

Prophylactic use of antibiotic for incomplete and missed miscarriage, prior to medical and surgical management: a randomized controlled trial

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Abstract

Introduction: Miscarriage is a common gynaecological problem in day to day practice. Post miscarriage care is a challenging area coming under reproductive health. Prevention of pelvic sepsis is a main component. Effective antibiotic prophylaxis at the time of treatment for incomplete and missed miscarriage may be the answer for it. But in current practice, there is conflicting evidence and no clear guidance for the necessity of antibiotic prophylaxis.

Objective: To determine the effectiveness of prophylactic doxycycline use, prior to surgical and medical evacuation of incomplete and missed miscarriage, in view of reducing the post-procedure pelvic infections.

Method: Three hundred and ninety four patients were randomized into two groups. One group (n=200) received 200mg doxycycline single dose and the other group (n=194) received placebo single dose, one hour prior to the medical and surgical management. Post procedure pelvic infection was assessed by five clinical parameters within three days and two weeks later. SPSS used for the data analysis.

Result: There were no statistically significant differences in the age, parity, number of children and gestational age in between the doxycycline and placebo groups. Post intervention pelvic infection was diagnosed 4% in the doxycycline group and 6.18% in the placebo group within three days, which was not statistically significant (P=0.367). It was 4.5% and 8.7% for doxycycline and placebo treated groups respectively at two weeks. It was also not clinically significant (P=0.104). There was no statistically significant difference in the type of miscarriage or the type of interventions in between the two groups.

Conclusion: The study revealed that single dose doxycycline prophylaxis prior to medical and surgical management of miscarriage was not able to achieve a statistically significant reduction in post intervention pelvic infection.

Key words: incomplete miscarriage, missed miscarriage, medical management, surgical management doxycycline, pelvic infection

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Introduction

Reproductive health is a human right and a universal need especially for women, because of their physiological capability of reproduction. Post miscarriage care is a challenging area recognized as a part of reproductive health service to answer the complications of miscarriage¹.

Miscarriage is defined as, loss of a pregnancy prior to achieve the viability, either by spontaneous or induced. Legally accepted gestational age (GA) of viability is 24 weeks^{2,3}. Pregnancy loss prior to 24 weeks is considered as a miscarriage and beyond this considered as a still birth. In Sri Lanka viability is considered from 28 weeks of gestation.

About 10%-20% clinical pregnancies are end up as a miscarriage.⁴ The rate of clinical pregnancy loss is known to be decreased with the gestational age, 50% at four weeks, 25% at five to six weeks and 2% after fourteen weeks.⁵

Incomplete miscarriage is defined as, persistence of products of conception within the uterine cavity⁵ Intra uterine gestational sac with a diameter of more than 25mm without a fetus or a fetal pole with a crown rump length more than 7mm without a heartbeat is defined as missed miscarriage⁶.

Management of incomplete or missed miscarriage can be expectant, medical or surgical depending on the clinical situation and the preference of the women. Prostaglandins are used for the medical management, either by vaginally or orally, with or without anti progestogens. Evacuation of retained products of conception (ERPC) or dilatation and evacuation (D&E) are considered as surgical management.

Currently, most of the gynecological units are practicing combination of medical and surgical techniques. Though, surgical management has shown a higher success rate (95-100%),² it has multiple complications compared to the medical management. Trauma to cervix, uterine perforation and postoperative infections (endometritis, PID) are some of the short term complications. Cervical incompetence, Asherman syndrome are some of the long term complications. Heavy bleeding, pain, pelvic infections and prolong hospital stay are some of the complications of medical management.

Prevention of pelvic sepsis is the main component of post miscarriage care. Effective antibiotic prophylaxis may be the answer to prevent post miscarriage pelvic infections and subsequent complications.

There is no consensus regarding antibiotic usage as a prophylaxis. Routine use of antibiotic prophylaxis is accepted in some medical units. But others, antibiotics usage is accepted only with the evidence of infection⁷. Treating with antibiotics in septic abortion is well recognized fact in literature. Use of broad spectrum antibiotics in early uterine evacuation had shown a reduction in morbidity and mortality of septic abortion⁸. Most of the past studies had been carried out for surgically induced miscarriage. There are very little studies on routine use of antibiotics as prophylaxis on medical or surgical management of incomplete or missed miscarriage.⁹

Most of the available evidences are not applicable to South Asian population, because they are from developed countries, where the prevalence of vaginal infections and PID is dissimilar to South Asian population.¹⁰ The available evidences are insufficient to recommend or abandon the routine practice of antibiotic prophylaxis in the management of miscarriage^{3,7}

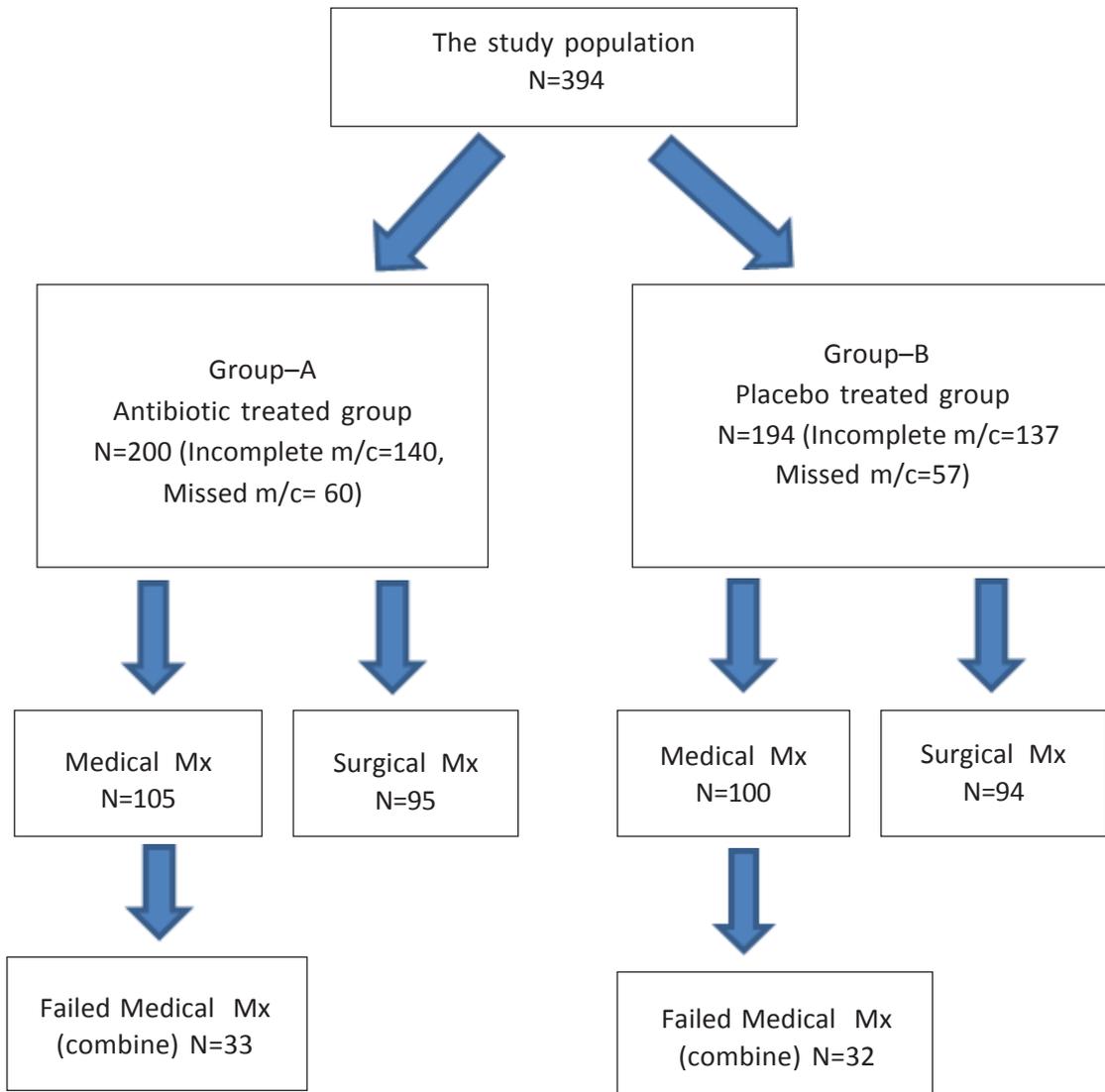
This gray area needs more attention, because it involves large number of women who seek medical care in day to day practice. Therefore, this study was carried to assess the effectiveness of prophylaxis antibiotic as a single dose at the time of surgical as well as medical management of incomplete and missed miscarriage.

Methodology

This study was a double blind randomized controlled trial, carried out at the Professorial Gynaecology Unit, Teaching Hospital Peradeniya, Sri Lanka. Ethical approval was obtained from the Ethical Review Committee, Faculty of Medicine, University of Peradeniya. Study was registered at Sri Lanka Clinical Trial Registry.

Incomplete miscarriage was considered as products of conception thickness > 1.5 cm in trans-vaginal scan and missed miscarriage as intra uterine gestational sac diameter >25mm without a fetal pole or a fetal pole >7mm without heart beat on trans vaginal scan.

Flow chart of the study



Inclusion criteria:

- All Women with incomplete or missed miscarriage, who are not having symptoms and signs of infection (as mentioned below in exclusion criteria).
- Pregnancy loss up to twenty weeks of gestation.

Exclusion criteria were as follows:

1. Women with signs and symptoms of infection as stated below

- Temperature > 37°C
- Severe lower abdominal tenderness
- Smelly vaginal discharge
- Cervical motion tenderness / adnexal tenderness

2. Allergy to doxycycline

Study subjects were allocated into two groups by randomization using computer generated random numbers. Those with odd numbers had antibiotics.

While others with even numbers had placebo. Sequentially numbered, sealed opaque envelopes were packed with antibiotics or placebo according to the computer generated order. Within each arm subjects were randomly allocated to medical or surgical management. Failed medical management proceeded to surgical management in both arms, considered as combine management.

Group A subjects received a prophylactic single dose oral doxycycline 200mg one hour prior to the medical or surgical intervention. Group B subjects received placebo capsule (identical appearance and size as same as the doxycycline) as same as the group A.

Clinical signs of infection were measured before discharge from the unit, and two weeks later by a third person at gynaecology clinic, who also blinded for the intervention (Senior Medical Officer).

Five parameters were measured.

1. History: fever, lower abdominal pain, smelly vaginal discharge
2. Temperature $>37^{\circ}\text{C}$.
3. Lower abdominal tenderness.
4. Positive cervical motion test with or without adnexal tenderness.
5. Presence of smelly vaginal discharge.

Presence of at least 3 out of 5 above parameters were taken as a clinical pelvic infection.

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 20. As the data was normally distributed the Student's

t-test and the Chi-squared test were used to compare means and proportions. $P < 0.05$ considered as statistically significant.

A total of three hundred and ninety-four women were recruited to the study (incomplete (277), missed miscarriage (117)). They were randomized into doxycycline treating group (A) and placebo treating group (B), as 200 and 194 respectively by computer generated random numbers.

Results

There were no statistically significant differences in age, parity, number of children and POA in between the two groups (Table 1).

The percentage distribution of incomplete and missed miscarriage in group A and B were in similar pattern. The P-value was 0.438. There was no statistically significant difference in the distribution of miscarriage types in the two groups.

There were 277 subjects with incomplete miscarriage randomly allocated into group A and B as 140 and 137 respectively. There was no statistically significant difference in type of intervention (medical, surgical or combine) within the incomplete miscarriage group in between the group A and B. (P-value = 0.124)

Hundred and seventeen women with missed miscarriage were randomized to group A and B, as 60 and 57 respectively. There was no statistically significant difference in type of interventions within missed miscarriage subjects in the group A and B (P-value was 0.325).

Table 1. Basic characteristics of group A and B. Age, parity, number of children, POA

	Group-A N= 200	Group-B N=194	P-Value
Age (y) - Mean (SD)	29.9 (6.885)	30.1 (7.215)	0.8
Parity - Mean (SD)	02 (01)	02 (1)	0.8
Number of children - Mean (SD)	01 (01)	01 (01)	0.9
POA (days) - Mean (SD)	73 (18)	70 (18)	0.1

The distribution of type of intervention showed similar pattern in between the two groups. 140, 189 and 65 women were managed medically, surgically and combine effort (failed medical management followed by surgical management) in two groups respectively. There was no statistically significant difference in type of interventions in between the doxycycline and placebo group. P-value was 0.47.

Hundred and forty women were managed by medical interventions, from that 72 were in the doxycycline treated group and 68 were in the placebo group. The distribution of incomplete and missed miscarriage within the medically managed women in the two groups were not statistically significant. The P-value was 0.635.

Hundred and eighty nine women were managed surgically as 95 and 94 in Group A and B respectively. There was no statistically significant difference in

distribution of type of miscarriages within surgically managed women in this two groups. (P-value = 0.29)

Sixty five women who had failed medical management followed by surgical evacuation (combine management) including 33 and 32 respectively in Group A and B. The distribution of type of miscarriage in this group was in similar pattern. The P-value was 0.205. Therefore, there was no statistically significant difference in type of miscarriage when combine management was done.

Presence of at least three out of five clinical parameters was considered as pelvic infection. Pelvic infection was diagnosed 4% in the group A and 6.18% in the group B within three days. The P-value was 0.367. OR and 95% Confidence Interval was 0.6 (0.25-1.58). There was no statistically significant difference of post intervention pelvic infection rate in between prophylactic doxycycline and placebo given groups within three days of duration (Table 2 & 3).

Table 2. Post intervention pelvic infection within three days

Pelvic infection	Group-A N=200 (%)	Group- B N=194 (%)	Total N=394	OR (95% CI)	P-value
Present	08 (04%)	12 (6.18%)	20	0.6(0.25-1.58)	0.367
Absent	192 (96%)	182 (94%)	374		

Table 3. Post intervention pelvic infection within two weeks

Pelvic infection	Group-A N=200 (%)	Group- B N=194 (%)	Total N=394	OR (95% CI)	P-value
Present	09 (4.5%)	17 (8.7%)	26	0.48 (0.21-1.10)	0.104
Absent	184 (92%)	168 (86.5%)	352		
Unknown	07 (3.5%)	09 (4.8%)	16		

Sixteen women were lost to follow up (4.06%). Seven patients in the doxycycline group (1.77%) and nine patients in the placebo group (2.28%). Therefore, the presence of pelvic infection was not known to them. Twenty patients who had pelvic infection within three days, in the group A (08) and group B (12), treated with antibiotics. Newly diagnosed pelvic infections at two-week assessment (after discharged from the hospital) plus earlier diagnosed pelvic infection within three days of hospital stay, was considered as total pelvic infections within two weeks. Therefore, total pelvic infections within two-week were 9 (4.5%) and 17 (8.7%) respectively in group A and B. The P-value was 0.104. OR and 95% CI was 0.48 (0.21-1.10).

There was no statistically significant difference of post intervention pelvic infection in between doxycycline and placebo group within two weeks.

The prevalence of pelvic infection for the entire study group was 6.59% (26/394). It was for the doxycycline

treatment group 4.5% (9/200) and for the placebo group 8.7% (17/194). The difference was 4.2%.

Out of 277 incomplete miscarriage women, 15 had pelvic infections in the study population as 07 (05%) and 08 (5.8%) respectively in the groupA and B, within three days. The P-Value was 0.79.

It was 08 (5.7%) and 11 (08%) for group A and B respectively within two weeks. The P-Value was 0.48. There was no statistically significant difference in view of pelvic infection in the incomplete miscarriage subjects in group A and B within three days or two weeks (Table 4 & 5).

The pelvic infection in missed miscarriage group within three days was 01 (1.6%) and 04 (07%) in the group A and B. The P-value was 0.20. It was for within two weeks 01 (1.6%) and 06 (10%) respectively for group A and B. The P-value was 0.06 for that. Therefore, there was no statistically significant difference in pelvic infection in the group of missed miscarriage subjects in group A and B, respectively in three days and two weeks.

Table 4. Comparison of pelvic infection in the mode of intervention groups within 3 days

Intervention Group	Group-A			Group-B			P-value
	Present N=08	Absent N=192	Total N=200	Present N=12	Absent N=182	Total N=194	
Medical	2 (2.7%)	70 (97.3%)	72	3 (4.4%)	65 (95.6%)	68	0.67
Surgical	3 (3%)	92 (97%)	95	5 (5.3%)	89 (94.7%)	94	0.50
Combine	3 (09%)	30(91%)	33	4 (12.5%)	28 (87.5%)	32	0.70

Table 5. Comparison of pelvic infection in the mode of intervention groups within two weeks

Pelvic infection	Group-A			Group-B		
	Medical N=72 (%)	Surgical N=95 (%)	Combine N=33 (%)	Medical N=68 (%)	Surgical N=94 (%)	Combine N=32 (%)
Present	02 (2.7)	04 (4)	03 (9)	04 (5.8)	06 (6)	07 (21)
Absent	66 (91.6)	89 (93)	29 (87)	62 (91)	84 (89)	22 (68)
Unknown	04 (5.7)	02 (3)	01 (4)	02 (3.2)	04 (5)	03 (9)

Discussion

Pelvic infections need to be considered in women who are undergoing medical or surgical management of miscarriage. The patho-physiology of pelvic infection involves, ascending of organisms like *Neisseria gonorrhoea*, *Chlamydia trachomatis* and other mixed aerobes, anaerobes from lower genital tract to upper genital tract. In the procedures like ERPC protective cervical barrier is compromised and the curette may act as a vehicle for introducing infections from vagina to uterine cavity. The open cervix seen in incomplete miscarriage may also facilitate the ascend of infection from the vagina to the uterine cavity. There are identified risk factors associate with increased risk of pelvic infections following active management of miscarriages^{11,19} multiple sexual partners, previous PID, nulliparity and age < 20 years are some of them.

Numerous studies have shown antibiotic prophylaxis at the time of suction curettage of induced first trimester miscarriages can significantly reduce the pelvic infections specially in high risk women^{11,12,13,14}. Some studies recommended antibiotics, prior to surgical evacuation^{12,13}. While others have advocated their use on women with a high risk of infection^{4,15,16}. But some authors do not recommend prophylactic antibiotics for management of the miscarriages¹⁷.

In our study there was no statistically significant difference considering the age, parity, POA, number of children in between the two groups. There was no statistically significant difference in type of miscarriage (incomplete or missed) and type of interventions carried out (surgical, medical or combine) in between two groups.

Pelvic infection was diagnosed 04% in the group A and 6.18% in the group B within three days. The P-value was 0.36. Diagnosis of pelvic infection at two-week time was 4.5% and 8.7% respectively for group A and B. The P-value was 0.11. Therefore, there was no statistically significant difference found in pelvic infections between doxycycline treated and placebo treated groups within three days and in two-week duration.

The rates of pelvic infections by *Chlamydia trachomatis* and *Neisseria gonorrhoea* has geographical variations, ranging from 5% to 20%^{13,15}. Prevalence of chla-

mydia, gonorrhoea in Sri Lanka was found as 8.2%, 7.6% and *Trichomonas vaginalis* as 2.3% in clinic setting²⁰. Therefore, doxycycline was selected as the prophylaxis for this study. It was selected instead of azithromycin because it was inexpensive, easily tolerable and effective for common pathogenic organisms causing PID. Previous studies also showed the use of oral doxycycline was effective in reducing post abortion sepsis relative to placebo^{11,13,18,21}. North American Abortion Federation found that doxycycline is the routinely used antibiotic prophylaxis in 91% for the miscarriages²². In our study we used single dose of doxycycline 200mg orally prior to interventions because of the compliance issues. We did not perform the vaginal swab cultures to identify pathogenic organisms. So, we missed the chance of identifying the causative pathogenic organisms and its prevalence.

Conclusion

This study revealed, prophylactic single dose of doxycycline 200 mg was unable to achieve a statistically significant reduction in pelvic infection, post medical or surgical management of incomplete and missed miscarriage.

Limitations

- 1) Pelvic infection was assessed by only using clinical parameters (symptoms and signs). Some of the symptoms assessed by the history were not much reliable because of subjective variations in the presentation of history like fever, lower abdominal pain, smelly vaginal discharge. Some may have exaggerated symptoms and some may have ignored them. But the clinical signs were more reliable compare to history parameters.
- 2) Pre and post procedural microbiological isolation of pathogenic organisms from genital tract were not performed to determine the exact pelvic infection.

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