Can fetal fibronectin testing improve the management of preterm labour?

P. Owen *MRCOG, Senior Lecturer and Consultant*, **A. Scott** *MRCOG, Registrar*
Department of Obstetrics & Gynaecology, Ninewells Hospital & Medical School, Dundee, Scotland (United Kingdom)

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Summary

The detection of fetal fibronectin (Ffn) in cervico-vaginal secretions has been proposed as a method to differentiate true from false threatened preterm labour. This study evaluates the impact of tocolysis in the management of threatened preterm labour and compares actual practice in our department with a hypothetical management strategy based upon fetal fibronectin (Ffn) testing. Over a 12 month period, 41 women were admitted in threatened preterm labour with intact membranes before 34 weeks gestation. In "actual practice", 13 received tocolysis but only three cases were considered to have benefitted from it (ratio 4.3:1). In the Ffn strategy, 34 women would receive tocolysis with 12 potentially benefitting (ratio 2.8:1). If tocolysis was given to all eligible women ("non-selective" policy) 41 women would receive tocolysis with 12 potentially benefitting (ratio 3.4:1).

The majority of women receiving tocolysis do not benefit from this treatment regardless of whether tocolysis is based upon clinical judgement, Ffn testing or a non-selective administration policy. Administering tocolysis on the basis of a positive Ffn result would be expected to increase the number of women receiving tocolysis but would make a small improvement in the treatment: potential benefit ratio when compared to "actual practice".

Key words: Fetal fibronectin; Tocolysis; Preterm labour.

Introduction

The primary prevention of preterm labour through education, increased antenatal care and alterations in work practises has largely been unsuccessful [1]. Secondary prevention entails the deterrence of preterm delivery when signs of preterm labour appear. Current tocolytic practice with ritodrine results in a short delay in delivery but is associated with adverse maternal effects [2] and antenatal indomethacin is associated with adverse fetal effects such as premature closure of the ductus arteriosus and necrotizing enterocolitis [3, 4]. Antenatal corticosteroids reduce the incidence of hyaline membrane disease and are not associated with subsequent adverse effects in infancy [5, 6] but may result in maternal hyperglycaemia and even pulmonary oedema when used in combination with beta-mimetic agents such as ritodrine [7].

It is recognised that a large proportion of women in apparent early preterm labour will not progress to preterm delivery, i.e. false labour. It would be desirable to be able to reliably discriminate between those in true and false labour, administering tocolysis and steroids to those in true preterm labour only. This targeted approach would be expected to result in a more appropriate use of tocolysis thus increasing its likely benefits and reducing the number of maternal adverse effects.

Fetal fibronectin (Ffn) is a protein found in amniotic fluid, placental tissue and the extra cellular substance of the decidua basalis next to the placental inter-villous space [8] and can be detected by bedside immunoassay following vaginal swabbing (MAST diagnostics, Merseyside, UK). The presence of Ffn in cervico-vaginal secretions is associated with an increased risk of preterm delivery [8, 9, 10]. Observational studies of the value of Ffn detection in the identification of women in threatened preterm labour subsequently delivering before and after 34 weeks gestation have suggested Ffn can usefully discriminate between true and false preterm labour [11, 12, 13, 14]. Since the administration of maternal corticosteroids is only of proven benefit before 34 weeks gestation [6] and requires a minimum of 24 hours, preferably 48 hours to become maximally effective, then a preterm labour managament protocol of tocolysis and corticosteroid administration based upon the Ffn result would appear to be attractive.

In order to test this hypothesis, we have evaluated the management of threatened preterm labour in our department over a 12-month period with particular emphasis on the use of tocolysis with intravenous ritodrine. We have subsequently applied a treatment schedule based upon the hypothetical application of Ffn testing to the same population. This allows us to compare the use of ritodrine based upon actual clinical practice with that which would have occurred had tocolysis been limited to women who were Ffn positive upon admission.

Methods

All women admitted in threatened preterm labour to our department over a 12-month period (1993-1994) were identified. Ninewells Hospital is a teaching hospital and tertiary referral centre for high risk obstetric patients with approximately 3,300 deliveries per annum. Gestational age was determined from the routine mid-trimester biparietal diameter measurement. Women were considered to be in idiopathic threatened preterm labour if they were experiencing regular uterine acti-

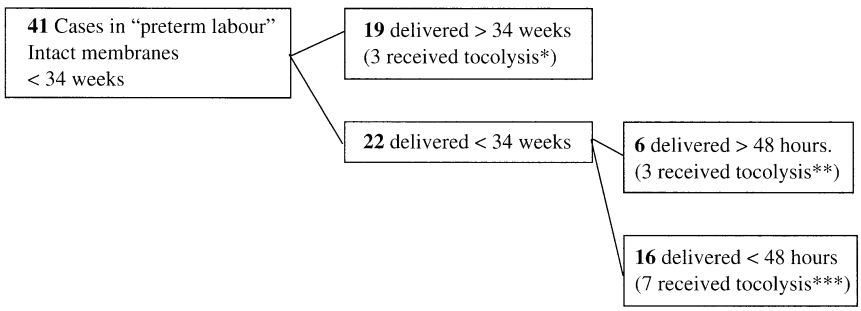

Figure 1. — "Actual practice" in the management of threatened preterm labour. * = Long intervals from tocolysis to delivery. ** = 3 cases possibly benefitted from tocolysis. *** = 7 tocolysis failures (9 potential beneficiaries).

vity, the cervix showed signs of effacement and dilatation was less than 4 cms. on admission.

Cases were excluded from the analysis if there was antepartum haemorrhage, clinical chorio-amnionitis, recognised cervical incompetence or a contra-indication to tocolysis. Cases with preterm premature rupture of the membranes (PPROM) were also excluded since these are not appropriate for comparison with the Ffn management strategy and also because there is no apparent benefit of tocolysis in the presence of ruptured membranes [15, 16].

In the "actual practice" management strategy, the administration of tocolysis was decided by the attending obstetrician based upon the assessment of uterine activity (palpation and tocography), cervical consistency and observation. Ritodrine is the only tocolytic agent employed in our department and is administered in stepwise infusion increments from 20 microg/min. to a maximum of 300 microg/min, titrated against uterine activity.

The following assumptions were made prior to the evaluation of "actual practice" and the Ffn strategies;

1. – Tocolysis with ritodrine can result in postponement of delivery to 48 hours following administration but not beyond this [17]. It is assumed that ritodrine has no other proven benefit in the management of preterm labour.

2. – Maternally administered corticosteroids are effective in reducing hyaline membrane disease at gestational ages of less than 34 weeks and require 48 hours to become maximally effective [6].

3. – When applied to women in threatened preterm labour at less than 34 sweeks gestation, a positive Ffn test will have a 64% positive predictive and 100% negative predictive value for delivery before 34 weeks gestation [11, 12, 13, 14].

4. – Women in the "actual practice" strategy can be considered to have potentially benefitted from ritodrine only if the following outcome criteria are met:

a) subsequent delivery before 34 weeks gestation;

b) subsequent delivery 48 hours or more following admission and administration of ritodrine.

Results

Sixty-one women were admitted in threatened preterm labour at less than 34 weeks gestation. Twenty women had PPROM therefore analysis was restricted to the 41 with intact membranes. The "actual practice" management and subsequent outcomes are presented in Figure 1. Thirteen cases received tocolysis with intravenous ritodrine. Of these 13 cases, three subsequently delivered at greater than 34 weeks with long admission to delivery intervals (7 weeks, 6 weeks, 6 weeks) and are not considered to have benefitted from tocolysis; three cases delivered less than 34 weeks but greater than 48 hours following admission and may have benefitted from tocolysis; seven cases received ritodrine but delivered within 48 hours of admission and are considered ritodrine failures. For a total of 13 cases treated with ritodrine, only three cases potentially benefitted. The treatment-to-potential benefit ratio is 4.3:1. A further nine cases delivered before 34 weeks and within 48 hours of admission, and are considered potential ritodrine beneficiaries who did not receive tocolysis.

By assuming a positive predictive value of 64% and negative predictive value of 100% for delivery before and after 34 weeks of Ffn testing, and subsequently limiting treatment with ritodrine to those who are Ffn positive, a hypothetical Ffn management strategy can be developed and is illustrated in Figure 2.

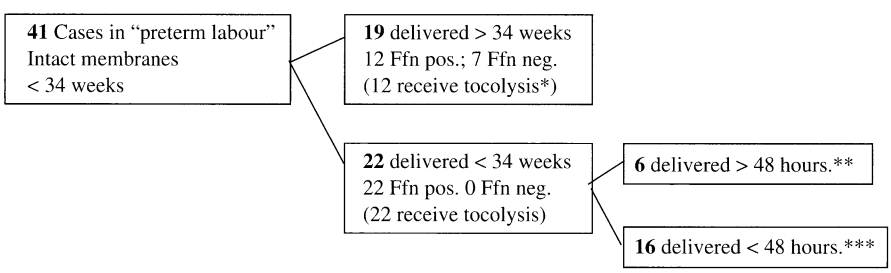

Figure 2. — Management outcome based upon the hypothetical application of fetal fibronectin testing in the management of threatened preterm labour. * = No cases benefit from tocolysis. ** = 3 cases possibly benefit from tocolysis. *** = 9 cases potentially benefit from tocolysis.

By applying the same criteria of potential benefit from tocolysis to this management strategy as was applied to the "actual practice" *(vide supra)* strategy and with the knowledge of the actual outcome of the cases, a total of 34 cases would be expected to be Ffn positive and would therefore have received ritodrine. Twelve cases would potentially benefit from treatment resulting in a treatment-to-benefit ratio of 2.8:1.

A further hypothetical management strategy can be applied whereby all women presenting with threatened preterm labour at less than 34 weeks and with intact membranes received tocolysis ("non-selective" model). This would result in 41 women receiving tocolysis with a possible benefit to 12. This results in a treatment-to-benefit ratio of 3.4:1.

By constructing 2x2 tables it is possible to compare the "actual practice" versus Ffn strategy. The Yates corrected chi squared value is 0.21 (p=0.65) with odds ratio 1.67 (0.35-10.33) i.e., not statistically significantly different.

Discussion

The application of a test to discriminate between true and false preterm labour might be expected to result in a more selective and rational administration of tocolysis and corticosteroids. This study has aimed to evaluate such a test by applying a hypothetical Ffn model and comparing it with actual clinical management. Whilst this method of study is not a substitute for a correctly performed randomised trial of Ffn testing in the management of threatened preterm labour, it can be expected to give a reliable indication of the magnitude of any likely benefit. We believe that applying the Ffn model to our population in this way to be valid since a previous study of Ffn testing from our department in a group of patients with similar characteristics [14] reported very similar results to other, comparable studies of Ffn testing [11, 12, 13].

One potential benefit of fetal Ffn testing might be a reduction in the number of women receiving tocolysis by obviating the need for tocolysis when Ffn testing is negative. The potential benefit of Ffn therefore will depend upon the prevalence of the use of tocolysis in any particular department. By applying the Ffn model to the population described here, the overall use of ritodrine would be increased (assuming that ritodrine was administered to all women with a positive test). This increase in ritodrine administration is associated with an increase in the number of women who would potentially benefit from tocolysis. The treatment-to-potential benefit ratio is improved from 4.3:1 to 2.8:1 with the introduction of Ffn testing, but this improvement is not statistically significant. Failure of the Ffn strategy to improve the treatment-to-benefit ratio further is principally because of the anticipated 36% false positive Ffn results which would result in a number of cases receiving unnecessary ritodrine.

Comparing the Ffn model with a "non-selective" practice of tocolysis results in an improved treatment-to-potential benefit ratio with Ffn since fewer women would receive ritodrine, but the number of cases that might benefit from tocolysis remains the same (high negative predictive value of the Ffn test).

Conclusion

The practice of managing threatened preterm labour with tocolysis and corticosteroids remains unsatisfactory since a significant proportion of women are unnecessarily receiving treatment. The results of this study suggest that introducing selective tocolysis on the basis of a positive Ffn alone would result in an increased number of women receiving tocolysis and a concomitant increase in the number who would potentially benefit from treatment. The Ffn strategy results in a non-statistically significant improvement in the ratio of numbers treated to the number who would pontentially benefit from tocolysis.

These results do not support the adoption of Ffn testing into the current management of threatened preterm labour where the incidence of ritodrine administration is low, but do suggest a potential benefit where the incidence of tocolysis is very high. It may be that combining Ffn testing with another independent discriminator of threatened preterm labour may yet improve our clinical decision making in the administration of tocolytic agents.

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Address reprint requests to:
PHILIP OWEN
Department of Obstetrics & Gynaecology
Ninewells Hospital & Medical School
Dundee, Scotland (United Kingdom)