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Horizon scanning prioritising summary

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A rapid foetal fibronectin assay as a predictive test for women suspected of being in pre-term labour.

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PRIORITISING SUMMARY

REGISTER ID: **000102**

NAME OF TECHNOLOGY: **RAPID FOETAL FIBRONECTIN ASSAY**

PURPOSE AND TARGET GROUP: **PREDICTIVE TEST FOR WOMEN SUSPECTED OF BEING IN PRE-TERM LABOUR**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☒	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number	
☐	No	☒	Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		

IMPACT SUMMARY:

Adeza Biomedical Corporation manufactures the Foetal Fibronectin Rapid System, an immunoassay used for the rapid detection of foetal fibronectin (FFN) in women suspected of entering pre-term labour. The United States Food and Drug Administration have approved the Foetal Fibronectin Rapid System, however approval by the Australian Therapeutics Goods Administration is not required as the immunoassay is a diagnostic test for in vitro use.

BACKGROUND

Foetal fibronectin is a glycoprotein, produced by the chorion, which appears to act like “glue” between the placenta and the decidua. FFN is present on cervicovaginal fluids from 16 to 20 weeks of gestation, but is typically absent until 34 weeks gestation, reappearing before term and pre-term birth. It is thought that the reappearance of FFN is a physiologic signal in preparation for labour. In addition, FFN may act as an indicator of the disruption of the choriodecidual interface due to infection, inflammation or placental shearing. Early detection of pre-term labour is difficult as clinical symptoms may be mild and can often occur during a normal pregnancy. The presence of FFN in cervicovaginal fluid after 22 weeks gestation is associated with a six-fold increased risk of pre-term birth before 35 weeks gestation, and a 14-fold increased risk of pre-term birth before 28 weeks (Iams 2003; Lowe et al 2004; Plaut et al 2003).

The rapid FFN test consists of a cassette to which the sample is added. The sample flows by capillary action, across a membrane containing a conjugate, forming fibronectin-conjugate

complexes. An antibody captures these complexes as they pass through the next zone, and it is the number of fibronectin-conjugate-antibody complexes that are measured by the Tli™ Analyzer (Adeza Corporation), which represents the amount of fibronectin present in the sample. Each cassette also contains a calibration sample. The average sample reaction time is 20 minutes and results are available from the laboratory to the clinician in less than two hours (Smith & Greer 2000, http://www.ffntest.com/).

Improving the ability to identify women at real risk of pre-term delivery, through the presence of FFN, may improve management of the pregnancy and improve outcomes for both mother and infant. Women with symptoms suggestive of pre-term labour identified with negative FFN values may avoid unnecessary clinical interventions, costly hospitalisations and, in rural Australia, the transfer of patients to a larger regional hospital. Although a negative fibronectin result is not predictive of non-pre-term labour if cervical dilation is present (ACOG Committee on Practice Bulletins 2001, Giles et al 2000).

CLINICAL NEED AND BURDEN OF DISEASE

The prediction and the effective management of pre-term labour (delivery <37 weeks gestation) is an important healthcare issue. Greater than two-thirds of singleton neonatal deaths occur preterm and the incidence of severe neonatal morbidity is inversely related to gestational age (French/Australian Atosiban investigators Group 2001). There were 257,238 babies born in Australia during the year 2000 and pre-term birth occurred in 7 per cent (17,947) of confinements. During the same time period the rates for foetal, neonatal and perinatal death were 7.0, 3.1 and 10.0 per 1,000 births, respectively. Pre-term births less than 37 weeks gestation accounted for 71.6% of foetal deaths and those less than 28 weeks gestation for 37.4% (AIHW 2003). The number of public hospital separations in Australia for patients with pre-term delivery (AR-DRG number O60), in 2001- 02 was 5,665. In addition, the number of public hospital separations for false labour <37 weeks (AR-DRG number O47.0) was 11,087 (AIHW 2004). The number of pre-term births may represent only approximately 30 per cent of all pre-term labours (personal communication, Adeza Biochemical Australia).

Threatened preterm labour is the most common cause of antenatal hospitalisation and may account for 33 per cent of all admissions prior to delivery, representing a major cost to the Australian health system. The standard protocol for the management of patients with threatened pre-term labour is a 24-hour admission to the delivery suite for tocolysis and corticosteroids and an average 7-day admission to the antenatal ward (Giles et al 2000).

DIFFUSION

The Foetal Fibronectin Rapid System is currently being utilised in a multi-centre trial. One of the participants in this trial is the Women and Children's Hospital, Adelaide. The Foetal Fibronectin Rapid System has been in use in the United States since 1998 (personal communication, Adeza Biochemical Australia).

COMPARATORS

Assessment of women suspected of pre-term labour may include digital and ultrasound examination of the cervix, outpatient monitoring of uterine contractions or by the detection of biochemical markers in blood, saliva and cervicovaginal secretions eg fibronectin (Iams 2003).

There are several assays available for testing levels of fibronectin in women threatening with pre-term labour, all manufactured by Adeza Biochemical. The ELISA assay is a solid phase immunoassay, where the cervicovaginal samples are incubated in a microtitre tray coated with a monoclonal antibody specific for fibronectin. The presence or absence of fibronectin is

determined by a spectrophotometer and results are available in three hours (Smith & Greer 2000). A semi-quantitative bedside assay, QuikCheck ffN® or the Foetal Fibronectin Membrane Immunoassay kit, is also available and in use in Australia. This test is a dipstick test, which involves the sampling of the cervical membrane with a Dacron swab. The mucous is mixed into an extraction medium for 10 seconds. The dipstick reader, similar to a home pregnancy kit, is placed into the solution and left for 10 minutes. The test strip is impregnated with a monoclonal antibody and fibronectin binding is detected by an immuno-gold complex, forming a visible spot on the test strip when fibronectin is present in concentrations >50 ng/mL. The dipstick test is not quantitative, giving a positive or negative result, can be done at the bedside and requires no additional laboratory equipment (Giles et al 2000).

EFFICACY AND SAFETY ISSUES

A randomised controlled trial (RCT) by Plaut et al (2003) reported on the impact of FFN testing using the Foetal Fibronectin Rapid System on the treatment of 108 women suspected of pre-term labour. The result of the FFN test was randomised into two groups; one group where the treating physician was aware of the FFN result and treated the woman accordingly and the other group where the treating physician was unaware of the FFN result and treated the women according to standard practice. Of 108 swabs, 10 were positive and 98 were negative for FFN. Sensitivity was reported as 33%, specificity was 91%, positive predictive value 10% and a negative predictive value 98%. The length of time in hospital was not significantly shorter for patients with a negative FFN test when the result was known to the clinician (6.8 hours) than when it was not known (8.1 hours, p=0.35). Lowe et al (2004) conducted an RCT where women were assigned randomly to receive management of suspected pre-term labour with or without a FFN test. Sensitivity was reported as 67%, specificity was 79%, positive predictive value 18% and a negative predictive value 97%, for delivery within 7 days. There was no difference between the groups for rate of inpatient admissions or the use of corticosteroids, antibiotics or magnesium sulphate. There was, however, a significant reduction in the number of admissions (p = 0.032) and the length of stay in hospital (p=0.008) for those women who tested negative for FFN compared to those who tested positive.

Only a report supplied by Adeza Biochemical Corporation compared the Foetal Fibronectin Rapid System to the established ELISA assay for FFN. This prospective study of 587 asymptomatic and symptomatic women (recruitment not described) reported equivalency between the two tests. Both tests were in agreement 95% of the time (Kappa coefficient =0.81, 95% CI [0.75, 0.88]).

COST IMPACT

Sample cassettes for the Foetal Fibronectin Rapid System cost approximately $250 each and the TLi™ Analyzer system is $17,000. Considerable costs are involved in the education and training of a dedicated technician to operate the TLi™ Analyzer. In contrast, the QuikCheck ffN® bedside test costs approximately $88 per test ($880 per box 10) (personal communication, Adeza Biochemical Australia).

A study by Giles et al (2000) reported on the hospitalisation and cost savings associated with fibronectin testing within the Australian health care system, using the standard ELISA assay. Following a positive FFN test, women were to be referred to the larger regional hospital from nine referring centres, the furthest being 814 km away and the nearest 15km. Ninety per cent of women admitted to the referral centres with threatened pre-term labour, who subsequently returned a negative FFN test, were not transferred to the regional hospital. This translates into a total cost saving of $30,000 if road or fixed-wing ambulance had transferred all patients. Hospital admissions were 7.6 days shorter for patients with a negative FFN test result, giving an average saving of $3,000 per patient (Giles et al 2000). There is currently no MBS item number for the FFN ELISA (personal communication Professor Warwick Giles).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Correct identification and management of women at risk of pre-term labour is especially important for women who live in the rural and remote areas of Australia. Women deemed at risk of threatened pre-term labour may need to be transported to larger regional hospitals. Unnecessary transportation of these women is stressful and disruptive to family life and may impact on these families financially (Giles et al 2000).

CONCLUSION:

Treatment of women suspected of pre-term labour may be affected by the knowledge of their FFN status. Despite good initial results with the Foetal Fibronectin Rapid System, this system requires advanced technical skills and laboratory equipment. An established bed side fibronectin test (QuikCheck ffN®), which may be used in all hospital settings is currently available in Australia.

HEALTH PACT ACTION:

Therefore it is recommended that this technology be archived.

SOURCES OF FURTHER INFORMATION:

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Ramsey, P. S. & Andrews, W. W. (2003). 'Biochemical predictors of preterm labor: fetal fibronectin and salivary estriol', *Clin Perinatol,* 30 (4), 701-733.

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SEARCH CRITERIA TO BE USED:

Glycoproteins/*analysis
Labor, Premature/*diagnosis/drug therapy/epidemiology/prevention & control
*Patient Admission
Pregnancy
Vagina/*metabolism/ chemistry
Cervix Uteri/chemistry
Biological Markers/analysis
Fetal Proteins/*analysis/metabolism
Fibronectins/*analysis/metabolism
Pregnancy Complications, Infectious/*diagnosis/drug therapy/epidemiology
Infant, Premature
Predictive Value of Tests
Risk Assessment
Risk Factors
Sensitivity and Specificity