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Targeted therapy for threatened preterm labor based on sonographic measurement of the cervical length: a randomized controlled trial

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KEYWORDS: cervical length; corticosteroids; preterm labor; tocolysis; ultrasonography

ABSTRACT

Objective *False positive diagnosis of preterm labor is common. As a consequence, medications including corticosteroids to promote fetal lung maturity and tocolysis are prescribed unnecessarily. We tested the hypothesis that management of threatened preterm labor based on measurement of cervical length by ultrasonography can reduce the number of women who receive inappropriate treatment.*

Methods *Forty-one women with threatened preterm labor for whom a clinical decision was made to prescribe antenatal corticosteroids and tocolysis were randomized to have their cervical length measured by transvaginal ultrasound (n = 21) or to receive therapy as planned (n = 20). Fourteen women in the ultrasound group had a cervix longer than 15 mm and the therapy was withheld, while the other seven with a short cervix were managed in the same way as the control group.*

Results *Three women (14%) in the ultrasound group were treated inappropriately with antenatal corticosteroids because they remained undelivered for more than a week. This compared favorably with the control group where 18 out of 20 (90%) received corticosteroids unnecessarily (relative risk (RR) 0.16; 95% confidence interval (CI), 0.05–0.39). Tocolysis was given to only seven women (33.3%) in the ultrasound group compared with 20 (100%) in the control group (RR 0.3; 95% CI, 0.15–0.54). There were no babies in either group who were born prematurely without being given a full course of antenatal corticosteroid therapy.*

Conclusion *Women with threatened preterm labor and cervical length more than 15 mm should not receive tocolysis. The issue of the safety of withholding corticosteroid therapy in this clinical scenario warrants further study. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The diagnosis of preterm labor is notoriously difficult. Meta-analysis of clinical trials of antibiotics in women with threatened preterm labor reported that only 18% of women in the 'no intervention' group actually delivered within 7 days of the diagnosis[1], while a large multicenter study of tocolytic therapy reported that, in the placebo arm, 49% of women in preterm labor still remained undelivered after 7 days[2]. Such a high rate of false positive diagnosis of preterm labor results in a large proportion of women being given antenatal corticosteroids and tocolysis unnecessarily. Antenatal corticosteroids (two injections 12 hours apart) not only promote fetal lung maturity and reduce the incidence of respiratory distress syndrome, but also reduce neonatal mortality and neonatal intracranial hemorrhage[3]. It is, therefore, understandable that clinicians try to avoid a situation where a preterm baby is born without exposure to corticosteroids.

When a presumed diagnosis of preterm labor has been made, tocolysis is commenced to delay labor for a minimum of 24–48 h, thus allowing time for the administration of a full course of corticosteroids. However, tocolytics, especially betamimetics, have unpleasant side-effects[4], while several episodes of threatened preterm labor in the same pregnancy may expose the fetus to multiple courses of corticosteroids with potentially serious long-term consequences[5].

We conducted an observational study in which cervical length was measured by transvaginal ultrasonography in

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216 singleton pregnancies presenting with painful uterine contractions before 36 weeks' gestation. We found that 99% of women with a cervical length of ≥ 15 mm did not deliver within 7 days, regardless of the use of tocolytics[6]. Based on these findings we conducted a randomized controlled trial to evaluate the hypothesis that in women presenting with threatened preterm labor the decision to administer tocolytics and steroids should be based on the sonographic measurement of cervical length.

PATIENTS AND METHODS

This multicenter randomized trial was conducted between 2003 and 2005 in five hospitals in the UK and one in Spain following approval by the local Research Ethics Committees. Women were eligible if they fulfilled the following criteria: (1) live, singleton pregnancy; (2) uterine contractions before 34 completed weeks' gestation; and (3) a clinical decision was made to use tocolytics and steroids. We excluded women with preterm premature rupture of membranes, or if a course of antenatal corticosteroids or oral steroid therapy had been given within 7 days of possible randomization. All the women had a vaginal examination on admission, however, a change in the Bishop score was not a prerequisite for randomization. None of the hospitals used fibronectin to confirm or refute the diagnosis of preterm labor.

A member of the research team assessed eligibility for the study after obtaining the appropriate information from the clinicians caring for the women. Following counseling by the members of the research team, eligible women who agreed to sign the written informed consent were randomized using consecutively numbered sealed envelopes kept in a secure drawer on the respective labor wards. The original computer-generated randomization sequence was kept separately.

Women randomized to routine care received tocolytics and antenatal corticosteroids as per the hospital's protocol and clinician's instructions. Women allocated to the experimental group had a transvaginal scan to measure the cervical length, which was performed by a member of the research team who was not involved in the care of the patient. If the cervical length was less than 15 mm women were given tocolytics and antenatal corticosteroids as per the hospital's protocol. Women with a cervical length of 15 mm or more were managed expectantly; tocolysis and antenatal steroids were not prescribed. Women with a cervical length of ≥ 15 mm in whom uterine contractions persisted had another transvaginal scan 4 h later, or earlier if clinically indicated, and the same protocol was followed.

The primary outcome of interest was the proportion of women still pregnant 7 days (168 h) after the last injection of antenatal steroids. Other outcomes of interest were appropriate treatment with corticosteroids (preterm birth with corticosteroids given within 1 week of delivery), duration of tocolysis and hospitalization, gestational age at delivery and incidence of preterm labor.

Statistical considerations

Data were analyzed according to intention to treat principles using parametric tests for normally distributed continuous variables and relative risks (95% confidence intervals for comparison of proportions). Our observational data[6] indicated that, in the control group, at least 90% of eligible women would still be pregnant 7 days after the administration of antenatal corticosteroid therapy. We hypothesized that ultrasound-aided management of preterm labor would reduce by 50% the number of women still pregnant 1 week after corticosteroid treatment. In order to prove this hypothesis we needed to recruit 40 women (power 80%, alpha of 5%).

RESULTS

Communication between labor ward clinicians and the research team proved difficult owing to the workload and we were, as a result, unable to collect data on the number of women with threatened preterm labor who fulfilled the inclusion criteria but were not offered participation in the study. In total, the research team was informed of 43 potentially eligible women. One woman declined participation and one woman was deemed ineligible because of vaginal bleeding. Demographic and clinical data were available for all 41 eligible women who agreed to participate (Figure 1).

As expected, the groups were balanced in respect of the demographic and clinical findings (Table 1). Twenty-one women were randomized to have a transvaginal scan; seven of them (33%) had a short cervix. One woman with a cervix < 15 mm also had a dilated cervix on vaginal examination (2 cm); the cervical os was thought

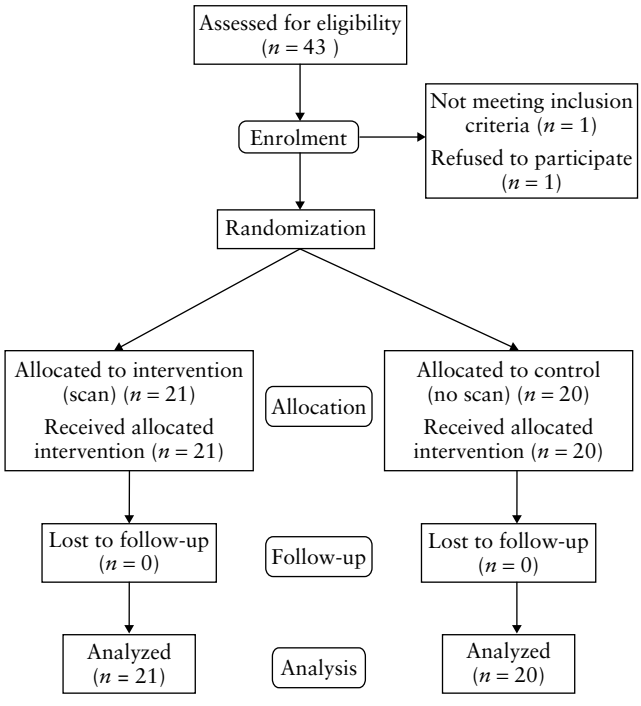

Figure 1 CONSORT flowchart.

Table 1 Status at randomization

Parameter	*Transvaginal scan* (n = *21*)	*Controls* (n = *20*)
Primpara	8	7
Previous preterm birth < 34 weeks' gestation	3	1
Height (cm, mean ± SD)	163 ± 7	163 ± 6
BMI (kg/m^2, mean ± SD)	25 ± 5	25 ± 5
Smokers	2	3
Gestation (days, mean ± SD)	218 ± 13	215 ± 19
Cervical length (mm, mean ±SD)	22.8 ± 13.1	
Cervix < 15 mm	7	—

to be closed in the others. All women with a cervix longer than 15 mm had a closed cervix on vaginal examination, apart from one woman in whom the cervix admitted a fingertip. In the control group 18 women had a closed cervix, in one woman the cervix admitted a fingertip, and in one the cervix was 1–2 cm dilated.

Management of the threatened preterm labor in both groups is summarized in Tables 2 and 3. In the ultrasound group, all fourteen women in whom the standard therapy was withdrawn because of a long cervix delivered more than 7 days after randomization (range 35–88 days). The remaining seven women with a short cervix were prescribed corticosteroids and tocolysis; three (42.9%) remained undelivered 7 days later. All women in the control group were prescribed a combination of steroids and tocolysis as per protocol; 18 of them remained undelivered 7 days later. There was, therefore, a significant difference in the proportion of women exposed to tocolytic therapy i.e. 33.3% in the ultrasound group vs. 100% in the controls (relative risk (RR) 0.3; 95% confidence interval (CI), 0.15–0.54). The difference between the two groups in the proportion of women who received inappropriate treatment, defined as giving birth more than 7 days after the administration of antenatal corticosteroids or preterm birth without corticosteroid treatment, was highly significant (RR 0.16; 95% CI, 0.05–0.39; $P < 0.0001$). Therefore 18 women in the ultrasound group received the appropriate treatment, defined as preterm birth with antenatal corticosteroids given ≤ 7 days previously ($n = 4$) or birth > 7 days after randomization without being given antenatal corticosteroids ($n = 14$), compared with only two women in the control group (Table 2).

Six women were prescribed antibiotics after randomization. In the scan group three women had antibiotics for a urinary tract infection (UTI) and one for prelabor rupture of membranes; two women were prescribed antibiotics for a UTI in the control group.

Fifteen women in the ultrasound group were discharged within 48 h, five within 24 h. Two out of 14 women with a cervical length > 15 mm needed a further transvaginal scan because of persistent uterine contractions, but in both cases the cervix remained long. Both women were discharged within 48 h and gave birth at term. In the control group, six women stayed in hospital for ≤ 24 h, six women for 24–48 h and eight for more than 2 days. The difference in the duration of hospital antenatal stay between the two groups was highly statistically significant ($P < 0.0001$).

Three premature babies in the control group and one in the scan group experienced breathing difficulties; there were no other neonatal morbidity or deaths recorded in either group.

DISCUSSION

Our study shows conclusively that cervical length measurement by transvaginal ultrasonography in women with threatened preterm labor reduces unnecessary exposure of pregnant women and their babies to corticosteroid and tocolytic therapy. The clinical benefits include reduction in the risk of maternal side-effects and minimization of the risk of repeated fetal exposure to corticosteroids if episodes of threatened preterm labor persist. Although we have not performed formal health economic analysis, the savings from the reduced use of tocolytic therapy and shortened antenatal hospital stay are likely to be substantial.

The high proportion of women who remain undelivered 7 days after the diagnosis of preterm labor (85%) and the preterm delivery rate before 34 weeks' gestation of only 12% indicate a relatively low-risk population despite the clinical diagnosis of preterm labor and decision to prescribe therapy. Unfortunately, it was not possible to collect the demographic and clinical data on potentially eligible women who did not take part in the study, but there was no indication that women at a particularly high risk of preterm birth were systematically denied the

Table 2 Administration of antenatal corticosteroids in relation to preterm birth

Treatment administerd	*Transvaginal scan* (n = *21*)	*Controls* (n = *20*)	*Relative risk (95% CI)*
Inappropriate treatment	3	18	0.16 (0.05–0.39)
Birth > 7 days after steroids given	3	18	
Preterm birth within 7 days but steroids not given	0	0	
Appropriate treatment	18	2	8.5 (2.75–30.8)
Steroids given within 7 days of preterm birth	4	2	
Delivered after 7 days without receiving steroids	14	0	

CI, confidence interval.

Table 3 Outcomes related to the management of threatened preterm delivery

Treatment administered	*Transvaginal scan* (n = *21*)	*Controls* (n = *20*)	*Relative risk (95% CI) or* P
Complete course of antenatal corticosteroids	7	20	0.3 (0.15–0.54)
Tocolysis	7	20	0.3 (0.15–0.54)
GTN	7	17	
Atosiban	0	3	
Duration (hours, median (range))	0 (0–24)	24 (0–67)	$P < 0.0001$
Onset of labor			
Spontaneous	19	11	
Induction of labor	0	1	
Cesarean section	2	8	
Mode of delivery			
Vaginal	16	9	
Cesarean section	5	11	
Gestational age at delivery (days, mean ± SD)	265 ± 22	262 ± 20	$P = 0.036$
Birth at < 28 weeks' gestation	0	0	
Birth at < 32 weeks' gestation	1	1	
Birth at < 34 weeks' gestation	2	3	

CI, confidence interval; GTN, glyceryl trinitrate.

opportunity to participate in the study at any of the centers involved.

Is there a possibility that the widespread use of transvaginal ultrasonography to confirm or refute the diagnosis of preterm labor may cause harm? Our study was not large enough to exclude the possibility that withholding antenatal corticosteroid therapy if the cervix is long (> 15 mm) may result in some preterm babies being born without adequate corticosteroid treatment. Our observational data show that the risk of this happening is unlikely to be greater than 2–3%[6]. However, large cohorts would have to be followed up after ultrasound-based management until 35 weeks' gestation to see how many women may miss getting corticosteroid prophylaxis before preterm birth. A combination of a long cervix and low levels of fibronectin is likely to reduce the risk of imminent preterm birth even further[7].

A non-inferiority trial to confirm that the targeted management of preterm labor based on transvaginal ultrasound with or without fibronectin is as safe as current management based on the combination of digital vaginal examination and clinical assessment would have to include in excess of 4000 women with threatened preterm labor. As such a large study is unlikely to be undertaken in the foreseeable future we believe that the implementation of our protocol, including repeated 2–4 hourly transvaginal scans when clinical suspicion persists, coupled with a careful review of all cases when a baby is born without exposure to antenatal corticosteroids is the best way forward.

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REFERENCES

1. King J, Flenady V. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. The Cochrane Database of Systematic Reviews: Reviews 2002 Issue 4 John Wiley & Sons, Ltd Chichester, CD000246.
2. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, Perry KG, Varner M, Goodwin TM, Lane R, Smith J, Shangold G, Creasy GW. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000; **182**: 1173–1183.
3. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. *Am J Obstet Gynecol* 1995; **173**: 322–335.
4. Gyetvai K, Hannah M, Hodnett E, Ohlsson A. Tocolytics for preterm labor: a systematic review. *Obstet Gynecol* 1999; **94**: 869–877.
5. Guinn DA, Atkinson MW, Sullivan L, Lee M, MacGregor S, Parilla BV, Davies J, Hanlon-Lundberg K, Simpson L, Stone J, Wing D, Ogasawara K, Muraskas J. Single vs. weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. *JAMA* 2001; **286**: 1581–1587.
6. Tsoi E, Akmal S, Rane S, Otigbah C, Nicolaides KH. Ultrasound assessment of cervical length in threatened preterm labor. *Ultrasound Obstetric Gynecol* 2003; **21**: 552–555.
7. Gomez R, Romero R, Medina L, Nien JK, Chaiworapongsa T, Carstens M, Gonzales R, Espinoza J, Iams JD, Edwin S, Rojas I. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. *Am J Obstet Gynecol* 2005; **192**: 350–359.

