with the 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 (see Appendix A) is available to facilities and allows fFN results within one hour of testing, depending on the laboratory protocol. Specimens that are not tested within 8 hours of collection must be stored, refrigerated (2^{o}- 8^{o} C), and assayed within 3 days of collection to avoid degradation of the fFN. 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
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.

G. If the fFN Test is 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.

H. If the fFN Test is Negative

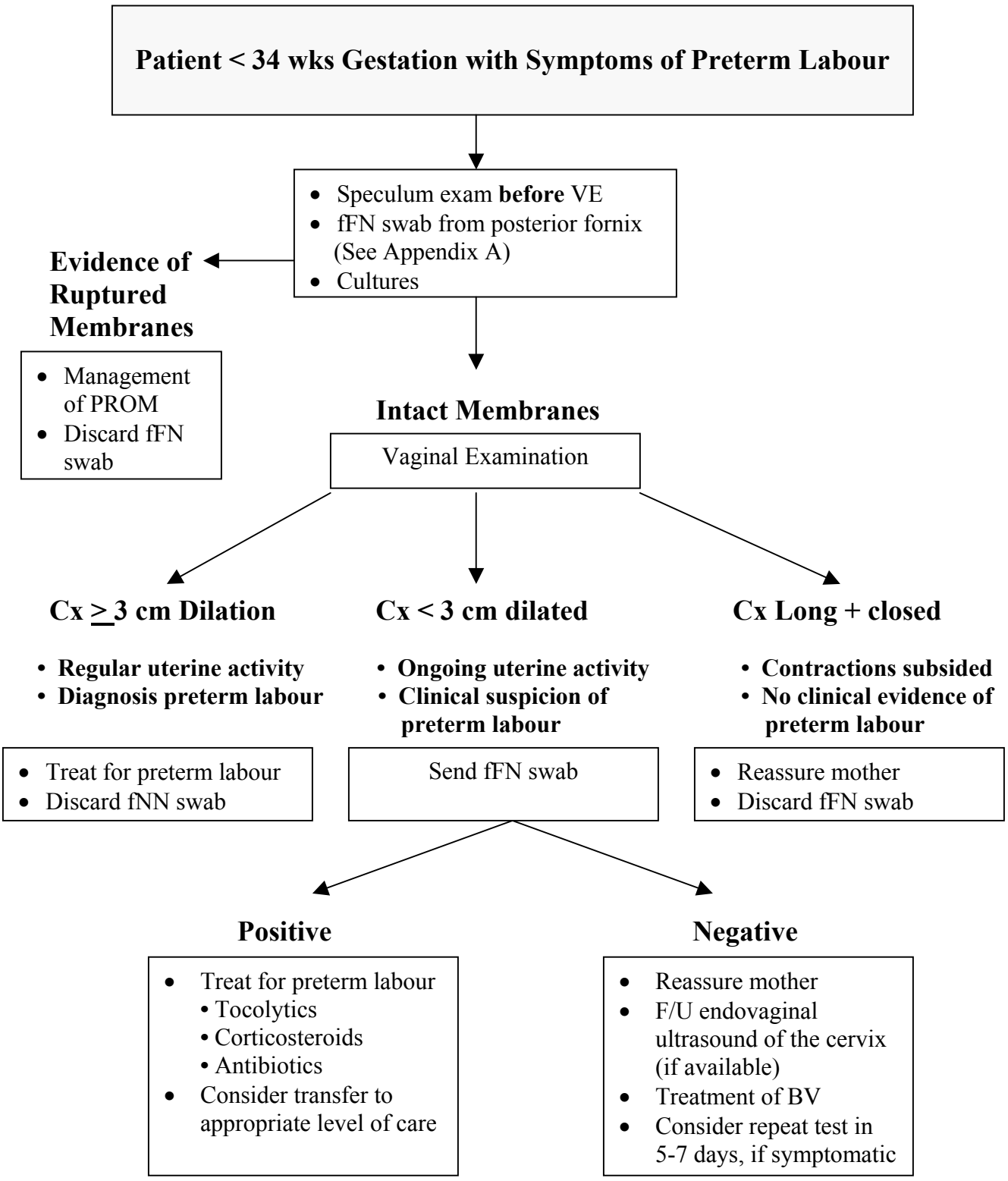
A negative test provides greater than 95% probability that the woman will not deliver within the next 7-10 days. Consideration should be given to having her stay in her community and treatment with tocolytic therapy and corticosteroids would not be justified. The patient should be educated about preterm 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 fFN test decreases with time and reevaluation should be considered if the patient continues to have symptoms suggestive of preterm labour.[44] Reevaluation should occur 5-7 days after the first symptomatic episode, providing the cervix is < 3 cms. dilated.

I. Monitoring fFN Testing and Patient Outcomes

For those centres in B.C. using fFN testing, a case review of all women presenting in preterm labour should occur to determine cost-benefit for your facility/region. Variables to evaluate include:

- Original location of the mother (Residence postal code)
- EDD
- Location of assessment
- Date of assessment
- Date of MedEvac (if appropriate)
- Cost of MedEvac
- Date of delivery
- Place of delivery
- LOS during assessment
- LOS for actual birth
- Use of tocolytics agents
- Use of corticosteroids

Fetal Fibronectin Testing for Suspected Preterm Labour



8. TREATMENT OF PRETERM LABOUR

- Offer support, reassurance, and attention to comfort measures
- Monitor fetal heart rate and contraction frequency using electronic fetal monitoring or intermittent auscultation. Always **palpate** the uterus to determine contraction strength.
- There is no evidence supporting the use of intravenous hydration to prevent or arrest preterm labour. Women with evidence of dehydration may, however, benefit from the treatment.[32]
- There is no evidence either supporting or refuting the use of bed rest at home or in hospital, to prevent preterm birth for women with singleton pregnancy.[33] Due to the potential adverse effects that bed rest could have on women and their families, and the increased cost for the healthcare system, clinicians should not routinely advise women to rest in bed to prevent preterm birth. Potential benefits and harms should be discussed with women facing an increased risk of preterm birth. [33]

8.1 FOR SUSPICIAN OF PRETERM LABOUR

- If fFN Test is negative then reassure the woman and consider:
  - endocervical ultrasound of the cervix
  - treatment of bacterial vaginosis
  - discharging the woman home
  - repeat fFN testing in 5-7 days if woman continues to be symptomatic
- If fFN Test is positive, then consideration should be given to transferring the woman to a care facility appropriate for her gestational age. Tocolysis and GBS management should be considered and corticosteroids administered to accelerate lung maturity.
- In the absence of fetal fibronectin testing, consider admission x 12 hours to determine if uterine irritability felt by patient and to assess for contractions
- Patient education regarding symptoms of preterm labour and need for early follow-up

8.2 FOR DIAGNOSIS OF PRETERM LABOUR

Management is oriented towards the stabilization of the mother and fetus and transport of the fetus in utero (when appropriate) to allow delivery to occur in a hospital with the resources to properly support the anticipated gestational age of the newborn.

- Monitor fetal heart and uterine contractions as indicated
- Consider maternal/fetal transfer – discuss with referral center and/or call provincial transfer (604) 875-2159 (See BCRCP Maternal/Newborn Transport Guideline for the organization of a transport)
- Administer antibiotic therapy for GBS prophylaxis
- Administer **corticosteroids** (see page 13)
- If < 32 weeks, consider **tocolysis** for 24-48 hours with Indomethacin (see page 13)

9. CORTICOSTEROIDS[16]

All pregnant women between 23^0 and 33^6 weeks gestation who are at risk of preterm birth within 7 days should be administered a single course of corticosteroids.

Giving a single course of corticosteroids to pregnant women at risk for preterm birth reduces the risk of death, respiratory distress syndrome, and intraventricular hemorrhage in their preterm newborns.

Betamethasone is the drug of choice and is the only steroid medication shown in clinical trials to be effective.

Betamethasone: 12 mg IM, 2 doses at 24 hour interval

At the time of the writing of this guideline, some practitioners still use Dexamethasone 6 mg IM, 4 doses at 12 hour intervals as it is widely available and cheaper than Betamethasone. However, there is a lack of evidence supporting its effectiveness on the maturation of the fetal lung and a recent study has shown concerns re: long term neurological outcome.[17]

Note: There is an additional improvement in outcome when there is the combined use of steroids in pregnancy and use of surfactant in the immediate newborn period.

10. TOCOLYTIC MEDICATION

There is no evidence demonstrating that the use of tocolytics to arrest preterm labour results in a reduction of perinatal mortality. This applies to both short term and long term use. Currently in BC, the only tocolytic recommended is Indomethacin. The major aim of Indomethacin is to allow safe maternal transfer to an appropriate center and to permit corticosteroids to be utilized to decrease neonatal morbidity**. Indomethacin is only recommended up to 32 wks gestation.**

Traditionally magnesium sulfate (MgSo4) therapy has been used as a tocolytic. However, there is no evidence that MgSo4 is an effective tocolytic.[18] The evidence suggests that MgSo4 is ineffective at delaying birth or preventing preterm birth, and its use is associated with an increased mortality for the infant.[34] **Magnesium sulfate should NOT be used as a tocolytic medication.**

Currently there is insufficient evidence to support the routine administration of nitroglycerin in the treatment of threatened preterm labour. [35]

10.1 CONTRAINDICATIONS TO TOCOLYSIS

- Non-reassuring fetal heart
- Lethal fetal anomaly
- Intrauterine fetal death
- Chorioamnionitis
- Severe gestational hypertension with adverse conditions
- Sever IUGR (<3^{rd} percentile)

10.2 INDOMETHACIN [19-26]

A. Indication

- Gestational age < 32 weeks. It is not recommended >32 weeks gestation because of associated premature closure of the ductus arteriosus.

B. Dosage

- Initial dose: 100 mg rectal suppository
- Maintenance dose: 25-50 mg orally or rectally q4-6h for 24 – 48 hours
- **Discontinue use after 48 hours**

C. Precautions

- Not recommended for gestational age > 32 weeks
- Course of therapy strictly limited to 48 hours only. Prolonged use (>48 hours) can be associated with development of ductal constriction and oligohydramnios
- Relative contraindications: maternal history of GI ulceration, non-steroidal anti-inflammatory induced (NSAID) or ASA induced asthma

11. OUTCOME INDICATORS FOR PRETERM LABOUR

A non-inclusive list of maternal and newborn outcome indicators for preterm labour is listed below. Data on these indicators may be accessed via the BC Perinatal Database Registry.

11.1 MATERNAL

- Singleton, multiple pregnancy
- Group B Strep – antenatal
- Lone parent
- Drugs, alcohol, cigarettes
- Prior low birth weight
- Steroids for lung maturation
- Drugs – tocolytics, antibiotics
- Maternal transfer
- Cervical dilation on admission
- Spontaneous preterm labour or intervention (e.g. induction or elective caesarean section)
- Final gestational age at delivery 20-27 weeks, 28-32 weeks, 33-36 weeks
- Weight association at delivery by gestational age: 20-27 weeks, 28-32 weeks, 33-36 weeks

11.2 NEWBORN

- Gestational age by exam
- Birth weight
- Apgars 1, 5, 10 minutes
- Cord arterial gases: pH, Base excess
- IPPV ETT, Mask
- Drugs for resuscitation
- Newborn transfer to higher level of care

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APPENDIX A

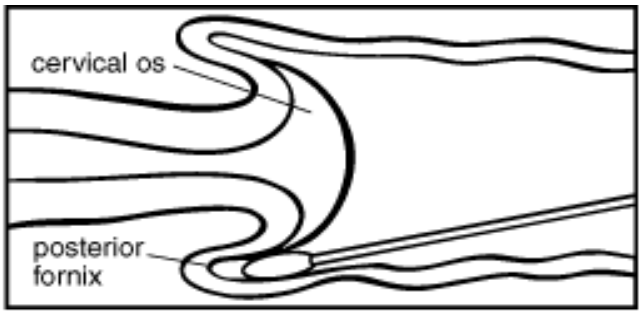
3 Easy Steps to Collect the fFN Swab

The fFN specimen should only be collected using the ADEZA fFN Kit. The kits and testing device are only available through:

******* ADEZA Customer Service at 1- 888 -567-3817 *******

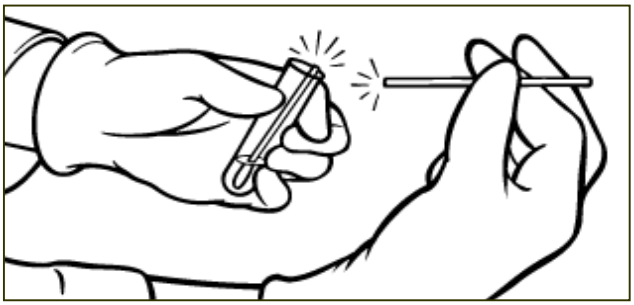
_____ 1 _____

During speculum examination, lightly rotate the swab across the posterior fornix of the vagina for 10 seconds to absorb cervicovaginal secretions.



_____ 2 _____

Remove swab and immerse tip in buffer. Break the shaft at the score even with the top of the tube.



_____ 3 _____

Align the shaft with the hole inside the tube cap and push down tightly over the shaft, sealing the tube. Ensure the shaft is aligned to avoid leakage.