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ORIGINAL ARTICLE

Oral Clindamycin to prevent Preterm Birth: A Randomized Placebo Controlled Trial in South India

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ABSTRACT

Objectives: Clindamycin is the only antibiotic shown effective, in a single study conducted in the United Kingdom, to prevent preterm birth, the leading cause of neonatal mortality. The study objective was to confirm whether oral clindamycin reduces preterm birth by two-thirds in women with vaginal pH > five in a developing country.

Materials and Methods: All women presenting to antenatal care were screened for study eligibility. Two hundred and ten consenting women were randomized at 13 to 17 weeks gestation in this double-blind randomized trial to 300 mg oral clindamycin twice daily for 5 days or an identical placebo at Jawaharlal Nehru Medical College, Belgaum, India. Outcomes were assessed using Chi-square and Student's t-tests.

Results: Twelve women lost to follow-up and three women with unexpected multiple gestation were excluded from analysis. The study group characteristics (n = 100 clindamycin, n = 95 placebo) were similar. The incidence of birth <37 and <34 weeks were 12.0 and 6.0% in the clindamycin compared with 24.2 and 14.7% in the placebo groups (p = 0.026 and p = 0.044, respectively).

Conclusion: Gestational infection accounts for ~40% of preterm births. This is the first confirmation of the only published trial demonstrating that oral clindamycin provided to women with vaginal pH > 5.0 early in gestation substantially reduces preterm birth.

Keywords: Bacterial vaginosis, Clindamycin, Gestational infection, Preterm birth.

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INTRODUCTION

Preterm delivery between 20 and 37 weeks gestation, remains the primary cause of neonatal mortality (NMR), accounting for 27% of nearly 3,100,000 annual deaths and contributing to the 2,600,000 million annual stillbirths worldwide.[1,2] Fifteen million babies are born premature every year.[3] The burden of prematurity is disproportionately born by the developing world with India contributing to over 30% of these deaths.[3]

Though the causes of prematurity are complex, ascending maternal infection is thought responsible for 40% of spontaneous preterm deliveries.[4] Women with abnormal vaginal flora, including bacterial vaginosis (BV), experience higher rates of preterm delivery. The pathogenesis of preterm birth may begin early in gestation,[5] and thus treatment of gestational infection may have its strongest effect when implemented in the first 3 to 5 months of pregnancy. Therapeutic obstetric care, such as cervical cerclage, bed rest, corticosteroid therapy and progesterone have improved fetal outcomes in developed countries,[6] however, in developing countries, like India with more neonatal deaths than any country on earth, such care is beyond the reach of most of the population.[7] Trials of antibiotics to treat maternal infection as a cause of preterm birth, have had discrepant results reflecting the heterogeneity in the antibiotics used, the timing of administration, and their formulations and routes of delivery.[8,9] The Cochrane Review of antibiotics for treating gestational BV found a 20% (p = 0.11) reduction in birth <37 weeks associated with oral or vaginal clindamycin.[8]

Another meta-analysis (5 trials, n = 1,523) of clindamycin for second trimester gestational infection found a 32% reduction (p = 0.02) in preterm birth.[9] The single published trial of oral clindamycin (n = 2,406),[10] included in both reviews found a 52% lower rate of spontaneous birth <37 weeks gestation (p = 0.004).[10] That study, conducted in two hospitals in the United Kingdom, provided oral clindamycin at 12 to 22 weeks gestation.

Clindamycin is a semi-synthetic antibiotic, rapidly absorbed with an average half-life of two and four tenths hours. The medication is not teratogenic, but can have side effects, particularly esophageal irritation, which are usually transient but sometimes require medical attention. Its oral consumption is recommended with a full glass of water to minimize esophageal irritation. Clindamycin is recommended by the Centers for Disease Control and American Congress of Obstetricians and Gynecologists to treat women to prevent early onset group B *Streptococcus* disease in newborns.[11,12] The drug is an affordable, promising mechanism to prevent prematurity and become a global standard of care. Further evaluation has been recommended.[8,9]

MATERIALS AND METHODS

We conducted a hospital-based, individually randomized, controlled double-blind study in the KLES Dr Prabhakar Kore Hospital and Medical Research Center, Belgaum, India, attached to Jawaharlal Nehru Medical College. With substantially higher rates of infection and prematurity than observed in the British trial,[10] the study tests whether providing 300 mg oral clindamycin twice daily for 5 days to women with vaginal pH at or above 5 between 13 and 17 weeks gestation reduces the incidence of preterm birth (<37 weeks) from 15.78 to 5.34%. With a type I error of 5%, 80% statistical power and a two tailed test, an *a priori* sample size of 132 women per group (total 264) was required. The secondary hypotheses test the effects of oral clindamycin on incidence of late miscarriage >28 weeks gestation, and delivery < 34 weeks gestation.

All women presenting for antenatal care were screened for study eligibility. Women were ineligible if they had multiple gestations, did not deliver in the study hospital, had known sensitivity to antibiotics, a history of antibiotic use within the previous 14 days of being screened, current placement of a cervical cerclage, currently receiving tocolytic therapy, a history of cone biopsy, a uterine or cervical anomaly, a life-threatening fetal anomaly, or any significant known medical complication, such as diabetes, renal conditions, collagen diseases, epilepsy, lupus, antiphospholipid syndrome, or essential hypertension.

Written informed consent was obtained for all eligible women. Consenting eligible women were screened for vaginal acidity (pH) by the study physicians. The vaginal pH screening is a simple procedure in which secretions from the posterior fornix of the vagina from a swab sample are tested with litmus paper. Vaginal acidity was assessed using a standard color chart. Consenting women were individually randomized, half to the clindamycin and half to the placebo study groups, using a computer-generated list produced by the clinical pharmacist who prepared and stored the 5 days active drug or placebo in opaque envelopes to prevent drug exposure to light and moisture. Each envelope contained the randomization code number, the hospital name, and the drug expiration date. The clindamycin and locally produced placebo capsules were indistinguishable in appearance. The clinical pharmacist then distributed the envelopes to the study investigators who used them in sequential order. Study participants and investigators were masked to study group allocation. The clinical pharmacist retained the randomization code within a sealed envelope until all study data were collected and analyzed. Women were followed up through delivery to assess the study outcomes. Data were entered and maintained securely at Jawaharlal Nehru Medical College in an encrypted microsoft access database and at Christiana Care Health Systems.

As the study was hospital-based, preterm delivery was defined as delivery <37 weeks following the occurrence of regular uterine contractions (≥ 4 contractions in 20 minutes or ≥ 8 contractions in 1 hour) and cervical changes (effacement ≥ 80% and dilatation ≥ 1 cm) in women with intact fetal membranes and gestational age ≥ 20 weeks. Gestation was assessed by last menstrual period (LMP) for all participants, and by early ultrasound scan and by clinician's estimated date of delivery (EDD) for 193 of the 195 participants analyzed. Two participants' had gestation solely assessed by LMP. Although gestation estimated by LMP can be unreliable,[13] to ensure generalizability of the results to developing country settings, where ultrasound assessment is uncommon, clinicians' recorded gestation was used in the analysis. Only five women had discrepancies of more than 1 week between the LMP, EDD and ultrasound estimates, For these five cases, the gestation as assessed by ultrasound or LMP was used depending upon which had the least difference with the EDD. This did not alter the classification of gestation < 37 or < 34 weeks in any case. We also conducted analyses to determine whether there was consistency of results with lower birth weight categories associated with prematurity.

Statistical Package for the Social Sciences (SPSS) 20.0 was used for data analysis after completion of the study enrolment and follow-up. Dichotomous and continuous outcomes were assessed using the Chi-square test and Student's t-tests, respectively. Fisher's exact p-values were used for analyses where the number of observations was less than five per cell.

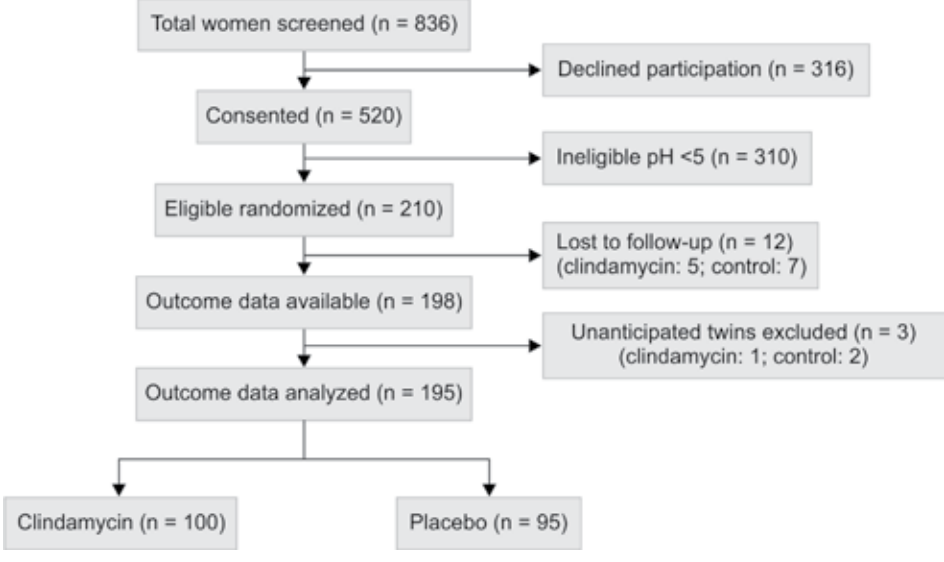
The study was approved on 14 October, 2009 by the institutional review board of Jawaharlal Nehru Medical College, reference number MDC/DOME and was conducted from January 2010 to December 2010 in accordance with the Declaration of Helsinki. The trial was registered with the Clinical Trials Registry—India (CTRI/2011/10/002045). An abstract, including preliminary results, was published in the 55th All India Congress of Obstetrics and Gynecology Conference proceedings. Support for the study was provided by Jawaharlal Nehru Medical College. The active study medication was purchased from Pfizer (Thane Belapur Road, KU Bazar Post, Turbhe, Navi Mumbai, Maharashtra, India).

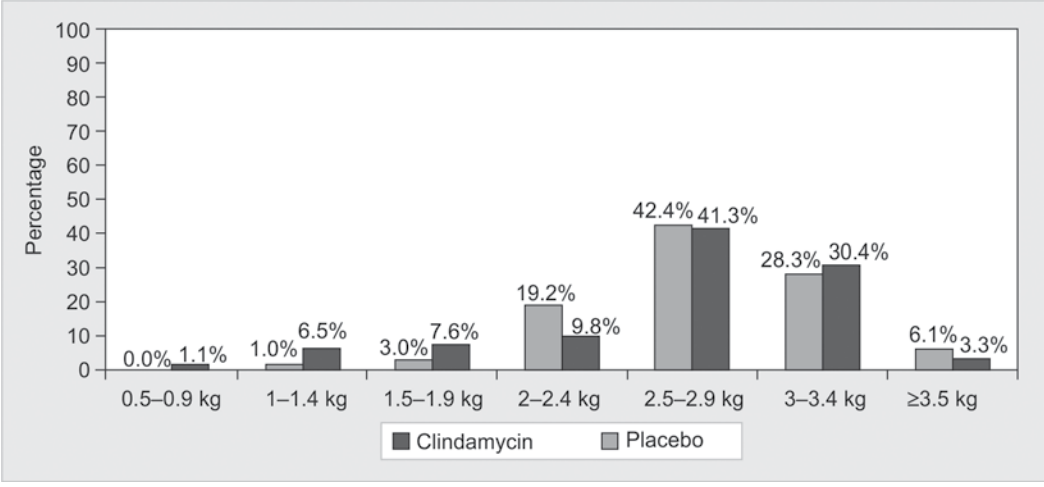
RESULTS

Eight hundred and thirty-six women presented for antenatal care during the study period, of whom 520 consented to participation. Of these, 210 met the pH eligibility criteria. Three cases of multiple gestation not previously identified were excluded, and 195 (clindamycin n = 100 and placebo n = 95) were studied and followed through delivery (Flow Chart 1). The groups had similar baseline demographic and reproductive health characteristics (Table 1). The average maternal age was 23 to 24, most women were housewives, and literate, and 33 to 40% were living below the Indian poverty line. The average vaginal pH level was 5.7 ± 0.4 in the clindamycin and 5.8 ± 0.3 in the placebo groups (NS). Gestation at presentation was 15 ± 2 weeks in both groups. Body mass index, blood pressure and hemoglobin levels were also similar at baseline. More women (74%) in the clindamycin than (64%) in the placebo group had normal (unassisted vaginal) deliveries, with more assisted vaginal deliveries and late miscarriages >28 weeks gestation occurring in the placebo group (Table 2, NS).

The mean gestation was 31 ± 5.7 weeks in those delivering <37 weeks and was 28 ± 5.8 weeks in those delivering <34 weeks. The incidence of <37 weeks delivery was 12% in the clindamycin and 24% in the placebo groups (p = 0.03; in analyses adjusted for prior preterm or assisted birth p = 0.04). Excluding abortions, the rate of preterm delivery was 11.1% in the clindamycin and 21.7% in the placebo groups, and the rate of spontaneous (i.e. not forceps or vacuum-assisted) preterm birth was 5.4% in the clindamycin and 19.8% in the placebo groups (both p = 0.004; in analyses adjusted for prior preterm or assisted birth p = 0.06, Table 3). The incidence of <34 weeks delivery was 6% in the clindamycin and 14.7% in the placebo groups (p = 0.044). The differences were marginally significant (p < 0.10) when limiting the analyses to spontaneous preterm deliveries and those excluding abortions. There were eight cases of induced prematurity in each study group. Mean birthweight and the proportion of babies with birthweight ≤2.5 kg was similar in both groups, however, the incidence of birthweight ≤1.5 kg was 1% in the clindamycin and 7.6% in the placebo groups (p = 0.03). The proportion of newborns in birthweight categories <2000 gm was constantly higher in the placebo than clindamycin groups (Graph 1). No side-effects (gastrointestinal irritation, nausea, vomiting, diarrhea, abdominal pain, rash, dermatitis, urticaria, throat irritation or headaches) were reported (data not shown).

Flow Chart 1: Consort diagram





Graph 1: Birthweight distribution by study group [clindamycin (n = 99), placebo (n = 92); excludes miscarriages]

Table 1: Baseline characteristics of the participants

Characteristics		*Clindamycin (n = 100)*	*Placebo (n = 95)*	*p-value*
Age (years)		24.6 ± 3.8	23.23 ± 3.1	0.10
Occupation				0.59
	House wife	86.0%	84.2%	
	Working	10.0%	12.6%	
	Laborer	4.0%	2.1%	
	Professional	0	1.1%	
Education				31%
	Illiterate	2.0%	1.1%	
	Read	19.0%	12.6%	
	Write	29.0%	25.3%	
	Primary	33.0%	31.6%	
	Secondary	16.0%	23.2%	
	Graduate	1.0%	4.2%	
	Postgraduate	0	2.1%	
Below the poverty level		33%	39.7%	0.48
pH-value		5.7 ± 0.43	5.8 ± 0.33	0.77
Parity		0.53 ± 0.69	0.55 ± 0.68	0.86
Gestation at randomization (weeks)		14.5 ± 1.9	14.7 ± 1.9	0.86
Had previous miscarriage		11%	10.5%	0.92
Had previous spontaneous preterm delivery		2%	4.21%	0.44[a]
Body mass index (kg/(cm^2)		20.1 ± 3.6	19.9 ± 4.7	0.73
Systolic blood pressure (mm Hg)		115.9 ± 8.8	114.8 ± 10.0	0.44
Diastolic blood pressure (mm Hg)		73.9 ± 7.0	74.1 ± 8.6	0.88
Hemoglobin (gm%)		12.6 ± 13.2	11.8 ± 9.4	0.60

[a]Fisher's exact significance test

Table 2: Delivery characteristics

	Clindamycin (n = 100)	*Placebo (n = 95)*	*p-value*
Normal delivery	74.0%	64.2%	0.14
Assisted vaginal delivery	7.0%	13.7%	0.12
Lower segment cesarean section	18.0%	19.0%	0.86
Miscarriage >12 weeks	1.0%	3.2%	0.36[a]
Late miscarriage >28 weeks	n = 99	n = 93	0.29[a]
	0	1.1%	

[a]Fisher's exact significance test

DISCUSSION

This double blind, randomized, placebo controlled trial found 300 μg oral clindamycin taken twice daily for 5 days in women with BV and other abnormal vaginal flora, as indicated by an elevated pH at or above five, significantly reduced the incidence of preterm birth by over 50% and spontaneous preterm birth by nearly 75%, similar to the nearly 60% reduction observed in the single published trial of the same regimen applied between 12 and 22 weeks gestation.[10] That study was conducted in two hospitals in Great Britain, where

Table 3: Outcome data

Outcomes	*Clindamycin (n = 100)*	*Placebo (n = 95)*	*OR (95% CI)*	*p-value*
Total preterm <37 weeks	12.0%	24.2%	0.427 (0.199, 0.917)	0.026
Total preterm <37 weeks excluding abortions	11.1% (n = 99)	21.7% (n = 92)	0.450 (0.202, 1.000)	0.047
Spontaneous preterm <37 weeks	5.4% (n = 92)	19.8% (n = 86)	0.233 (0.082, 0.664)	0.004
Spontaneous preterm <37 weeks excluding abortions	4.4% (n = 91)	17.9% (n = 84)	0.211 (0.067, 0.666)	0.004
Total preterm <34 weeks	6.0%	14.7%	0.369 (0.136, 1.005)	0.044
Total preterm <34 weeks excluding abortions	5.1% (n = 99)	12.0% (n = 92)	0.392 (0.131, 1.174)	0.085
Spontaneous preterm <34 weeks	3.3% (n = 92)	10.5% (n = 86)	0.288 (0.075, 1.103)	0.074[a]
Spontaneous preterm <34 weeks excluding abortions	2.2% (n = 91)	8.3% (n = 84)	0.247 (0.050, 1.225)	0.090[a]
Induced preterm	8%	6.3%		
Due to abruption	1%	2.1%		
Due to IUD	1%	1.1%		
Due to eclampsia	1%	0		
Due to oligohydramnios	1%	1.1%		
Due to pre-eclampsia	2%	1.1%		
Due to intrauterine growth retardation	2%	0		
Due to anencephaly	0	1.1%		
Birth weight (kg) excluding abortions	2.73 ± 0.44 (n = 99)	2.60 ± 0.61 (n = 92)	– 0.132 (– 0.284, 0.019)	0.086
Birth weight <2.5 kg excluding abortions	23.2% (n = 99)	25.0% (n = 92)	0.908 (0.468, 1.763)	0.775
Birth weight <1.5 kg excluding abortions	1.0% (n = 99)	7.6% (n = 99)	0.124 (0.015, 1.027)	0.030[a]

[a]Fisher's exact significance test

the incidence of gestational infection was much lower, around 8%, where gestation was universally estimated by ultrasound, and where genital tract infection was identified by gram stain using Nugent's criteria. The incidence of BV and other abnormal vaginal flora as determined by pH at or above five was 40% in our study hospital. Regardless of the different study environments, methods to estimate gestation and to identify gestational genital tract infection, both Ugwumadu et al[10] and we found oral clindamycin reduced spontaneous prematurity by well over 50%. Our study also found that oral clindamycin had an even greater (~75%) effect on prevention of preterm birth <34 weeks, particularly important as babies born <34 weeks gestation disproportionately contribute to neonatal mortality and societal burden.[14] The consistency of our results with that of Ugwumadu et al[10] is striking and distinct from the lack of effect observed with topical application of clindamycin.[8,9] This suggests that an oral route of administration may be critical to effectively treat abnormal vaginal flora.

The results of our study and Ugwumadu et al[10] supports the theory that treatment between 13 and 22 weeks gestation can be effective. Independent research is needed to evaluate whether treatment in later gestation can be efficacious. Longitudinal studies have observed that spontaneous resolution of bacterial vaginosis later in pregnancy is not associated with a reduction in risk of preterm birth, suggesting that treatment later in pregnancy may not be beneficial. In neonates for whom prematurity was not prevented, provision of oral clindamycin may result in unnecessary fetal expose. In our study, the intervention was provided after organogenoesis. Although larger, systematic assessments of the potential adverse effects of fetal exposure to clindamycin are needed, gestational administration of the medication is recommended by the Centers for Disease Control and American Congress of Obstetricians and Gynecologists to prevent early onset neonatal group B *Streptococcus* disease.[11,12] No side-effects were reported by women participating in our study, however, women may not have reported nausea, vomiting or stomach upset thinking these to be normal in pregnancy. There were no study group differences in the incidence of induced prematurity for obstetric indications (abruption, eclampsia, intrauterine death, oligohydramnios, pre-eclampsia, intrauterine growth restriction and anencephaly).

While our study and Ugwumadu et al[10] found fewer late miscarriages after 28 weeks gestation in women who received clindamycin than placebo, neither finding was significant. Neither study observed a difference in average birthweight, howevers, our study found that oral clindamycin significantly reduced the incidence of very low birthweight (VLBW ≤ 1.5 kg); 89% of preterm babies were LBW and 34% were very LBW.

Gestational age may have been more accurately assessed if it had been estimated by ultrasound for all women. However, such estimation is not generally

available in developing country settings. The inaccuracies in gestational estimation would tend to reduce the significance of the observed effects. The observed pattern that the proportion of newborns in weight categories <2000 gm (91% of whom were preterm), consistently greater in the placebo than clindamycin groups, suggests the gestation estimates have validity.

The Amsel score is the gold standard for BV screening, but the procedure is difficult to reliably implement and expensive for developing country settings. While there is variation across settings. Elevated pH (above four and seven tenths) has been shown to have high sensitivity and specificity. Still, bacterial vaginosis and abnormal vaginal flora as represented by a pH at or above five can feasibly be identified between the first 12 and 22 weeks of pregnancy in countries that experience high rates of prematurity, and may be supplemented or replaced by the Nugent test, estimated to have higher sensitivity and specificity,[15] where possible. As oral clindamycin is an affordable and widely available medication in such settings, this studies confirmation that it can effectively reduce prematurity and its consequences in women with abnormal vaginal flora indicates it can become a global standard of care.[7] Logistical constraints of study continuation beyond the proposed and implemented period, compelled us to halt the trial before enrolling 264 eligible women. While possible, it is unlikely that the enrolment of the outstanding 69 women, half to each group, would have reversed our findings. Larger definitive evaluation has been recommended and is underway.[8,9] Whether gestational infection can be feasibly identified early in gestation and effectively treated in community-based settings in countries where the burden of prematurity and neonatal mortality is greatest remains to be seen. We have initiated a community-based trial in rural Belgaum and Bagalkot Districts of Karnataka State in 2013.

Gestational infection accounts for ~40% of preterm births. Our findings are the first confirmation of the only published trial and indicate providing oral clindamycin to women with vaginal pH at or above five early in gestation substantially reduces prematurity and may consequently help to reduce global neonatal mortality.

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