Antenatal steroids for fetal lung maturity: Time to target more frequent doses to fewer women?

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Abstract

Antenatal corticosteroids for fetal lung maturation have become mainstay treatment in women thought to be at high-risk of premature birth. To ensure treatment efficacy before delivery, the current practice is to administer steroids early to a woman considered at risk; however, neonatal benefit is lost after the seven-day treatment-to-delivery window. Over half of women who deliver before 34 weeks' gestation do not receive antenatal corticosteroids within this timeframe, but many still deliver prematurely; however, clinicians are reluctant to administer repeated courses of steroids due to concerns, among others, of impaired fetal growth. However, evidence is mounting regarding the optimal timing for steroids, including substantive benefits close to delivery, and the benefits of repeated courses if delivery has not occurred. Better targeted treatment is required to allow for maximum benefit; reducing unnecessary treatment in low-risk women, while targeting therapy in the high-risk cohort and offering repeat courses if the seven-day window is exceeded. Novel tools to aid prediction may help implement this strategy.

Keywords

Antenatal corticosteroids, prediction, preterm birth, respiratory distress syndrome, timing

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Background

Preterm birth (PTB), delivery prior to 37 weeks' gestation remains a challenging problem within the field of maternal-fetal medicine. Affecting 5–18% of pregnancies in the UK, and many more globally, it is the leading cause of neonatal morbidity and mortality worldwide.^{1,2} Despite extensive research into prophylactic and therapeutic interventions, few have been found to be effective and incorporated into clinical practice. However, the administration of antenatal corticosteroids (ACS) to promote fetal lung maturation before delivery has been shown to improve fetal outcomes in developed country settings, and has been an established treatment for women at high risk of preterm delivery for the last 20 years.

While the evidence for the benefit of ACS use is established, data regarding the optimal timing and repeated courses are not always considered. As a result, the ingrained clinical approach of early administration to avoid missing the opportunity for benefit prior to preterm delivery, has remained unchallenged, despite substantive benefit when given close to delivery. Given that most women who present with preterm contractions do not deliver within seven days (the window of benefit for steroids),³ this frequently results in ACS being given too early, thereby necessitating repeated courses if the risk of prematurity remains high. This review will present the up to date evidence for ACS administration, particularly related to the timing and frequency of administration, with consideration given to the use of prognostic tools to predict time of delivery and optimise ACS benefit.

History of ACS

The therapeutic effect of ACS for fetal lung maturation was discovered incidentally by Liggins⁴ while researching the impact of dexamethasone on premature parturition in a sheep model. Liggins found that despite premature delivery, there was lung inflation amongst the fetal sheep.⁴ Liggins and Howie⁵ performed the first seminal randomised controlled trial (N=282) in women with preterm labour <37 weeks of gestation using betamethasone for the prevention of respiratory

distress syndrome (RDS). A reduction of 11% and 20% in neonatal death and RDS, respectively, was observed in the treatment group.⁵ Despite the evidence, the Lancet rejected this initial publication as it lacked general interest.⁶

A number of trials followed suit, and the first meta-analysis was published by Crowley et al.,⁷ including 12 studies and over 3000 women, which demonstrated that a course of ACS reduced RDS and neonatal mortality by approximately 50% in infants born prior to 34 weeks of gestation. Two years later the Royal College of Obstetricians and Gynaecologists (RCOG) produced a guideline on the use of antenatal steroids for threatened PTB, the National Institutes of Health (NIH) followed suit in 1994,⁸ followed by the American College of Obstetricians and Gynaecologists (ACOG) in 2002⁹: all over 20 years after the original RCT findings, with Crowley's systematic reviews finally laying the foundations for the clinical guidelines. It is no coincidence that the Cochrane Collaboration logo (Figure 1), a forest plot, represents the systematic review of the first seven ACS studies, chosen to remind us of the importance of systematic reviews in revealing and translating evidence into clinical practice. The Collaboration was quick to point out the lives lost in the delay of implementing this evidence.¹⁰

Evidence of benefit

The most recent Cochrane review (2006; 21 studies, 3885 women and 4269 infants) reiterated this message; when comparing ACS versus placebo, there was an overall reduction in combined fetal and neonatal death (RR 0.77, 95% CI 0.67–0.89) and a 44% reduction in RDS (RR 0.66, 95% CI 0.59–0.73).¹¹ ACS therapy was also associated with a 46% reduced incidence of cerebroventricular haemorrhage

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Figure 1. The logo of the Cochrane Collaboration.

(RR 0.54, 95% CI 0.43–0.69).¹¹ When longer term outcomes were considered, treated children had reduced developmental delay at three years compared with placebo/no treatment, with a trend towards a reduction in cerebral palsy (RR 0.60, 95% CI 0.34–1.03).¹¹

Timing of steroids

When presented with an intervention with such clear benefit, clinicians strive to administer steroids to all women with threatened PTB. However, the timing of steroid administration is crucial to conferring this benefit. Sub-group analysis of the Cochrane review revealed that while there was a significant reduction in combined fetal and neonatal death for infants born within 24 h (RR 0.60, 95% CI 0.39 to 0.94, three studies, 293 infants) and within 48 h (RR 0.59, 95% CI 0.41 to 0.86, one study, 373 infants) of corticosteroid therapy, this was not seen in those infants who delivered between one and seven days (RR 0.81, 95% CI 0.60 to 1.09, three studies, 606 infants) and after seven days (RR 1.42, 95% CI 0.91 to 2.23, three studies, 598 infants).¹¹ The observed reduction in RDS was more consistent between 24 h and seven days after steroid administration, but not after seven days (RR 0.82, 95% CI 0.53 to 1.28) nor before 24 h (RR 0.87, 95% CI 0.66 to 1.15).¹¹ Given that the majority of women who present with threatened PTB do not deliver within seven days of presentation,¹ but may deliver prematurely, many women will receive steroids distant from delivery after the benefit has subsided. The benefit of reduced perinatal death within 48 h (but not after) is often overlooked by clinicians who tend to aim for early administration to allow time for the steroids to confer the reduced risk of RDS after 24 h of administration.

Equally the potential adverse effects of single course of steroids, given within a week are not always appreciated, in spite of their clear benefit. Sub-group analysis of the same dataset revealed reduced birth weight of infants born between one and seven days after steroid administration (mean difference -105.92 g, 95% CI -212.52 to 0.68 g) compared with placebo/no treatment, and also in those who delivered more than seven days after the first dose (mean difference -147.01 g, 95% CI -291.97 to -2.05 g).¹¹ Given Barker's seminal work suggesting a link between impaired fetal growth and future type 2 Diabetes Mellitus and cardiovascular disease,¹² as well as a number of animal studies demonstrating increased blood pressure in the adult offspring exposed to ACS,¹³ concerns regarding the adverse effects have caused the obstetric community to be cautious about administering repeated doses of steroids to women who remain undelivered after seven days of ACS

treatment, but who remain at high risk of imminent PTB. However, these effects are also apparent with delayed delivery after single courses.

Important to remember is that the beneficial effect of steroids is not seen in those women who deliver after 34 weeks of gestation. More worrying is the potential for harm; in the Cochrane analysis,¹¹ for infants who received a single course of corticosteroids, but who delivered after 36 weeks of gestation, a non-significant trend towards an increase in combined fetal and neonatal death (RR 3.25, 95% CI 0.99 to 10.66, two trials, 498 infants) was observed, as well as in neonatal death alone (RR 2.62, 95% CI 0.77 to 8.96, three trials, 514 infants). With this theoretical risk in mind, combined with a reduction in birth weight and potential adverse effects on the fetal birth weight, accurate timing of steroids to those most at risk of delivery within seven days, and prior to 34 weeks of gestation is vital.

Repeated doses of corticosteroids

This topic was addressed in a Cochrane review in 2011, including 10 trials of over 4730 women, evaluating the use of repeat doses of ACS compared with no repeat corticosteroid treatment in women between 23 and 34 weeks' gestation who remained at risk of preterm delivery for seven or more days after initial treatment with corticosteroids.¹⁴ Of note, treatment regimes and dosing intervals varied between trials. A repeated course of steroids was associated with a reduction in RDS in infants compared with placebo or no treatment (RR 0.83, 95% CI 0.75 to 0.91). While no difference was observed in fetal or neonatal mortality (RR 0.94, 95% CI 0.71 to 1.23), a reduction in composite serious infant outcome (variably defined between trials as a composite measure including mortality and morbidity outcomes) was observed (RR 0.84, 95% CI 0.75 to 0.94). This benefit comes at the expense of a slight reduction in mean birth weight (mean difference -75.79 g, 95% CI -117.63 to -33.96), but no change in the proportion of small for gestational age (SGA) infants. Available data showed no difference in longer term outcomes including cerebral palsy or development delay, nor differences in various measures of body size in childhood.¹⁴ There is some concern that both single or repeat doses of ACS could increase the incidence of adult hypertension and insulin resistance with subsequent onset of diabetes mellitus.¹⁴ Long-term evidence is lacking with regards to long-term adverse effects of multiple steroid courses and further investigation is required.

While preterm neonates undoubtedly benefit from repeated antenatal steroids in terms of short-term outcomes, the optimal dose and timing of these are still unclear. Sub-group analysis of the Cochrane data showed no difference in fetal outcomes when the second dose was administered 7 days or 14 days after the first course, when risk of imminent delivery remained high. Furthermore, the frequency of re-administration is not clear; in their trial published in the *Lancet* (2006), Crowther et al. administered repeated single doses (11.4 g of betamethasone) weekly (until 32 weeks of gestation) to women thought to be at high risk of PTB but who remained un-delivered seven days after the previous dose of steroids, compared with placebo ($N = 982$);¹⁵ 42% of women in the treatment arm received one repeat dose, while 25% received four or more repeat doses. Fewer infants in the repeat steroid group had respiratory distress and fewer had severe lung disease than in the placebo group. Mean birth weight did not differ between the groups.¹⁵ Recent follow up of the infants found no increase in risk factors for cardiometabolic disease (fat mass, insulin sensitivity, blood pressure and renal function) at early school age.¹⁶ In contrast, the Multiple Courses of Antenatal Corticosteroids (MACS) trial for PTB, $N = 1858$,¹⁷ also included in the Cochrane review, administered multiple full courses of antenatal steroids (2×12 mg, 24 h apart) every 14 days until week 33 or delivery; approximately 40% received only one additional course, and 10% of women received seven doses. The authors found that the treatment and placebo groups had similar morbidity and mortality (12.9% vs. 12.5%), but those receiving multiple doses of steroids had a lower birth weight (2216

vs. 2330 g, $p < 0.01$) with a slight but significant reduction in length and head circumference.¹⁷ Similarly, Wapner et al. reported reduced birth weight in infants exposed to four or more doses of ACS (weekly) between 23 and 32 weeks of gestation (mean birth weight (MD) –161 g, 95% CI –290.52 to 31.48) and were more likely to be SGA compared with the placebo arm (RR 2.00, 95% CI 1.07 to 3.73, 368 infants); the trial was stopped early due to safety concerns, with a trend seem towards a reduction in the primary outcome (composite neonatal morbidity and mortality), which did not reach statistical significance (23.3% vs. 38.5%, RR 0.61, 0.34–1.08).¹⁸

So how should these findings influence our obstetric practice? Current guidelines from the Royal College of Obstetricians recommend administering a single course of ACS between 24⁺0 and 34⁺6 weeks' gestation to women at risk of PTB and that a single rescue course may be considered with caution where the initial course was given at less than 26 weeks of gestation,¹⁹ on the basis that there is uncertainty about the safety of multiple courses particularly the effects growth and brain function. While the optimal timeframe for administration is 24 h to seven days, they rightly emphasise the merit of administering an emergency dose of steroids, even if delivery is expected imminently (within 24 h), as the beneficial effect to the neonate is likely to be conferred even if a full course cannot be completed.¹⁹

However, there appears to have been a disproportionate reaction to the evidence, which associates repeat ACS with slightly reduced fetal growth in light of the clear clinical benefit (reduction in RDS and potentially severe morbidity/mortality); as a result, clinicians in the UK are reluctant to administer a second course of ACS to women who remain at high risk of PTB and the associated complications. While clearly more research is needed, we argue that prior to 32 weeks, when the risk of neonatal complications is highest, one repeat dose of corticosteroids should be given if delivery has not occurred within seven days of the first course and prematurity risk (within seven days) remains high. The evidence, the likely benefit for the neonate and the uncertainty surrounding longer term outcomes, should be shared with the parents in a process of joint decision making.

More important, however, is to move forward from the traditional dictum which encourages administration of steroids to all women who present with threatened PTB or other risk factors for preterm delivery, and target the first dose of steroids more appropriately to those at the highest risk of delivery within 48 h to seven days, reducing the need for repeated doses. Given that one course of ACS which exceeds the seven-day window to delivery is associated with a reduction in birth weight (mean difference –147.01 g, 95% CI –291.97 to –2.05 g)¹¹ with a further reduction following repeated doses (mean difference –161 g, 95% CI 290.52 to 31.48),¹⁸ our focus should be on avoiding unnecessary administration to low-risk women to begin with.

Over two-thirds of the women who present with suspected PTB go on to deliver after 34 weeks' gestation, most having received an unnecessary course of ACS.²⁰ Yet amongst women who deliver before 34 weeks' gestation, ACS administration rates within seven days of delivery range from only 41–48%.¹ Given that the reduction in neonatal mortality and cerebral haemorrhage was not conferred after 48 h of steroid treatment (arguably more important than RDS), there may be further merit in delaying dosing even closer to delivery, which may also reduce the risk of growth restriction.

It is crucial, therefore that we can identify these high-risk women. Currently cervicovaginal fluid (CVF) fetal fibronectin (fFN) concentration and cervical length (CL) measurement by transvaginal ultrasound are the leading predictors of PTB in both symptomatic and asymptomatic high-risk women.²¹ fFN is a glycoprotein found in placental tissue, amniotic fluid and at the choriodecidual interface. Usually detectable only in low levels after 18–22 weeks of gestation, its presence in CVF after this time may imply mechanical or inflammatory disruption to this interface, which may precede PTB. Traditionally used as a qualitative bedside test (HologicTM), with a concentration of 50 ng/ml as the threshold for a 'positive' test, the value of fFN lies largely in its negative prediction; the ability to 'rule out'. In a cohort study of 192 women, Iams et al. found that fFN predicted premature

birth within seven days in women who presented with contractions between 24 and 34 weeks of gestation, with sensitivity of 93%, specificity of 82%, positive predictive value (PPV) of 29% and negative predictive value (NPV) of 95%.²² That is, 95% of women who would have been given steroids on the basis of contractions alone, but who had a negative test, did not deliver within seven days, and steroids could have been withheld. Although some cases are missed at presentation, the clinical circumstance is likely to dictate the need for steroids nearer to delivery, where benefit is still apparent, i.e. the risk of delaying steroids, with the considerable advantage of avoiding multiple doses.

More recently, it has been recognised that quantification of fFN (qfFN), a measure of absolute fFN concentration enhances prediction. A cohort study of 300 women symptomatic of preterm labour demonstrated that fFN concentration (detectable range 0 to >500 ng/ml) directly correlated with the risk of spontaneous PTB (sPTB); only 1.8% of women with a qfFN concentration of <10 ng/ml (comprising 57% of the cohort of 300 women) delivered within two weeks of testing.²³ Furthermore, the PPV for sPTB within 14 days increased with the use of incremental thresholds for qfFN, whereby women with levels >10 ng/ml had an 11% chance of delivery within two weeks, compared with levels over 200 ng/ml and 37% chance of delivery.²³ Use of these thresholds could enable clinicians to make decisions based on individual risk; for example, steroids could be withheld to those with levels below 10 ng/ml, whereas interventions such as magnesium sulphate and in utero transfer could be targeted to those with higher levels, e.g. >200 ng/ml.

A number of other bedside tests are available with predictive value for PTB in symptomatic women. Detection of the presence of phosphorylated (insulin-like growth factor binding-1 (IGFBP-1), produced by placental decidual cells, in cervical secretions using an immunochromatography-based dipstick test (Actim Partus TM) is another predictor of PTB. Used as a positive/negative test, it has high negative prediction for delivery within seven days (>95%)²⁴ but as with the traditional fFN test, positive prediction is suboptimal. Finally, placental alpha microglobulin 1 (PAMG-1) is a glycoprotein synthesised by the decidua, and found in low levels in the CVF, detected from a swab inserted into the vagina using an immunoassay bedside 'dipstick test' (PartoSureTM). While further study is warranted, a small observational cohort study ($n = 101$)²⁵ found that a positive test had 97% NPV and 78% PPV for sPTB within seven days, with similarly high predictive value for delivery within two weeks.

These tests may be enhanced if used in conjunction with CL assessment. Transvaginal ultrasound assessment of the CL has demonstrated value when risk assessing women who present with threatened preterm labour, allowing early identification of opening of the internal cervical os and cervical shortening which precedes clinically apparent cervical effacement and dilation. A prospective case cohort study ($N = 253$) demonstrated that for symptomatic women with a CL <15 mm at <32 weeks' gestation the PPV for delivery within seven days was 47% (over five times the risk of sPTB than women with a cervix measuring >15 mm).²⁶ NPVs for CL thresholds 15, 20 and 25 mm are 95–97%.²⁷ The adjuvant use of biomarker tests such as those described are likely to further enhance this prediction.²⁸ Unfortunately, use of ultrasound to assess women in preterm labour is restricted by the availability of a trained operator and equipment availability.

To prevent overtreatment with ACS, and the need for repeat courses, consideration of a woman's risk of delivery within the therapeutic window is vital. While further research is required to evaluate the use of these predictive tests to guide targeted ACS therapy, the high negative predictive value of these tests are a reassuring basis upon which to withhold steroid treatment to those unlikely to deliver within seven days. Given that the positive prediction is sub-optimal, many of those with 'positive' tests who receive steroids will not deliver during this time-frame; in this group of women, predictive tests and ACS treatment can be repeated if the risks remain high.

Timing of steroid administration is of course relevant not only for threatened spontaneous birth, but also for women at risk of iatrogenic premature delivery (for example pre-eclampsia or other fetal/maternal

indication). Clinicians too frequently administer steroids to every women diagnosed with preterm pre-eclampsia without consideration of the window of benefit. Tests such as placental growth factor (PlGF), shown to predict need for delivery within two weeks for women with suspected preterm pre-eclampsia may assist with this decision making.²⁹

Evidence pertaining to the use of ACS at late preterm (>34 weeks' gestation) or term in women undergoing planned elective caesarean section is less clear. Birth by caesarean section without labour before 39 weeks of gestation has been demonstrated to confer increased risk of respiratory morbidity for the infant (including transient tachypnea of the newborn, requiring admission to the neonatal intensive care unit. A Cochrane review (2009) which identified one unblinded UK study of 942 women given a course of intramuscular betamethasone vs. no treatment 48 h before term elective caesarean section, demonstrated a reduction in admission to the neonatal unit (RR 0.15, 0.03–0.64), particularly for respiratory complications, but no reduction in the incidence of RDS (RR 0.32, CI 0.07 to 1.58); transient tachypnea of the newborn (RR 0.52; CI 0.25 to 1.11); need for mechanical ventilation (RR 4.07; 95% CI 0.46 to 36.27); or duration of stay in neonatal intensive care unit (MD 2.14 days; 95% CI –5.58 to 1.30).³⁰ In spite of only one unblinded prospective study with no demonstrable improvement in respiratory morbidity, the RCOG recommend administration of steroids to all women undergoing planned elective caesarean section prior to 38⁺6 weeks of gestation.¹⁹ The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZOG),³¹ recommend 'consideration' of administration in these circumstances. However, although there may be some benefits to administration, we urge caution in this practice; as there may well be unrecognised harm. Given the aforementioned trend towards worse outcomes in infants given ACS but who delivered close to term,¹¹ as well as the impact on fetal growth and potential negative long-term health outcomes, we feel that more research is needed before this practice should become commonplace.

Finally, the risk of steroid administration to women with Diabetes Mellitus, without appropriate blood glucose monitoring must not be overlooked. More targeted steroid treatment will prevent over-use in this population, preventing the need for monitoring and insulin treatment for the duration of the steroid course.

ACS therapy is a success story in modern obstetrics, but important details regarding timing to optimise neonatal outcome are not always considered. We must utilise predictive tools to allow us to target ACS more specifically to women at the highest risk, preventing 'blanket' treatment to all thought to be 'at risk', and reducing the need for repeated doses when the benefit of the first course is lost. Finally, in those women who remain at high risk of prematurity seven days after their first dose, the benefit of a repeated dose of steroids must not be overlooked.

Declaration of conflicting interests

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References

- Adams TM, Kinzler WL, Chavez MR, et al. The timing of administration of antenatal corticosteroids in women with indicated preterm birth. *Am J Obstet Gynecol* 2014; 212: 645.e1–4.
- March of Dimes, PMNCH, Save the Children, WHO. *Born too soon: the global action report on preterm birth*. CP Howson, MV Kinney and JE Lawn (eds.). Geneva: World Health Organization, 2012.
- Peaceman AM, Andrews WW, Thorp JM, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial. *Am J Obstet Gynecol* 1997; 177: 13–18.
- Liggins GC. Premature delivery of foetal lambs infused with corticosteroids. *J Endocrinol* 1969; 45: 515–523.
- Liggins GC and Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972; 50: 515–525.
- The Wellcome Trust. Graham Liggins, lambs' lungs and babies' lives, <http://blog.wellcome.ac.uk/2011/07/13/graham-liggins/> (2011, accessed 15 February 2015).
- Crowley P, Chalmer I and Keirse MJ. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 1990; 97: 11–25.
- The effect of antenatal steroids for fetal maturation on perinatal outcomes. *NIH Consensus Statement* 1994; 12: 1–24.
- Committee on Obstetric Practice. ACOG committee opinion: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol* 2002; 99: 871.
- Cochrane Community (beta). The story of the Cochrane logo, <http://community.cochrane.org/features/story-cochrane-logo> (2013, accessed 15 February 2015).
- Roberts D and Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Syst Rev* 2006; 3: CD004454.
- Barker DJP. *Mothers, babies and health in later life*, 2nd ed. London: Churchill Livingstone, 1998.
- Dodic M, Wintour EM, Whitworth JA, et al. Effect of steroid hormones on blood pressure. *Clin Exp Pharmacol Physiol* 1999; 26: 550–552.
- Crowther CA, McKinlay CJD, Middleton P, et al. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database of Syst Rev* 2011; 6: CD003935.
- Crowther CA, Haslam RR, Hiller JE, et al. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. *Lancet* 2006; 367: 1913–1919.
- McKinlay CJ, Cutfield WS, Battin MR, et al. Cardiovascular risk factors in children after repeat doses of antenatal glucocorticoids: an RCT. *Pediatrics* 2015; 135: e405–e415.
- Murphy KE, Hannah ME and Willan AR. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. *Lancet* 2008; 372: 2143–2151.
- Wapner RJ, Yoram S, Thom EA, et al. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. *Am J Obstet Gynecol* 2006; 195: 633–642.
- Royal College of Obstetricians and Gynaecologists. *Antenatal corticosteroids to reduce neonatal morbidity and mortality* [Green-top Guideline No. 7]. London (UK): RCOG, 2010.
- Sanya R, Al Naggar E, Gasim M, et al. Use or overuse of antenatal corticosteroids for suspected preterm birth. *J Matern Fetal Neonatal Med* 2014; 27: 1454–1456.
- Bolt LA, Chandiramani M, de Greeff A, et al. The value of combined cervical length measurement and fetal fibronectin testing to predict spontaneous preterm birth in asymptomatic high risk women. *J Matern Fetal Neonatal Med* 2011; 24: 928–932.
- Iams JD, Casal D, McGregor JA, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. *Am J Obstet Gynecol* 1995; 173: 141–145.

23. Abbott DS, Radford SK, Seed PT, et al. Evaluation of quantitative fetal fibronectin test for spontaneous birth in symptomatic women. *Am J Obstet Gynecol* 2013; 208: 122.e1–6.
24. Cooper S, Lange I, Wood S, et al. Diagnostic accuracy of rapid pHIGFBP-I assay for predicting preterm labor in symptomatic patients. *J Perinatol* 2011; 32: 460–465.
25. Nikolova T, Bayev O, Nikolova N, et al. Evaluation of a novel placental alpha microglobulin-1 (PAMG-1) test to predict spontaneous preterm delivery. *J Perinat Med* 2014; 42: 473–477.
26. Fuchs I, Henrich W, Osthues K, et al. Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor. *Ultrasound Obstet Gynecol* 2004; 24: 554–557.
27. Sotiriadis A, Papatheodorou S, Kavvadias A, et al. Transvaginal cervical length measurement for prediction of preterm birth in women with threatened preterm labor: a meta-analysis. *Ultrasound Obstet Gynecol* 2010; 35: 54–64.
28. DeFranco EA, Lewis DF and Odibo AO. Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review. *Am J Obstet Gynecol* 2013; 208: 233.e1–6.
29. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation* 2013; 128: 2121–2131.
30. Sotiriadis A, Makrydimas G, Papatheodorou S, et al. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. *Cochrane Database Syst Rev* 2009; 4: CD006614.
31. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. *Timing of elective caesarean section at term*. College Statement C-Obs 23, 2014.