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Fetal fibronectin test for threatened preterm delivery 48h after admission: Cost-effectiveness study.

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Abstract

Objective: The aim of this work was to assess the cost-effectiveness of the fetal fibronectin (fFN) test at 48 hours after admission for threatened preterm delivery to promote early discharge.

Study design: Before-and-after study to calculate the incremental cost-effectiveness ratio (ICER). Patients were enrolled 48 hours after admission in a tertiary care centre for threatened preterm delivery between 24^{+0} and 34^{+6} weeks. fFN testing was performed. During the first period, physician was blinded to fFN test and discharge occurred after apparent reduced symptomatology at physician's discretion. During the second period, fFN test was revealed to physician and discharge was immediately proposed to negative test patients. The costs considered in this analysis were the direct medical costs from the hospital perspective: costs of hospitalisation, treatment, and imaging procedures. The efficacy criterion selected was the number of deliveries at 7 and at 14 days after admission for threatened preterm delivery.

Results: The study included 178 pregnant patient, 99 during the first period (July 2008-October 2009) and 79 during the second (March 2010-February 2012). The lengths of hospital stays were shorter during the second period, with more than 50% of women discharged home between 48 and 72 hours ($p < 0.0001$) resulting in a cost-saving of 76 051 euros. The number of deliveries at 7 and at 14 days was similar between the two periods.

Conclusion: The fFN test at 48 hours after admission supported early discharge and was safe and cost-effective.

Key words: fibronectin, preterm delivery, cost-effectiveness analysis

INTRODUCTION

Spontaneous preterm birth continues to be the major driver of perinatal morbidity and mortality. The use of antenatal corticosteroids, delivery in a hospital with appropriate neonatal facilities, and improvements in neonatal care have all had a favourable impact on neonatal survival and well-being [1,2]. Nevertheless, a significant number of patients presenting with threatened preterm delivery (TPD) will not be in "true" preterm labour. These women are therefore likely to spend unnecessary time at the maternal-fetal hospital unit – with all the associated social, emotional and economic costs that admission entails – before a decision is made to discharge them [3]. Fetal fibronectin (fFN) is a placental and membrane glycoprotein found in the extracellular choriodecidual matrix [4]. Identified in the cervicovaginal secretions of pregnant women, it is well-established as a useful diagnostic test for preterm birth in women both with and without symptoms of preterm labour [3,5–9]. This association is thought to result from a subclinical disruption of the choriodecidual space that allows fFN to leak into the lower genital tract [10]. Because fewer than 2% of symptomatic women deliver within 7 to 10 days of a negative fFN test, it has a strong negative predictive value [11]. Testing for fFN is readily available, relatively inexpensive, and easy to apply in clinical settings. It has therefore been introduced into clinical practice to help determine which women with TPD require further assessment and treatment and thus avoid unnecessary interventions for those at lower risk. Early simulation studies showed that the strategy of treating only women with a cervical length measurement < 30 mm and a positive fFN test was the most cost-effective and had no effect on neonatal health status [12,13]. Evidence from a systematic review of the literature suggested that fFN did not increase adverse outcomes and might reduce resource use [8]. A modest cost difference, largely dependent on whether or not this testing reduced hospital admission, was reported to support it, with shorter length of stay after its use began and a reduction in both corticosteroid and tocolytic treatments [14]. In

daily practice, some patients are admitted or referred with the association of shortened ultrasound cervical length and uterine contractions without fFN test available. In this situation, physicians can decide early discharge after tocolysis and corticosteroid therapy to reduce length of stay and to contribute to cost saving. We hypothesized that delayed use of fFN test could support early discharge.

Our objective was to assess the economic interest of the fFN test at 48 hours after admission for TPD to promote early discharge.

MATERIAL AND METHOD

Population

Inclusion criteria were threatened preterm labour after 24^{+0} and before 34^{+6} weeks' gestation (painful uterine contractions confirmed by external tocography and clinical alteration of the cervix) , with cervical dilatation < 3 cm, ultrasound cervical length ≤ 30 mm, intact membranes, and admission for 48-72 hours to the high-risk pregnancy department. Exclusion criteria were triplets or greater, vaginal bleeding, polyhydramnios or known congenital anomaly, placenta praevia overlapping the internal os, cervical cerclage and uterine malformation. Gestational age was assigned by the crown-rump length measured during the first-trimester ultrasound.

The institutional review board approved the study (CE-CIC-GREN-09-14).

Patient management

Both periods

At admission, one operator measured cervical length by transvaginal ultrasonography with a 5.0 MHz transvaginal probe (Voluson E8, General Electric) placed in the anterior fornix after

emptying the bladder, as recommended [15]. The operators verified the absence of amniotic fluid leakage during the speculum examination and systematically evaluated vaginal pH.

Women received intramuscular betamethasone (12 mg, two doses at a 24-h interval) and a nifedipine or atosiban tocolytic regimen during the first 48 hours, in accordance with our hospital guidelines. At 48 hours after admission, fFN testing was performed at speculum examination with no use of lubricant, before any other internal examination. Samples were taken from the posterior fornix by using a Dacron swab as specified in the manufacturer's guidelines (Hologic Cytyc™, Villepinte, France). Two operators collected all the samples. They verified the absence of amniotic fluid leakage during the speculum examination and systematically evaluated vaginal pH. The hospital biochemistry laboratory processed the samples with a rapid fFN detection system, the QuikCheck fFN™ test (Hologic Cytyc™, Villepinte, France).

First Period (July 2008 to October 2009)

Physician was blinded to fFN test result and women were discharged home with advice when physicians considered that symptoms of threatened preterm labour had durably regressed and when appropriate follow-up was arranged as recommended by our hospital guidelines.

Second Period (March 2010 to February 2012)

Physician received fFN test result from the laboratory as soon as available (within 2 hours). If the fFN test was negative, physician was encouraged to discharge the patient immediately with appropriate advice. Physician could also decide to prolong hospital stay despite a negative fFN test, if he considered that risk of imminent preterm birth remained high (mainly based on persistent uterine activity). Patient could decline early discharge. In case of positive test, decision of early discharge or not was taken at physician's discretion (based on uterine activity and distance from home to hospital).

Economic analysis

This before-and-after cost-effectiveness study was conducted from the hospital perspective.

The costs considered in this analysis were the direct medical costs: costs of hospitalisation, treatment and imaging procedures. They were obtained by the microcosting method. That is, we considered for each woman the length of her stay in the department, the duration and dosages of treatments administered, the number of laboratory tests and the number and types of imaging procedures performed. Next, each length of stay was multiplied by the hourly cost of the hospitalisation in the department to obtain the total hospitalisation cost for each woman. The hospital financial department provided the cost per year from its general chart of accounts, and the analytic accounting of the costs (labour charges and supplies). The hospital central pharmacy provided the drug costs. The laboratory department assessed the costs of laboratory tests. Finally, the cost of imaging procedures was calculated using the national index of common costs: the number of "Relative Costs Index" (RCI) points attributed to ultrasound examinations was multiplied by the value of RCI points in effect in our hospital (value calculated by the financial department from the analytic accounting).

The cost of fFN test was added for the women of the second period: 35 EUR per test. In summary, the costs considered for period 1 were those for hospitalisation and ultrasound, and for period 2, hospitalisation, ultrasound and the fFN test. As we got the actual costs for each year, there was no need to update the cost data [16].

The efficacy criterion selected was the number of deliveries at 7 and at 14 days after admission for TPD.

The incremental cost-effectiveness ratio (ICER) was calculated as follows:

$$\frac{\text{costs period 2} - \text{costs period 1}}{\text{effectiveness in period 2} - \text{effectiveness in period 1}}$$

The comparative points of each ratio (at D7 and D14) were represented on the cost-effectiveness graph to reach a conclusion about the cost-effectiveness of the fFN test at 48 hours [17] (see Figure 1).

RESULTS

A total of178 women were recruited, including 99 during the first period and 79 during the second. The groups did not differ for maternal age, BMI, proportion of primigravida, or history of TPD during any previous pregnancy (Table 1). Most of cases were singletons and delivered spontaneously. The rate of preterm delivery did not differ significantly (33.3% vs 36.7%) (Table 1). Gestational age at admission and at delivery were similar for the two periods. Mean cervical length at admission was shorter during the second period (p=0.02) (Table 2). The fFN test was more often positive during the first period (p =0.004).The length of hospitalisation was shorter during the second period, with more than half of women discharged home at 48 to 72 hours after admission (p <0.0001). The number of deliveries at 7 and at 14 days was similar between the two periods (Table 2). Among the 178 women recruited in the study, 127 (71.3%) had a negative fFN test result and 51 (38.7%) a positive result (Table 3). Gestational age at delivery was earlier in the fFN+ group (p =0.01), with a higher portion of women with a cervical length ≤ 10 mm at admission (p =0.02). Hospital stays were longer in the fFN+ group (p =0.004) with a higher number of deliveries at 7 (p =0.002) and 14 days (p =0.03), but the frequency of preterm delivery was not significantly different between the two groups (Table 3).

Value of ICER were -3 019 263 at day 7 and -2 753 680 at day 14. Both ratios were in the bottom right quadrant of the cost-effectiveness graph, on the side of the dominant strategies post-admission (see Figure 1). In the second period, the costs associated with the length of

stay were lower with similar effectiveness. This savings amounted to 76 051 EUR and demonstrated the cost-effectiveness of the fFN test at 48 hours.

COMMENT

In our study, the fFN test performed 48 hours after admission for TPD to promote early discharge appeared to be cost-effective. The earlier economic studies focused principally on the utility of the test to decide for admissions and they demonstrated cost savings due to a reduction in the number of admissions [13,14]. In our study, costs fell because of earlier discharge. This reduction of the length of hospitalization was observed because of the physicians' and women's adherence to the new policy of early discharge when fibronectin test was negative. This benefit was not lost by the existence of positive tests that could have caused unnecessary worry.

The rate of preterm delivery (birth before 37 weeks) was similar to that reported in other studies using this fFN test as a screening examination. Il underlined that admitted patients with TPD were still at high risk of preterm delivery at 48 hours post-admission [3,18,19]. Nevertheless the number of deliveries at 7 days in our study was lower, especially in the group of women with a negative fibronectin test [3,18,19]. This statement was not surprising because our population consisted in women who had been admitted for TPD for 48 hours and had not yet given birth. It was thus a population with a lower risk for delivery during the week because they were already clinically stable. The negative fFN test allowed us to confirm the stability of the disease and provided decision assistance for the physician in favour of early discharge. The fFN test did not allow us to distinguish between patients delivering at term or before term, but its main interest remained its strong negative predictive value for delivery

within two weeks of testing, as previously described for fFN testing at admission [5,20]. The fFN test could therefore make it possible to identify objectively the women with TPD unlikely to deliver in the next two weeks. Early discharge after a negative fFN test thus appeared to be a safe option.

Ultrasound measurement of cervical length at admission made it possible to select high-risk women for PTD, but the difference of the mean cervical length between the fFN-positive and fFN-negative test groups appeared to be very small (<1-3 mm) and within the range of the observed inter- and intra-observer variability [21,22]. Therefore, the fFN test did not appear to be redundant with this parameter in our study.

The prevalence of fFN+ tests was higher during the first period although patients characteristics were clinically comparable in both periods. The strong variation of positive fFN test prevalence had already been reported in the literature and remained poorly understood for the moment [6,11,23]. The high proportion of negative tests during second period could make its use questionable as discharge could thus be based only on the clinical evaluation. Indeed this strategy would also save the cost of the test. Nonetheless, its strong negative predictive value was confirmed once more and participated to reassure both clinicians and women. It served as a decision support for discharge, especially for women residing a substantial distance from the maternity ward with a risk of outborn preterm neonates.

In conclusion, our study demonstrated that the use of the fFN test at 48 hours after admission for TPD supported early discharge and was safe and cost-effective. A new discharge policy based on early discharge and appropriate follow-up at home after the fFN test may be a safe alternative, especially for patients living far away from an adequate perinatal care center.

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Conflicts of interest

Authors declare to have no conflict of interest

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Figure legends

Figure 1: Cost-effectiveness graph and cost-effectiveness ratio at D7 and D14

Figure 1: Cost-effectiveness graph and incremental cost-effectiveness ratio (ICER) at D7 and D14

Table 1 Patients characteristics

	Period 1 n=99	Period 2 n=79	p
Maternal characteristics			
Maternal age	26.9±5.2	27.4±5.3	0.57
<=20	8.1	8.9	0.78
20-30	64.7	59.5	
30-40	27.3	31.7	
BMI	22.0±4.1	22.0±4.3	0.96
<=18.5	13.1	20.3	0.64
18.5-24.9	63.6	58.2	
25-29.9	17.2	15.2	
>=30	6.1	6.3	
Primigravida	65.7	67.1	0.84
Threatened PTD during any previous pregnancy	12.1	11.4	0.88
Characteristics of the pregnancy			
Type of pregnancy			
singleton	74.8	81.0	0.37
Mode of labour onset			
spontaneous	69.7	79.5	0.26
induction	22.2	12.8	
planned caesarean	8.1	7.7	
Preterm birth	33.3	36.7	0.64
Spontaneous	66.7	65.5	0.92
Induced	33.3	34.5	0.92

BMI: body mass index

PTD: preterm delivery

Table 2: Comparison of clinical monitoring data during hospitalisation between the two periods.

	Period 1 n=99	Period 2 n=79	p
Gestational age at admission (WG)	30.9±2.4	30.5±2.3	0.25
Gestational age at delivery (WG)	37.4±2.4	37.5±3.1	0.76
Mean cervical length at admission (mm)	18.5±6.5	16.5±4.8	0.02
<=10	11.1	11.5	0.03
10-20	53.5	71.8	
20-30	35.4	16.7	
Length of stay (days)	5.5±3.9	4.7±6.6	0.33
2 days	17.6	55.7	<0.0001
3 days	20.9	17.7	
≥4 days	61.5	26.6	
Fibronectin test + (%)	39.4	15.2	0.004
Delivery within 7 days (%)	5.1	2.5	0.47
Delivery within 14 days (%)	9.1	6.3	0.50

WG; weeks of gestation

mm: millimeters

Table 3: Comparison of clinical monitoring data during hospitalization as a function of fibronectin test result.

	fFN - n=127	**fFN + n=51**	**p**
Gestational age at admission (WG)	30.7±2.4	30.7±2.3	0.94
Gestational age at delivery (WG)	37.7±2.6	36.6±2.9	0.01
Mean cervical length at admission (mm)	17.9±5.0	16.7±7.0	0.21
<=10mm	7.1	22.0	0.02
10-20	65.4	52.0	
20-30	27.6	26.0	
Length of stay (days)	4.2±3.7	7.9±7.9	0.004
2 days	42.5	14.0	<0.0001
3 days	23.6	7.0	
≥4 days	33.9	79.1	
Delivery within 7 days (%)	0.8	11.8	0.002
Delivery within 14 days (%)	4.7	15.7	0.03
Preterm delivery (<37 WG) (%)	32.3	41.2	0.26

fFN: fetal fibronectin, WG: weeks' gestation

mm: millimeters