Chapter 2 Does prophylactic administration of clindamycin 2% vaginal creme reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk? A randomised placebo-controlled double-blind study.

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ABSTRACT

Objective: To test the hypothesis that prophylactic administration of clindamycin 2% vaginal creme can reduce the incidence of preterm birth in a high risk population.

Design: A multicentre, randomised, double-blind, placebo-controlled trial.

Setting: Twelve city hospitals in the Netherlands.

Participants: One hundred forty-two women with a singleton pregnancy and a history of a spontaneous premature delivery in the preceding pregnancy.

Interventions: Clindamycin 2% vaginal creme or placebo creme daily administered for seven days at 26 and 32 weeks of pregnancy.

Main outcome measures: Spontaneous preterm birth less than 37 weeks, admission for threatened preterm labour and neonatal infectious morbidity.

Results: No difference was found in overall preterm birth between clindamycin and placebo (29% versus 19% resp). In the subgroup without bacterial vaginosis more preterm birth before 34 weeks were seen in the clindamycin group (2% versus 10% resp, p<0.05). The length of admissions for threatened preterm labour did not differ. More infectious neonatal morbidity was seen in the clindamycin group (5/70 versus 0/72, p<0.05).

Conclusion: Clindamycin 2% vaginal creme administered prophylactically to women with a spontaneous preterm birth in the preceding pregnancy did not prevent preterm delivery nor influence the number of admissions for threatened preterm labour. The increase of neonatal infectious morbidity in the group treated with clindamycin was a major concern.
INTRODUCTION

Premature birth before 37 completed weeks of pregnancy is a major problem in obstetrics and neonatology. Premature birth can either be spontaneous or artificially induced as in cases of intra uterine fetal growth retardation (IUGR); pregnancy induced hypertension (PIH) related problems or abruptio placentae. Prevention of spontaneous premature birth is a method to reduce the incidence of premature delivery. Educational programs, monitoring for contractions, frequent cervical examinations and risk scoring have not shown to be effective in reducing preterm birth \(^1,2\).

The cause of spontaneous premature birth is largely unknown, but accumulating evidence suggests that inflammation and infection of the chorio-decidual interface play a role in the onset of premature birth \(^3\). The incidence of premature delivery increases in women with bacterial vaginosis \(^4,5,6\), where the normal lactobacilli-dominant vaginal flora is replaced by anaerobe micro-organisms as *Bacteroides* species, *Mobiluncus* species, *Prevotella* and *Gardnerella* vaginalis \(^7,8\). These micro-organisms are capable of initiating the synthesis of prostaglandins, which can lead to premature birth \(^3,9\).

If vaginal micro-organisms play a role in the aetiology of spontaneous premature birth, it can be hypothesised that prophylactically administering of antibiotics capable of restoring the normal lactobacilli dominant vaginal flora may reduce the incidence of premature birth in a population at high risk of premature delivery. Several studies have shown clindamycin 2% vaginal creme to be as effective as metronidazol in the treatment of bacterial vaginosis by restoring the lactobacilli dominant vaginal flora \(^10,11,12\). At the start of this project it was the only antimicrobial agent approved by the FDA for the treatment of bacterial vaginosis in pregnancy and for this reason it was chosen for this study.
To test this hypothesis clindamycin 2% vaginal creme was given prophylactically to women with a spontaneous preterm birth in the preceding pregnancy at 26 and 32 weeks of pregnancy in a randomised multicentre double-blind placebo-controlled study. This selection criterion was chosen since preterm birth in the penultimate pregnancy remains a major risk factor\textsuperscript{13, 14, 15}. The aim of this study was to determine whether this treatment reduces the incidence of spontaneous preterm birth in this high-risk group.
METHODS

Patient selection

From 1 January 1994 to 31 December 1996 pregnant women attending the antenatal clinics of 12 hospitals in the Netherlands were asked to participate in this randomised multicentre placebo-controlled double-blind study. They fulfilled the following criteria:

- spontaneous preterm birth between 24 and 36 completed weeks of gestation in the penultimate pregnancy with or without a preceding period of ruptured membranes;
- a viable pregnancy without major fetal congenital anomalies;
- gestational age at entry less than 26 weeks determined by menstrual history and confirmed by ultrasound

Patients excluded from the study had previous preterm births associated with intra-uterine growth retardation, hypertension or pre-eclampsia, placental disorders, congenital uterine anomalies, maternal diseases or a known allergy to clindamycin. The study protocol for each hospital was approved by its ethical committee for experiments on human beings.

Randomisation, treatment and medication

Randomisation was stratified by centre and by bacterial vaginosis since treatment for premature labour can differ between various hospitals and bacterial vaginosis is an independent risk factor for preterm birth. After receiving written consent a vaginal smear was taken from each women according to the method described by Nugent et al. All specimens were analysed by the Department of Microbiology at the University Hospital Utrecht, Utrecht, the Netherlands. Bacterial vaginosis was considered to be present when the Nugent score was seven or more. A research co-ordinator allocated medication or placebo using a prefixed randomisation list so that care providers were blinded to medication and the presence of bacterial vaginosis.
participating women collected their medication at the pharmaceutical department of each hospital. The medication or an identical looking placebo had to be applied for seven days intravaginally at 26 and 32 weeks of gestation. Compliance to medication was analysed by the evaluation of the non-collected medication at the pharmaceutical department of each hospital. Upjohn Nederland supplied the medication and the identical looking placebo.

**Outcome variables and data analysis**

The main predefined outcome variable was the incidence of premature delivery. Admissions for threatened preterm labour and neonatal infectious morbidity as defined by proven sepsis, infectious morbidity associated with sepsis (sepsis-like disease) and pneumonia were considered as secondary outcome variables. Apart from these variables, medication with antibiotics other than the study medication was recorded. Women were also asked how often sexual intercourse took place in the week preceding the scheduled visits at week 25, 31 and 35. Data were analysed using the SPSS/PC statistical software (SPSS Inc., Chicago, Illinois, USA) and when appropriate chi-square, Wilcoxon tests and correlations were applied. A p-value less than .05 was considered significant.

**Sample size**

The study aimed to achieve a sample size of 566 based on the hypothesis that treatment was able to reduce the incidence of preterm birth from 20% to 10% with a 90% power to detect a significance of 0.05. Several studies reported a recurrence of 20% of preterm birth in a group of women with a spontaneous preterm birth in the preceding pregnancy. The study was scheduled for a three-year period and in this period the intake of eligible women was only 168. With this number of participants the hypothesised significant reduction from 20 % to 10 % in the incidence of preterm birth would only have had a power of 0.38. A possible cause of this
low recruitment is that in the Netherlands the majority of women with a history of preterm birth in the preceding pregnancy are treated in the first line of obstetrical care by independent midwives and general practitioners and only a minority of these women is seen by obstetricians.
RESULTS

The study group consisted of 168 women with a history of preterm birth in the preceding pregnancy and for various reasons, 26 women were excluded from analysis. This resulted in a study group of 142 with 72 women in the placebo group and 70 in the clindamycin group. During the study period clinicians did not find it necessary to break the blinding code for medical reasons. Only after the last patient had delivered and the files were completed the code was broken able (Table I).

Table I

Patients and dropouts from the study

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>clindamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>total number entered</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>withdrawal after entering</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>protocol violation</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>transfer to other hospital</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>birth before start of medication</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>suitable for analysis</td>
<td>72</td>
<td>70</td>
</tr>
</tbody>
</table>
Table II shows the relevant characteristics of the two groups. No differences were found in history of preterm births as well as the duration of the penultimate pregnancy. The number of women with bacterial vaginosis was equally divided among the groups, as well as the number of women who smoked.

*Table II*

**Characteristics of women at time of randomisation**

<table>
<thead>
<tr>
<th></th>
<th>placebo(72)</th>
<th>clindamycin(70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at intake in years (sd)</td>
<td>30.9 (3.7)</td>
<td>31.4 (4.1)</td>
</tr>
<tr>
<td>history with more than one preterm birth</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>parity (sd)</td>
<td>1.4 (0.8)</td>
<td>1.6 (1)</td>
</tr>
<tr>
<td>primiparae</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>smokers</td>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>length of penultimate gestation in days (sd)</td>
<td>222 (27)</td>
<td>223 (32)</td>
</tr>
<tr>
<td>week at intake (sd)</td>
<td>20.5 (3.0)</td>
<td>19.5 (3.8)</td>
</tr>
<tr>
<td>bacterial vaginosis at intake</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

(sd) = standard deviation
The incidence of preterm delivery, the main outcome variable, did not differ between the placebo and the clindamycin group (19% and 29% respectively) while significantly more births occurred before 34 weeks in the clindamycin group (Table III). This difference was still present when only those women without a bacterial vaginosis at intake were analysed. It was no longer found in women with a bacterial vaginosis at intake. Hospital admissions for threatened preterm labour were equal in number as well as in duration for both groups.

*Table III*

**Outcome variables**

<table>
<thead>
<tr>
<th></th>
<th>placebo(72)</th>
<th>clindamycin(70)</th>
<th>ns</th>
</tr>
</thead>
<tbody>
<tr>
<td>birth before 37 weeks (%)</td>
<td>14 (19%)</td>
<td>20 (29%)</td>
<td></td>
</tr>
<tr>
<td>birth before 34 weeks(%)</td>
<td>1 (1.4%)</td>
<td>6 (9%)</td>
<td>*</td>
</tr>
<tr>
<td>birth before 34 weeks (%) without vaginosis</td>
<td>1/64 (2%)</td>
<td>6/62 (10%)</td>
<td>*</td>
</tr>
<tr>
<td>birth before 34 weeks (%) with vaginosis</td>
<td>0/8</td>
<td>0/8</td>
<td>ns</td>
</tr>
<tr>
<td>admissions for threatened preterm labour (%)</td>
<td>19 (26%)</td>
<td>20 (29%)</td>
<td>ns</td>
</tr>
<tr>
<td>duration of admission for threatened preterm labour in days</td>
<td>14.4</td>
<td>12.3</td>
<td>ns</td>
</tr>
<tr>
<td>neonatal infectious morbidity</td>
<td>0</td>
<td>5</td>
<td>*</td>
</tr>
</tbody>
</table>

ns not statistical significant

* p<0.05
On three occasions during admission for threatened preterm labour antibiotics were given in both groups due to lower urinary tract infection; bronchitis and fever. There was no case of neonatal infectious morbidity in the placebo group versus five cases in the clindamycin group, which was a significant difference of $p < .05$ (Table IV). One neonate in the clindamycin group born at 32 weeks of pregnancy had a congenital pneumonia with *Streptococci Pneumoniae* and the neonate died immediately after birth.

*Table IV*

**Neonatal infectious morbidity in the clindamycin group**

<table>
<thead>
<tr>
<th>gestational age in weeks</th>
<th>clindamycin treatment</th>
<th>type infection</th>
<th>superficial cultures</th>
<th>&gt;12 hour</th>
<th>prom</th>
<th>infection</th>
<th>strept pneumoniae</th>
<th>death</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>during</td>
<td>sepsis-like</td>
<td>neg</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>4 weeks after</td>
<td>sepsis-like</td>
<td>enterobacter</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 2/7</td>
<td>4 weeks after</td>
<td>sepsis-like</td>
<td>e.coli</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 6/7</td>
<td>4 weeks after</td>
<td>sepsis-like</td>
<td>group B strept</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 4/7 *</td>
<td>during</td>
<td>pneumonia</td>
<td>strept pneumoniae</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td>died</td>
</tr>
</tbody>
</table>

* died immediately after birth
In the five neonates with neonatal infections none of the mothers had bacterial vaginosis. The four surviving neonates were all discharged in good condition. One fetus in the clindamycin group died in utero. However the autopsy showed no abnormalities nor infection and the cause of death remains unexplained.

The use of antibiotics other than the study medication did not differ in the groups (7/72 in the placebo group versus 9/70 in the clindamycin group). Antimicrobial medication other than the study medication was prescribed for lower urinary tract infection, bronchitis and flu like fever. The number of incidences of sexual intercourses in the week preceding the visits at intake (0.8 in the placebo versus 0.8 in the clindamycin group), at 31 weeks (0.6 versus 0.4 resp) and at 35 weeks (0.6 versus 0.3 resp) was equal for both groups. In the ‘drop-out’ group four preterm births occurred in the placebo-designated group and three in the clindamycin-designated group. The overall incidence of preterm birth in the ‘drop-out’ group was 27%, not different from the study group.
DISCUSSION

It was concluded that the hypothesis that clindamycin 2% vaginal creme prophylactically given at 26 and 32 weeks of gestation in this well randomised group of women with a history of preterm delivery in the preceding pregnancy could reduce the incidence of preterm delivery when compared to placebo, had to be rejected. Clindamycin 2% vaginal creme did not prevent premature birth nor did this medication have any effect on the incidence of admissions for preterm labour (see Table II and III). One might argue that this conclusion is invalid because the predefined sample size was not reached. This would have been true if a difference in favour of clindamycin had emerged; however the fact that no difference in the main outcome variable, premature birth before 37 weeks, was found with an even significantly less favourable outcome in the clindamycin group in preterm birth before 34 weeks, justifies this conclusion.

The incidence of spontaneous preterm birth in the study population (19% in the placebo and 29% in the clindamycin group) indicates that the hypothesis was tested in a population with an increased risk for premature delivery. This is in agreement with the recurrence of prematurity using a history of premature birth in the preceding pregnancy as selection criterion.13,14,15 Our findings are similar to the results of a study by Hauth et al.17 They tested whether metronidazole combined with erythromycin prophylactically given to women with an increased risk for premature delivery (a history of preterm birth or a low prepregnancy weight (<50 kg)) could reduce the incidence of preterm birth. A group of 358 women was treated once between 22 and 24 weeks in a double-blind, placebo-controlled study. The incidence of prematurity (22% in the medication vs. 25% in the placebo group) was not different between the groups. In our study, clindamycin was given twice (at weeks 26 and 32) during pregnancy. We opted for a second treatment because the therapeutic effect of antibiotics at restoring the normal lactobacilli dominant vaginal flora varies from 75% and 90%.7,18 Since a quarter of women
with bacterial vaginosis is not cured after one course of treatment, a second was scheduled 6
weeks after the first treatment. Despite a second treatment, clindamycin 2% vaginal creme
showed no effect in the prevention of premature delivery. These results, together with the
study of Hauth, indicate that antibiotic prophylaxis does not prevent preterm delivery in
women with a history of premature birth in the preceding pregnancy. An alarming observation
was found in the clindamycin group where significantly more births before 34 weeks were
seen. The neonatal infectious morbidity was also significantly higher in the clindamycin group.
Two of the five neonates with infectious morbidity were born during the week that clindamycin
was administrated (26 and 32 weeks). One of them (born at 32 weeks) died of a fatal
congenital pneumonia due to Streptococci Pneumoniae infection. The others were born several
weeks after treatment.

Hillier\textsuperscript{12} demonstrates that one week after treatment with clindamycin 2% vaginal creme the
vaginal flora was altered with a short lasting increase of Enterococci and E.coli. This was also
reported by Hill\textsuperscript{18}, who found an increase in Enterococci and aerobic Gram negative rods after
treatment with clindamycin. These findings may explain the increase in neonatal infectious
morbidity in our study.

In contrast to the inability of antibiotic prophylaxis to reduce the incidence of spontaneous
premature delivery in a group of women with a high risk of preterm birth based on the
obstetric history, Morales and Hauth found an effect of antibiotic prophylaxis in a group of
women with both an increased risk based on the obstetric history and a bacterial vaginosis\textsuperscript{17,19}.

In the study by Morales, the incidence of preterm birth in the group treated with metronidazole
was 18% versus 39% in the placebo group. Hauth reported 31% preterm deliveries in the
group treated with metronidazole and erytromycin and 49% in the placebo group. However,
treatment with clindamycin 2% vaginal creme of women without an increased risk of preterm
birth but with bacterial vaginosis was not successful in reducing the incidence of prematurity \(^{20,21}\).

The observed increase in birth before 34 weeks and the increase of neonatal infectious morbidity in the clindamycin group strongly suggests that this antibiotic should not be administered prophylactically to women with an increased risk for spontaneous preterm delivery with a normal vaginal flora.

At present only treatment of bacterial vaginosis in pregnant women with an increased risk of preterm birth has resulted in a significant reduction of premature delivery. Whether treatment of bacterial vaginosis in pregnancy without additional risk factors for prematurity is justified, needs to be investigated.
REFERENCES


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