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Bacterial vaginosis diagnosed at the first antenatal visit better predicts preterm labour than diagnosis later in pregnancy

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Summary
This study was conducted as part of a double-blind randomised placebo-controlled trial, the aim of which was to determine whether vitamin C could reduce the recurrence risk of pre-term labour. In this study, women with a history of pre-term labour in a preceding pregnancy were randomised to receive either 250 mg vitamin C or a matching placebo twice daily until 34 weeks’ gestation. They attended a dedicated pre-term labour clinic every 2 weeks. All women were screened for bacterial vaginosis (BV) at each visit. It was first determined that vitamin C did not have any effect on the presence of BV. Women who were diagnosed with BV before 20 weeks’ gestation were at higher risk of delivering pre-term than those who developed BV after 20 weeks.

Introduction
Pre-term birth occurs in approximately 5 – 10% of all pregnancies and has not, despite many efforts, shown any decrease in the past 30 years (Challis et al. 2001). Pre-term delivery (PTD) and low birth weight (LBW) are the leading causes of perinatal mortality in the USA (Hauth et al. 1995) and the second largest cause of perinatal death in the Western Cape (Prins et al. 1997). In certain populations, the rate of PTD is higher than 10%, with South Africa being no exception. In the population served by Tygerberg Hospital, PTD occurs in 20.3% of pregnancies and 37.5% of all neonatal deaths can be attributed to prematurity (Tygerberg Hospital database, unpublished data). These figures are some of the highest described in the literature.

For more than 35 years, multiple studies have shown an association between infection and PTD (Lockwood et al. 1999; Robinson et al. 2001; Romero et al. 2001). It is estimated that genital tract infections and intrauterine infection contribute to between 40 and 50% of all pre-term deliveries, especially those that occur before 30 weeks’ gestation (Challis et al. 2001; Lockwood and Kuczynski 1999). There is evidence suggesting that infection contributing to PTD is already present at a very early gestation and can remain undetected for several weeks before delivery (Wenstrom et al. 1998).

Particularly striking is the association between bacterial vaginosis (BV) and PTD (Hillier et al. 1995). It has been reported that the presence of BV in early pregnancy (before 20 weeks), significantly increases the risk of PTD (Lamont 2003). Others have found that BV rarely develops as the pregnancy progresses, but rather persists from the first or second trimesters in those women who deliver pre-term (Hay et al. 1994). Antenatal treatment of BV in order to reduce the rate of PTD has been studied in many different populations (high-risk/low-risk, developed/developing populations) with conflicting results (Hauth et al. 1995; McDonald et al. 1997; McGregor et al. 1995; Odendaal et al. 2002; Vermeulen and Bruinse 1999). The most consistent finding from these studies is that oral treatment, early in pregnancy (< 20 weeks' gestation), reduces the risk of PTD in women at risk for PTD, with the risk factor being a prior history of PTD (Hauth et al. 1995; McDonald et al. 1997; Vermeulen 2000).

A previous randomised clinical trial (RCT) among 491 high-risk women at this hospital surprisingly demonstrated that more women who received metronidazole for BV had pre-term deliveries than the control group who received vitamin C as a placebo (Odendaal et al. 2002).

A double-blind RCT was therefore undertaken to assess the effect of vitamin C on the frequency of pre-term labour in high-risk patients. These results have been published elsewhere (Steyn et al. 2003). However, the report did not include the effect of vitamin C on BV or the predictive values of BV on pre-term labour, as found in early or late in pregnancy. Those subjects will be covered in this article.

Methods
Women with a history of a previous mid-trimester miscarriage (spontaneous abortion between 13 and 26 weeks’ gestation) or a previous pre-term delivery (spontaneous onset of labour with subsequent delivery between 27 and 36 weeks’ gestation) were invited to participate in the study. If a woman had received metronidazole less than 2 weeks before enrolment, they were only entered into the study later, provided they were still less than 26 weeks’ pregnant. Patients with iatrogenic causes of PTD or abortion, e.g. induction of labour for medical reasons, were not included in the study. Women at risk for pre-term labour in the index pregnancy, due to factors such as multiple gestation or known cervical incompetence, were also excluded. After giving written consent, women were recruited from the antenatal clinic if they were between 14
and 26 weeks' gestation and randomised to receive either 250 mg vitamin C twice daily until 34 weeks' gestation, or an exact matching placebo.

All the patients were followed-up fortnightly at a dedicated ‘Pre-term Labour Clinic’ until 33 weeks' gestation and were seen by the same consultant at each visit. After 33 weeks, the women were referred back to the routine antenatal care, either the high-risk clinic at the hospital or a midwife obstetric unit. A posterior fornix smear was obtained at each visit. These were Gram-stained and evaluated for BV only after delivery, using Nugent’s criteria (Nugent et al. 1991). All smears were evaluated by the same person (J.S.). Bacterial vaginosis was not treated as part of the study, but when a patient had received metronidazole from another healthcare provider (e.g. after-hours admissions), it was noted on the data sheet. All women were followed-up until delivery, the primary outcome being PTD.

Results
A total of 200 women were included in the analysis; 100 in each group. The demographic characteristics of the women in both groups were comparable and they did not differ in terms of obstetric history (Steyn et al. 2003). The median gestational age at delivery for the vitamin C group was 36.5 weeks and 38 weeks for the placebo group, but the difference was not significant ($p = 0.24$).

Of the 200 women, 51 received metronidazole after entry into the study, which may have influenced the results of the later Gram-stain smears. As the numbers were quite small and there were many variations in the presence of BV, only the first and last smears of each patient were used. The first smears (at enrolment) were also divided into two groups, i.e. those taken before 20 weeks and those taken at or after 20 weeks’ gestation. For the analysis, the intermediate scores were grouped with the positive group, as the numbers in the intermediate group were very small.

Vitamin C did not have any effect on the duration of pregnancy (Steyn et al. 2003) nor on the prevalence of abnormal and intermediate Nugent scores for BV. In the vitamin C group, the proportion of patients with intermediate and positive smears changed from 34.3% to 32.6% while, in the placebo group, the proportion changed from 32.3% to 28.9%. The number of women screened for BV was slightly less at the end of the study ('last smear'), as some of them miscarried after the first visit, or had delivered before 32 weeks’ gestation.

The vitamin C and placebo groups were subsequently combined for further analyses. For the first analysis, all women who received metronidazole during their pregnancies were excluded. Bacterial vaginosis was not a risk factor for pre-term delivery in this group, neither for women who were positive at their first visit to the clinic or for those positive at their last visit. Women who were BV positive before 20 weeks’ gestation did not have a higher risk for pre-term labour either. When all women were included in the analysis, it was found that those who were positive for BV before 20 weeks’ gestation, were in fact at risk for pre-term delivery ($p = 0.025$) (Table I).

Discussion
The study showed clearly that the administration of vitamin C, 250 mg twice daily during pregnancy, did not change the prevalence of BV.

Our results did, however, confirm that significantly more women who were positive for BV early in pregnancy, had a higher risk of pre-term delivery (Lamont 2003). This result was only significant when all women were included in the analysis. This can be explained by the fact that many women who received metronidazole were in pre-term labour at that time and treated according to Tygerberg Hospital’s standard protocol, which includes metronidazole and amoxicillin. Many clinical trials have been conducted to determine whether treatment of BV during pregnancy will reduce the rate of PTD, but, because of the conflicting results, no ‘gold standard’ of reference could yet be found. However, it has been found that oral treatment, early in pregnancy (< 20 weeks), reduces the risk of PTD in women at risk for PTD, with the risk factor being a prior history of PTD (Hauth et al. 1995; McDonald et al. 1997; Vermeulen 2000). A possible explanation for this reduction is that in 40 – 50% of the woman recruited, the prior pre-term deliveries may have been infection-related and with early treatment in the subsequent pregnancies, the recurrence risk was reduced. Bacterial vaginosis has also been associated with first trimester miscarriage (Hobel et al. 1999), lending support to the suggestion of early, rather than late, treatment, of the condition.

It does therefore make sense to screen women as early as possible, as spontaneous resolution of bacterial vaginosis does not reduce the risk of pre-term birth (Ugwumadu 2004). There is little evidence that low-risk pregnant women who are BV positive will benefit from metronidazole therapy (Carey et al. 2000) but treatment with oral clindamycin in early pregnancy reduce the rate of late miscarriage and spontaneous pre-term birth in a general obstetric population (Ugwumadu 2003).

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