Cervico-vaginal foetal fibronectin: A predictor of cervical response at pre-induction cervical ripening

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Summary

Context: **Not all pregnant women with an "unripe" cervix can be successfully ripened by the cervical ripening agents; therefore tests with predictive information are justified.**

Objectives: **To examine the effect of the presence of foetal fibronectin (FFN) in the cervico-vaginal secretions on pre-induction cervical ripening with either intravaginal Misoprostol or transcervical Foley catheter.**

Methodology: **Twenty (20) patients managed at a tertiary health institution in South-western Nigeria between March and May 2003 were randomised for cervical ripening by either intravaginal Misoprostol or Transcervical Foley catheters. Cervico-vaginal secretions were assessed for presence of FFN with Foetal Fibronectin Enzyme Immunoassay Kit (Adeza Corp.) prior to commencement of cervical ripening.**

Main outcome measures: **FFN status, Pre-ripening and Pre-induction modified Bishop scores and duration of cervical ripening.**

Results: **Ten of the fifteen patients with positive membrane immunoassay for FFN achieved ripened cervix (modified Bishop score ≥ 6) within 6 - 12 hours of exposure to the agents of cervical ripening. In the FFN negative group, only 2 of the five patients achieved ripe cervix within the >12 - 18 hours period, the rest being in the >18 - 24 hours period.**

Conclusion: **Foetal fibronectin test may offer useful predictive information prior to institution of processes of cervical ripening in patients with unfavourable cervices.**

Key-words: ***Foetal fibronectin, Foley catheter, Misoprostol, Pre-induction cervical ripening.***

Résumé

Contexte: Pas toutes les femme enceintes atteintes du col de l'utérus qui n'est pas mûr peuvent vivre jusqu' à un âge avancé a travers un agent cervical de maturation; donc des méthodes avec information prédicative sont justifiées.

Objectif: Examiner l'effet de la présence du fibronectin foetal (FNF) dans les sécrétions cervico-vaginal sur la maturation préinduction cervicale avec soit misoprostol intravaginal soit Foley Catheter transcervical.

Méthodologie: Vingt patients (20) soignées dans une institution de la santé tertière du sud ouest du Nigeria entre mars et mai 2003 étaient randomisés pour la maturation cervicale à travers soit Misoprostol intravaginal soit Foley Catheter transcervical. Sécrétions cervico-vaginal ont été évaluées pour la présence de FNF avec le kit immunoassay Enxyme de Fibronection foetal (Adeza corp.) avant le début de la maturation cervicale.

Des mesures principales: Status FNF, prématuration et préinduction score de Bishop modifié et la durée de la maturation cervicale.

Résultats: Dix entre quinze avec immunoassay membrane positif pour FNF avaient réalisé maturation cervicale (score de Bishop modifié ≥ 6) entre 6 - 12 heures d'exposition au agents de la maturation cervicale. Dans le groupe de FNF négatif 2 seulement entre cinq patients avaient réalisé maturation cervicale entre la durée > 12 - 18 heures, les autres étaient la durée entre > 18 - 24 heures.

Conclusion: La méthode Fibronectin foetal pourrait donner une information prédicative valable avant application du processus de la maturation cervicale chez des patients avec le col de l'utérus défavorable.

Introduction

Planned pre-induction cervical ripening and induction of labour has become an established part of modern obstetric practice, especially whenever continuation of pregnancy poses greater risk to either the mother or the foetus.

One of the factors that influence successful induction of labour is the state of the uterine cervix. If the cervix is "unripe" - Bishop's cervical score less than 6 - then the conventional method of induction of labour by surgical amniotomy is technically difficult and titration with intravenous oxytocin results in prolonged labour with risks of maternal and foetal complications and unsuccessful inductions, unnecessarily increasing the rates of caesarean section. The presence of ripened cervix correlates closely with successful induction of labour[1].

Many methods of cervical ripening are available. Some tried and discarded, from the less orthodox - sexual intercourse, nipple stimulation, a variety of herbs and homeopathic solutions, castor oil, enemas and acupuncture[2] to more orthodox methods, such as stripping the membranes, mechanical dilation, amniotomy and pharmacological preparations[3]. In the preparation of the cervix for labour and delivery, a variety of mechanical or pharmacological methods have been developed to induce cervical ripening. These methods include – Hygroscopic dilators, Transcervical Balloon catheter, Antiprogesterone, Relaxin gel, and

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Prostaglandins preparations[2]. Most of the information available on this subject in our population, resulted from studies on mechanical methods of cervical ripening, especially transcervical Foley catheter. Even though studies have shown the benefits of local administration of prostaglandin E_2 (PGE_2), the experience with use of Prostaglandins as pre-induction cervical ripening agents in this environment is very limited, largely due to cost and inadequate infrastructures to maintain these agents in the narrow temperature range required to maintain potency. Misoprostol (Prostaglandin E_1 analogue) shows promises because it is cheaper and is of comparable cervical ripening abilities with PGE_2 and has good shelf-life at even 30°C environmental temperature, such as obtainable in tropical climates.

In clinical practice, not all pregnant women with an "unripe" cervix can be successfully ripened by the cervical ripening agents. These failures lead to anxiety and may evoke un-cooperative attitude in patients under the circumstance. In this regard, reports had suggested that the presence of foetal fibronectin from cervico-vaginal secretions in patients with Bishop score <5 was predictive of a favourable response to induction by prostaglandin pessary (PGE_2) [3], while its absence in cervico-vaginal secretions of patients at 39 weeks' gestation may predict prolonged pregnancy[4]. Foetal fibronectin, a complex adhesive glycoprotein is present in high concentration in both the amniotic fluid and chorio-decidual interface. Matsura et al described a monoclonal antibody called FDC-6 which distinguishes it from the adult fibronectin [5]. It contains a specific epitope referred to as "oncofoetal" domain and its molecular weight is higher than adult plasma fibronectin. The exact mechanism by which foetal fibronectin enters into cervico-vaginal secretions is unclear, however, it has been suggested that changes in the connective tissues of the cervix occurs synchronously with changes in the membranes in the lower pole of the uterus. These changes may result in micro-leakage of amniotic fluid into the vagina, in which foetal fibronectin is found [6].

Therefore, we sought to determine the possible correlation of the presence or otherwise of foetal fibronectin in cervico-vaginal secretions of our patients and the ease of pre-induction cervical ripening with either intravaginal Misoprostol or transcervical Foley catheter. We hypothesize that if any correlation exists with the presence of foetal fibronectin (FFN) in the cervico-vaginal secretions and the response to cervical ripening process with either or both of these agents, it might be possible to rationally utilise FFN to predict the outcome of cervical ripening process with these agents of cervical ripening.

Materials and methods

The study was carried out between March and May 2003 as part of a larger randomised study evaluating transcervical Foley catheter and Intravaginal Misoprostol as pre-induction cervical ripening agents amongst pregnant women, with singleton gestations who presented for antenatal care and delivery at the University College Hospital (UCH), Ibadan. Patients recruited were randomised by means of computer-generated random numbers with blocks of two to either receive 50µg Intravaginal Misoprostol (Cytotec® tablet, Searle & Co., Chicago) or transcervical Foley catheter (Size 16F, with 30ml balloon capacity). All patients were managed on the antenatal wards preparatory to induction of labour.

The study was approved by the institutional review committee. All patients were adequately counselled and their informed consent obtained before their inclusion in the study. The inclusion criteria were, all consenting pregnant women with singleton pregnancy at 37 weeks gestational age or above, cephalic presentation, intact foetal membranes, Bishop's score of 5 or less and normal foetal heart rate. Those with ruptured foetal amniotic membranes were excluded from the study, as the amniotic fluid contains high levels of foetal fibronectin [7].

Cervico-vaginal secretion was obtained by speculum vaginal examination prior to digital examination for assessment of Bishop score by the Principal Investigator (AOA). The procedure for the assay of FFN was as detailed in the Adeza Biochemical Specimen collection kit (Adeza Biomedical Corporation, Sunnyvale, California USA) [8]. A Dacron® polyester tipped applicator was inserted into the vagina and rotated around the ectocervix and the posterior fornix for about 10 seconds to ensure saturation of the applicator with cervico-vaginal secretion. The cervix was thereafter assessed by digital vaginal examination. Those patients with Modified Bishop score of ≥ 6 were excluded. The cervico-vaginal secretion applicator was then processed with a qualitative foetal fibronectin membrane immunoassay kit (Adeza Biomedical Corporation, Sunnyvale California, USA). The foetal fibronectin membrane immunoassay is a qualitative fast-reacting solid-phase immunogold assay, whereby specimens obtained are combined with anti-human fibronectin-gold colloid conjugate. Presence of foetal fibronectin leads to the formation of a complex with the anti-fibronectin-gold conjugate, which is then passed through a membrane containing monoclonal antibody (FDC-6) specific for foetal fibronectin. A visible ring near the perimeter of the membrane provides an assay control. A positive sample will appear within 5 minutes as a spot in the membrane within the control ring. The intensity of the colour of the test ranges from lightly visible pink spot to a dark pink/purple spot.

The Obstetricians directly involved in the patients care were blinded to the results of the foetal fibronectin assay. Subsequent management followed the larger study protocol. Those randomised to the transcervical Foley catheter group had the transcervical Foley catheter passed aseptically in the hospital labour ward after explanation of the procedure and informed consent had been obtained. The patient was placed in the lithotomy position using leg supports; vagina was cleaned with antiseptic solution (chlorhexidine). Cusco's speculum was then inserted into the vagina and the cervix was visualised. The catheter was then gripped with the sponge forceps and advanced up the endocervical canal The balloon was then slowly inflated with the 30ml of sterile water or normal saline. The catheter was pulled down such that it was under strain and strapped onto the thigh with the adhesive tape[9]. Mobilisation was encouraged while the catheter was tightly strapped down to the thigh to effect the mechanical dilatation part of the process. The catheter was deflated, removed after 12 hours and cervix re-assessed, if no

spontaneous expulsion had occurred. A new catheter was re-passed for another 12 hours, if Bishop score was less than 6.

Those randomised to the Misoprostol group received 50 μg intravaginally in the posterior fornix. The dose was repeated every 6 hours until satisfactory Bishop score of ≥ 6. Patients who developed spontaneous labour had Bishop score assessed and recorded at the point of the diagnosis.

The maximum dose of Misoprostol was 200 μg or 4 doses of the drug. The time of maximum exposure to either agent was thus 24 hours. Oxytocin induction and active management of labour was commenced in those patients with satisfactory Bishop scores of ≥ 6. Oxytocin infusion was not started before 6 hours after the last dose, in those patients who received intravaginal Misoprostol. By use of a standardized hospital protocol, oxytocin infusion was by gravity-assisted method commencing with 4mU/min and increasing at interval of 30 - minute to achieve adequate contraction pattern (3 - 5, strong uterine contractions, each lasting 40 - 60 seconds) [10].

Baseline data included maternal age, parity, estimated gestational age, indication for induction of labour, assay for presence of fetal fibronectin in cervico-vaginal secretions and pre-ripening modified Bishop score. Outcome measures included, pre-induction modified Bishop score and duration of cervical ripening.

Data entry was into a standard pro-forma and the variables described by number (percentage), mean ± standard deviation/median and range. Differences between groups' Bishop scores were analysed by Mann-Whitney U test. Maternal age and estimated gestational age were analysed with Student's t - test, differences in parity and interval to achieve ripe cervical score in group/sub-groups by X^2 and Fisher's exact as appropriate, all using Statistical Package for Social Science (SPSS) for Window version 11.0.1.

Results

Twenty patients with term or post-term pregnancies and a pre-cervical ripening Bishop score < 5 were recruited in the study. Both groups (15 in FFN positive and 5 in FFN negative) were similar in their socio-demographic characteristics (Maternal age, parity and estimated gestational age) and the indication for the planned induction of labour. There was no statistical difference in the pre-cervical ripening and pre-induction of labour modified Bishop score in both groups (Table 1). Fifteen of the twenty patients {7 (Misoprostol) and 8 (Foley catheter)} had a positive membrane immunoassay for foetal fibronectin. There was no statistical difference in the distribution of all the patients with positive or negative assay tests for maternal age, parity, estimated gestational age, pre-ripening cervical and pre-induction cervical scores.

Table 1 Cervical assessment by modified Bishop score

Bishop score		Misoprostol n = 10	Foley catheters n = 10	Significance***
Pre-ripening score	01	1 (10.0%)	- (0.0%)	
	02	2 (20.0%)	2 (20.0%)	
	03	4 (40.0%)	5 (50.0%)	
	04	3 (30.0%)	2 (20.0%)	
	05	0 (0.0%)	1 (10.0%)	0.63 (NS)
Mean group Bishop score		2.9 ± 0.9	3.2 ± 0.9	
Pre-induction of labour score				
	06	3 (30.0%)	2 (20.0%)	
	07	3 (30.0%)	6 (60.0%)	
	08	4 (40.0%)	1 (10.0%)	
	09	-	1 (10.0%)	0.87 (NS)
Mean group Bishop score		7.1 ± 0.9	7.1 ± 0.9	

Data presented as number and percent, mean ± SD, NS = Not significant
**** Mann-Whitney U test*

Table 2 Duration of cervical ripening according to presence or absence of fetal fibronectin in the cervico-vaginal secretions (Hours)

	6 - 12	>12 - 18	>18 - 24	P-value****
Positive for fetal fibronectin (n = 15)	10 (66.7%)	3 (20.0%)	2 (13.3%)	**0.027 (S)**
Negative for fetal fibronectin (n = 5)	-	2 (40.0%)	3 (60.0%)	

Data presented as number and percent, S = significant.
*****Pearson's Chi square*

Positive fetal fibronectin assay test (Table 2)

Sixty-seven percent (10/15) of the patients with positive

membrane immunoassay for FFN achieved ripened cervix (modified Bishop score ≥ 6) within 6 - 12 hours of exposure to the ripening agents. The entire patients (7/7) with positive FFN test in the Misoprostol group and 3 of the 8 patients in the Foley catheter group were distributed in this category. The remaining 5 patients in the Foley catheter group were distributed in the >12 - 18 hours (3 patients) and >18 - 24 hours (2 patients) periods respectively.

Negative fetal fibronectin assay test (Table 2)

In this category, none of the patients achieved ripened cervix in the period 6 - 12 hours. Two patients (1 each in Misoprostol and Foley catheter) in this group however achieved ripe cervices in the period of >12 - 18 hours, with the remaining 3 {Misoprostol (1), Foley catheter (2)} patients were distributed in the period >18 - 24 hours.

Discussion

This study shows that the presence of foetal fibronectin in the cervico-vaginal secretions of women with unripe cervices indicates a favourable response in majority of patients, within 6 - 12 hours of exposure to either intravaginal Misoprostol or transcervical Foley catheter, in the process of pre-induction cervical ripening. All of the patients randomised to the Misoprostol group and who had foetal fibronectin demonstrated in their cervico-vaginal secretions, achieved favourable modified cervical Bishop scores, at most within 6 - 12 hours of exposure to 50μg Intravaginal Misoprostol. While, this showed possible association in the Misoprostol group, the observation in the Foley catheter group was less remarkable, at least from this study, as only 37.5% (3/8) of the patients in this group had achieved favourable cervical scores in the same period. From this study, the possible confounding effects of parity, estimated gestational age at cervical ripening and pre-ripening cervical score were explored and excluded, as there were no significant differences between the foetal fibronectin positive and negative categories before the institution of either Misoprostol or Foley catheter for cervical ripening.

This study probably may be one of few, if any, that had explored the possible association of foetal fibronectin and the ease of cervical ripening with either intravaginal Misoprostol or transcervical Foley catheter. Consequently, it was difficult to compare our findings with any other report(s). However, Tam and associates demonstrated a favourable response to induction by prostaglandin pessary in women with Bishop score <5 in the presence of foetal fibronectin from cervico-vaginal secretions [3].

If the findings of this preliminary study could be reproducible in other centres, it will be possible to predict more accurately the outcome in patients undergoing cervical ripening and thus minimise anxiety associated with unsuccessful pre-induction cervical ripening.

The major limitation of this study was the small population enrolled due to cost of the assay kit. Moreover, it was difficult to exclude in this study, the effects primarily due to Misoprostol as a cervical ripening agent demonstrated in our earlier study[11]. We recommend larger, possibly multi-centre and quantitative assay test studies to accurately predict the effects and the significant levels of foetal fibronectin in cervico-vaginal secretions predictive of cervical response in the ripening process.

Conclusion

We conclude that foetal fibronectin test may offer useful predictive information prior to cervical ripening with intravaginal Misoprostol or transcervical Foley catheter in patients with unfavourable cervices.

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