

## Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery

Herbert Kiss, Ljubomir Petricevic, Peter Husslein

### Abstract

**Objective** To evaluate whether a screening strategy in pregnancy lowers the rate of preterm delivery in a general population of pregnant women.

**Design** Multicentre, prospective, randomised controlled trial.

**Setting** Non-hospital based antenatal clinics.

**Participants** 4429 pregnant women presenting for their routine prenatal visits early in the second trimester were screened by Gram stain for asymptomatic vaginal infection. In the intervention group, the women's obstetricians received the test results and women received standard treatment and follow up for any detected infection. In the control group, the results of the vaginal smears were not revealed to the caregivers.

**Main outcome measures** The primary outcome variable was preterm delivery at less than 37 weeks. Secondary outcome variables were preterm delivery at less than 37 weeks combined with different birth weight categories equal to or below 2500 g and the rate of late miscarriage.

**Results** Outcome data were available for 2058 women in the intervention group and 2097 women in the control group. In the intervention group, the number of preterm births was significantly lower than in the control group (3.0% *v* 5.3%, 95% confidence interval 1.2 to 3.6;  $P = 0.0001$ ). Preterm births were also significantly reduced in lower weight categories at less than 37 weeks and  $\leq 2500$  g. Eight late miscarriages occurred in the intervention group and 15 in the control group.

**Conclusion** Integrating a simple infection screening programme into routine antenatal care leads to a significant reduction in preterm births and reduces the rate of late miscarriage in a general population of pregnant women.

### Introduction

Preterm delivery (birth before 37 completed weeks of gestation) is the leading cause of neonatal morbidity and mortality. In recent years the birth weight of premature babies has been found to be an important determinant of outcome, such that preterm birth is no longer defined solely by gestational age but also in

terms of a birth weight below 2500 g. The main focus has been on preterm infants with a birth weight below 2000 g, who bear the greatest burden of morbidity and mortality. The costs of neonatal care for infants born at less than 33 weeks of gestation (birth weight below 2000 g) rise exponentially as gestational age decreases and rise further with birth weights below 1000 g.<sup>1</sup>

Although the causes of preterm delivery are complex and manifold, a history of late miscarriage or preterm delivery remains the most predictive risk factor.<sup>2</sup> Compelling evidence now exists that infection is not only associated with preterm delivery but that it is a causative factor.<sup>3-4</sup> Vaginal infections, particularly bacterial vaginosis, have consistently been shown in many longitudinal population studies to be associated with late miscarriage and preterm delivery.<sup>5-9</sup> A review of the current literature shows conflicting data on the benefits of routine screening for bacterial vaginosis,<sup>10-11</sup> particularly in populations at low risk.<sup>12</sup>

We evaluated a simple antenatal programme to prevent preterm births. This programme entailed general screening for and standardised treatment of the vaginal infections with the highest prevalence, regardless of whether the infection is clearly associated with preterm delivery or whether no link has been established, as is the case in candidiasis.<sup>13</sup> The goal of the programme was to reduce the rate of preterm births and late miscarriages.

### Methods

Between January 2001 and October 2002, 25 non-hospital based obstetricians in the Vienna area enrolled pregnant women presenting for their routine prenatal visits between 15+0 (15 weeks plus 0 days) and 19+6 weeks (19 weeks plus 6 days) of gestation. Patients' obstetricians determined gestational age on the basis of the date of a woman's last menstrual period and confirmed this by ultrasonography before 19 weeks of gestation.

In addition to the routine antenatal examinations the women's obstetricians obtained vaginal smears. To diagnose bacterial vaginosis we Gram stained all

Department of Obstetrics and Gynaecology, University of Vienna Medical School, Währinger Gürtel 18-20, A-1090 Vienna, Austria

Herbert Kiss  
*associate professor of obstetrics and gynaecology*

Ljubomir Petricevic  
*research fellow*

Peter Husslein  
*professor of obstetrics and gynaecology*

Correspondence to:  
H Kiss  
herbert.kiss@  
akh-wien.ac.at

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**Table 1** Normal and abnormal vaginal flora in screened patients. Values are numbers (percentages) of pregnant women

Microscopic finding	Intervention group	Control group
Normal flora	1611 (78.3)	1656 (79.0)
Abnormal flora:	447 (21.7)	441 (21.0)
Bacterial vaginosis	151 (7.3)	146 (7.0)
Bacterial vaginosis+Candida	24 (1.2)	32 (1.5)
Bacterial vaginosis+Candida + <i>Trichomonas vaginalis</i>	0 (0.0)	1 (0.0)
Bacterial vaginosis+ <i>T vaginalis</i>	2 (0.1)	0
<i>Candida</i>	270 (13.1)	259 (12.4)
<i>T vaginalis</i>	0	3 (0.1)

preparations in a central laboratory and used the scoring system proposed by Nugent et al.<sup>14</sup> The study protocol differentiated between bacterial vaginosis (Nugent grade 3), vaginal candidiasis (spores and hyphae), infection with *Trichomonas vaginalis*, or combinations of any of the three.

### Randomisation

After the obstetricians had enrolled the women into the study, the case report forms and smear samples went to the central laboratory, where they were used to randomly assign women to the intervention group

**Table 2** Cumulative distribution of preterm births (<37 weeks) by birth weight and gestational age in intervention (n=2058) and control group (n=2097)

	No (%) in intervention group	No (%) in control group	Difference (95% CI)	P value ( $\chi^2$ test)
Total of preterm births	61 (3.0)	112 (5.3)	2.4 (1.2 to 3.6)	0.0001
≤2500 g	35 (1.7)	74 (3.5)	1.8 (0.9 to 2.8)	0.0002
≤2000 g	15 (0.7)	33 (1.6)	0.8 (0.2 to 1.5)	0.011
≤1500 g	5 (0.2)	17 (0.8)	0.6 (0.1 to 1.0)	0.012
≤1000 g	3 (0.1)	7 (0.3)	0.2 (-0.1 to 0.5)	0.211
Gestational age:				
Week 33+0 to 36+6	48 (2.3)	88 (4.2)	1.9 (0.8 to 2.9)	0.0007
Week 23+0 to 32+6	13 (0.6)	24 (1.1)	0.5 (-0.1 to 1.1)	0.079

**Table 3** Spontaneous and medically indicated (iatrogenic) preterm birth, miscarriage, and intrauterine death

Type of birth	No (%) in intervention group (n=2058)	No (%) in control group (n=2097)	Difference (95% CI)	P value ( $\chi^2$ test)
Birth at term	1955 (95.0)	1947 (92.8)	-2.1 (-3.6 to -0.7)	0.004
Spontaneous preterm birth (<37 weeks of gestation)	61 (3.0)	112 (5.3)	2.4 (1.2 to 3.6)	0.0001
Medically indicated (iatrogenic) preterm birth*	24 (1.2)	14 (0.7)	-0.5 (-1.1 to 0.1)	0.091
Intrauterine death	10 (0.5)	9 (0.4)	-0.1 (-0.5 to 0.4)	0.786
Miscarriage†	8 (0.4)	15 (0.7)	0.3 (-0.1 to 0.8)	0.156
Medically indicated (iatrogenic) preterm birth due to*:				
Pre-eclampsia	9 (0.4)	8 (0.4)		
HELLP (haemolysis, elevated liver, low platelet) syndrome	4 (0.2)	1 (0.0)		
Severe intrauterine growth retardation	3 (0.1)	0		
Fetal malformation	2 (0.1)	2 (0.1)		
Placental abnormalities (placenta praevia, placental abruption)	4 (0.2)	3 (0.1)		
Non-obstetrical causes (appendicitis, peritonitis)	2 (0.1)	0		
Miscarriage by weeks of gestation†:				
16-20 weeks	4 (0.2)	11 (0.5)		
>20 weeks	4 (0.2)	4 (0.2)		

\*Medically indicated preterm birth, listing the different diagnoses for iatrogenic induced preterm births.

†Explains the two different groups.

or the control group. In the intervention group, obstetricians were provided with vaginal smear results. In the control group, obstetricians and participating women remained blinded to the test results.

### Treatment

Bacterial vaginosis was treated for six days with clindamycin 2% vaginal cream. Persistent or recurrent disease was treated with oral clindamycin 300 mg twice daily for seven days. Candidiasis was treated with local clotrimazole 0.1 g for six days. Trichomoniasis was treated with local metronidazole 500 mg for seven days and included treatment of the partner. Women's obstetricians took follow up vaginal smears at the next routine antenatal visit, between 24+0 and 27+6 weeks of gestation. Treatment for persistent or recurrent candidiasis or trichomoniasis was repeated.

### Evaluation of results

The primary outcome variable was the rate of spontaneous preterm delivery (vaginal or caesarean delivery at less than 37 weeks). Secondary outcome variables were spontaneous preterm delivery at less than 37 weeks in combination with birth weights equal to or below 2500 g, 2000 g, and 1500 g.

### Results

Between January 2001 and October 2002 we considered a total of 4429 pregnant women for enrolment into the study. Of these, 4155 women completed the screening programme (see [bmj.com](#)). The mean age of the women was 28.9 (SD 5.6) years. Mean gestational age at the time we obtained the smears was 17 (1.6) weeks. The number of primiparous and multiparous women and the number of previous preterm births were comparable between groups (see [bmj.com](#)). Almost 80% of examined smears did not show any evidence of infection. The remaining 20% showed an abnormal vaginal flora, with no differences between the intervention and control groups (table 1).

The rate of spontaneous preterm birth was lower in the intervention group than in the control group (3.0% v 5.3%, 95% confidence interval 1.2% to 3.6%; P=0.0001). The number of preterm infants with a birth weight equal to or below 2500 g was significantly lower in the intervention group than in the control group (1.7% v 3.5%, 0.9 to 2.8; P=0.0002). The number of spontaneous preterm births in the lower weight categories was 50% lower (table 2) than in the control group. The rate of late miscarriage was also reduced by 50%, whereas the number of intrauterine deaths was comparable between the two groups (table 3).

Among the 447 women who had a follow up Gram stain after the first course of treatment, asymptomatic vaginal infection was still present in 123 (27.5%). We treated all women again according to the study protocol. None of the women reported adverse events during the treatment period.

The groups did not differ significantly with regard to passage of meconium, necrotising enterocolitis, neonatal sepsis, and neonatal death during hospitalisation. Among preterm infants with a birth weight below 1500 g no case of necrotising enterocolitis during the stay at the neonatal intensive care unit was documented in the neonatology (NICU) records.

## Discussion

A simple screening and treatment programme for sub-clinical vaginal infections early in the second trimester reduces the rate of spontaneous preterm deliveries by 50%. This reduction is likely to be associated with relevant reductions in the direct and indirect costs associated with preterm delivery.

### Comparison with other studies

In a report on a non-randomised trial McGregor et al advocated that screening for common infections of the genital tract should be offered to pregnant women to reduce preterm births.<sup>5</sup> To date, however, screening for vaginal infection has not become a routine part of antenatal care, mostly because there have been no studies to confirm that screening and treating pregnant women at low risk for bacterial vaginosis significantly reduces the rate of preterm birth, particularly with regard to low birthweight infants.<sup>10–11</sup> Screening for candidiasis is not recommended because a large study has shown that moderate to heavy *Candida* colonisation is not associated with preterm birth.<sup>13</sup> Yet candidiasis is common during pregnancy and is the infection most commonly associated with subjective symptoms, which is why we included it in our screening programme for common infections of the genital tract. Even though we also screened for *T vaginalis*, this pathogen was rare in our population and is therefore unlikely to affect the results of our study. In contrast to most previous studies investigating the role of screening for bacterial vaginosis only, we assessed the benefits of a simple screening programme for asymptomatic vaginal infection in a general population of pregnant women. Our study also shows a notable reduction in preterm delivery for birth weights below 2500 g.

Ugwumadu et al showed recently that screening for and treating asymptomatic abnormal vaginal flora and bacterial vaginosis early in the second trimester reduces the rate of preterm birth in a general obstetric population.<sup>15</sup> Lamont et al showed that topical treatment with clindamycin vaginal cream early in the second trimester reduces the incidence of preterm birth,<sup>16</sup> despite the reservations regarding topical treatment of bacterial vaginosis that were expressed by many authors.<sup>11</sup> In contrast to these studies, we assessed a screening strategy for common infections of the genital tract. A subgroup analysis showed that treating asymptomatic vaginal infections reduces the rate of preterm birth (see bmj.com). However, because the sample sizes are small, this subgroup analysis must be interpreted with caution.

### Possible reason for results

The clear reduction in the rate of preterm births seen in our study, particularly in the lower weight categories, was surprising, not only in view of the data previously published in the literature,<sup>10–12</sup> but also against the backdrop of the publications mentioned above.<sup>15–16</sup> Our results may be due to the fact that women were included in a screening programme. In the intervention group, women without vaginal infection were informed that their vaginal flora was normal. On the other hand, doctors may well have provided a different level of care to women in the study group in whom an infection had been identified. In view of the known

### What is already known on this topic

Preterm delivery is the most important cause of perinatal mortality and morbidity

Vaginal infection is associated with preterm delivery

### What this study adds

Integrating a simple infection screening programme into routine antenatal care can halve the rate of preterm births

Screening and treatment of asymptomatic infections should be done early in the second trimester (week 17)

association between bacterial vaginosis and preterm birth, obstetricians consider women with bacterial vaginosis or persistent or recurrent vaginosis as patients at high risk and handle them with particular care.

### Outlook

We believe that our results are generalisable to other countries with comparable populations and patterns of antenatal healthcare delivery. Routine screening for asymptomatic vaginal infection and the ensuing decrease of 50% in the rate of preterm births will probably translate into a reduction of more than 50% in the costs of prematurity.

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- 1 St John EB, Nelson KG, Cliver SP, Bishnoo RR, Goldenberg RL. Cost of neonatal care according to gestational age at birth and survival status. *Am J Obstet Gynecol* 2000;182:170-5.
- 2 Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. *Am J Obstet Gynecol* 1999;181:1216-21.
- 3 Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL. A review of premature birth and subclinical infection. *Am J Obstet Gynecol* 1992;166:1515-28.
- 4 Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. *N Engl J Med* 1988;319:972-8.
- 5 McGregor JA, French JI, Parker R, Draper D, Patterson E, Jones W, et al. Prevention of premature birth by screening and treatment for common genital tract infection: results of a prospective controlled evaluation. *Am J Obstet Gynecol* 1995;173:157-67.
- 6 Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent associations of bacterial vaginosis and chlamydia trachomatis infection with adverse pregnancy outcome. *JAMA* 1986;256:1899-903.
- 7 McGregor JA, French JI. Bacterial vaginosis in pregnancy. *Obstet Gynecol Survey* 2000;55(suppl):1-19.

- 8 Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ* 1994;308:295-8.
- 9 Meis PJ, Goldenberg RL, Mercer B, Moawad A, Das A, McNellis D, et al. The preterm prediction study: significance of vaginal infections. *Am J Obstet Gynecol* 1995;173:1231-5.
- 10 Brocklehurst P, Hannah M, McDonald H. Interventions for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2000;(2): CD000262.
- 11 Leitich H, Brunbauer M, Bodner-Adler B, Kaidler A, Egarter C, Husslein P. Antibiotic treatment of bacterial vaginosis in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 2003;188:752-8.
- 12 Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. *N Engl J Med* 2000;342:534-40.
- 13 Cotch MF, Hillier SL, Gibbs RS, Eschenbach DA. Epidemiology and outcomes associated with moderate to heavy *Candida* colonization during pregnancy. *Am J Obstet Gynecol* 1998;178:374-80.
- 14 Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of Gram stain interpretation. *J Clin Microbiol* 1991;29:297-301.
- 15 Ugwumadu A, Manyonda I, Ried F, Hay P. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. *Lancet* 2003;361:983-8.
- 16 Lamont RF, Dunchan SLB, Mandal D, Basset P. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. *Obstet Gynecol* 2003;101:516-22.

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## Commentary: Does screening reduce preterm births?

Anna Alanen

Department of  
Obstetrics and  
Gynaecology,  
University of Turku,  
Kiinamyllynkatu  
4-8, FIN-20520  
Turku, Finland  
Anna Alanen  
senior consultant  
anna.alanen@utu.fi

Preterm birth is one of the most important problems in modern obstetrics. As the connection between ascending infection and preterm birth is undisputed, much research has focused on finding infectious risk factors suitable for screening. In the study by Kiss et al, asymptomatic pregnant women were screened and randomised to treatment during the second trimester for bacterial vaginosis, *Candida*, and trichomoniasis.<sup>1</sup> Bacterial vaginosis has proved to be associated with an increased risk of preterm birth. Unfortunately, in several trials, intervention with antenatal antibiotic treatment—vaginal or systemic—has mostly failed to reduce the rate of preterm births, in spite of successful eradication of bacterial vaginosis.<sup>2</sup>

Although the incidence of preterm birth was lower in the intervention group in the study by Kiss et al, the treatment of bacterial vaginosis did not significantly reduce the rate of preterm birth. The difference occurred mostly in women with a normal vaginal flora, who received no treatment, and among women colonised with *Candida*, which is surprising since *Candida* has not been considered to be a risk factor for preterm birth. The study of Kiss et al is therefore in agreement with most previous studies concerning the failure of antenatal treatment of bacterial vaginosis to prevent preterm birth. The rate of preterm birth was, however, significantly lower in the intervention group, implying that factors connected to the screening programme, including the role of candidiasis, deserve further studies.

It is interesting to speculate why successful treatment of bacterial vaginosis does not reduce the increased risk of preterm birth. There might be several reasons for this. Bacterial vaginosis is not an infection caused by a single microbe such as *Candida* or *Chlamydia*, but a condition where normal vaginal flora is replaced by a microbiota, which contains a wide variety of bacterial species. It is not known whether differences in the flora of bacterial vaginosis are important, and if so, what the characteristics of a “risky” flora are. Antibiotic treatment is bound to cause selection among the bacterial species and may leave the “dangerous” bacteria alive, although the treatment seems successful. Metronidazole and clindamycin have been used most often in trials. Metronidazole has proved ineffective,<sup>3</sup> but systemic clindamycin may reduce the rate of preterm birth.<sup>4</sup>

Different tests can be used to detect bacterial vaginosis. The tests used might lead to differences in study populations, although no difference was observed in the accuracy of the various tests to predict preterm birth.<sup>5</sup>

Another feature typical of bacterial vaginosis is the lack of lactobacilli in the vagina. Normal flora anywhere in the body is usually protective, and it may be the lack or incomplete restoration of this protection that allows pathogens to ascend. Little is known about the local immune function and protection in the vagina and cervix, which surely has an important role in preventing ascending infection. Abnormal vaginal microbiota could even be secondary to defective protection of the mucosal immune system.

We should know more about the specific factors that are responsible for the increased risk of preterm birth so that more accurate screening tests and more effective prophylactic treatment can be developed.

- 1 Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. *BMJ* 2004;329:371-4.
- 2 McDonald H, Brocklehurst P, Parsons J, Vigneswaran R. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2003;(2):CD000262.
- 3 Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 2000;342:534-40.
- 4 Ugwumadu A, Manyonda I, Reid F, Hay P. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. *Lancet* 2003;361:983-8.
- 5 Honest H, Bachmann LM, Knox EM, Gupta JK, Kleijnen J, Khan KS. The accuracy of various tests for bacterial vaginosis in predicting preterm birth: a systematic review. *BJOG* 2004;111:409-22.

### Endpiece

#### No hands

I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work.

Harvey Cushing. Letter to Dr Henry Christian,  
20 November 1911

Syed Hasan, senior house officer in surgery,  
Great Yarmouth