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Research Article

Herbal remedies and other risk factors for preterm birth in rural Kenya

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Background: Premature infants contribute substantially to infant morbidity and mortality especially in low resource settings. Information on herbal remedy use, previous preterm birth and low social-economic status and their association with incidence of preterm birth in Kenya is scanty.

Objectives: To determine the use of herbal remedy use in pregnancy, previous preterm birth and low socio-economic status as risk factors for Preterm Birth in Kitui County among the immediate post-partum mothers.

Methods: Unmatched case control study with a 1:4 ratio of cases to controls. The study was done in Kitui and Mwingi District Hospitals. A total of 107 mothers with preterm birth (cases) and 453 mothers with term births (controls) were eligible and administered structured interviews.

Results: Of the sample, 98% of cases resided in rural areas compared to 90% of controls. The cases had a higher parity and were more likely to belong to the lowest three and four levels of socio-economic status. On multivariate logistic regression analysis, predictors of preterm birth were: preeclampsia (OR=9.06 [2.60-31.63], p=0.001), previous preterm, (OR=9.31 [2.82-30.68], p<0.001), low socioeconomic status (OR=1.51 [1.05-2.16], p=0.03), herbal use in first trimester for 2-5 days (OR=11.10 [4.34-28.41], p<0.001), herbal use in first trimester for 6-10 days (OR=44.87,[4.99-403.87] p=0.001), and herbal use in second trimester for 6-10 days (OR=16.43 [4.53-59.57], p<0.001). Use of prescribed folic acid in second trimester for more than 31 days was associated with lower risk of preterm birth (OR=0.20 [0.12-0.34], p<0.001).

Conclusion: Herbal use in pregnancy regardless of gestation, previous preterm birth and low socio-economic status and are risk factors for preterm birth in Kitui County Kenya. Interventions targeted to reduction of these risk factors will be an important additional prong in the reduction of preterm birth.

Key words: Preterm birth, herbal remedy, risk factors

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1. Introduction

Preterm labour is defined as the presence of uterine contractions of such frequency and intensity as to cause dilatation of the cervix prior to 37 completed weeks of gestation, leading to Preterm Birth (PTB) (Mahande et al. 2013). PTB is associated with increased infant mortality and morbidity. Worldwide, approximately one in 10 babies is born prematurely. This translates into about 15 million premature infants annually (Kinney et al. 2012), making PTB a major worldwide paediatric health problem. It is estimated that in developed nations, one third of infant mortality is related to PTB (Lumley 2003). Children born prematurely are also at a higher risk of long-term mental and physical disability, adversely affecting their

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quality of life (Beck et al. 2010). Sub-Saharan Africa carries a disproportionately heavier burden of death and disabilities attributable to PTB. Estimates of incidences of PTB vary widely but are higher than in developed world (Beck et al. 2010), averaging about 12% (Wessel et al. 1996) and as high as 25% (Steer, 2006). Unlike the developed nations, where most preventable risk factors are routinely controlled, mothers in Africa still have to contend with preventable causes of PTB, due to inadequate public health interventions. Due to the adverse outcomes of PTB, prevention of PTB remains an important intervention in obstetric care. Prevention of preterm labour in the clinical setting is focussed on case management of individual mothers who present with symptomatic preterm labour. Though this approach in itself does not lead to significant reduction on preterm deliveries, it affords the health professionals time for foetal lung maturity with antenatal steroids and transfer to tertiary facilities equipped to manage preterm infants. This prong does not mitigate the underlying factors of PTB. Hence, a need for a two pronged approach that includes identification and reduction of factors associated to PTB.

Herbal remedies are commonly used by pregnant women in most African settings, and has been identified as a risk factor to PTB. Herbal remedies are defined as medicinal products containing aerial or underground parts of plants, or combinations of plant materials either in their crude form or as a refined plant preparation. These products may also contain organic or inorganic ingredients that may not be of plant origin, such as honey (Bodeker et al. 2005). They constitute many phytochemicals, including carbohydrates, glycosides, sterols, flavonoids, tannins and alkaloids (Glover et al. 2003) many of which are biologically active. Herbs could cause adverse pregnancy outcomes due to adulteration, contamination with unlabelled toxins, inappropriate formulations and interaction between conventional medications and herbs (Elvin-Lewis 2001). In Kenya the use of herbal remedies is deep rooted and on an upward trend. In addition to the traditional herbalists in the rural areas, many herbal practitioners are setting up shops in the urban areas as well.

Obstetric and gynaecological history plays an important role in predicting the incidence of preterm birth. History of preterm birth and previous induced abortion are strongly associated with preterm birth. Other conditions such as preeclampsia, eclampsia, ante-partum haemorrhage and placenta praevia put the mother at risk for preterm birth (Feresu et al. 2004)

Low social-economic status is an important risk factor for preterm birth in Sub-Saharan Africa. This is because other controllable risk factors for preterm birth are associated with low income. Poor maternal nutrition is a significant risk factor for preterm birth. In fact, incidence of preterm birth has been known to rise in the months of drought due to poor access to nutrition (Rayco-Solon et al. 2005). Moreover, low maternal body mass index (BMI) is an independent determinant of preterm birth (Goldenberg et al. 2008). Low social-economic status is also linked to risky maternal lifestyles, such as tobacco use and alcohol consumption, both of which are associated with a higher incidence of preterm birth (Cox et al. 2013)

We undertook a study to determine exposure to herbal remedies in pregnancy, previous preterm birth and low socio-economic status as risk factors for preterm birth and other associated risk factors in Kitui County Kenya.

2. Methodology

2.1 Study Design: This was a non-matched hospital based case control study with a ratio of 1:4 for cases to controls.

2.2 Study setting: The Kitui and Mwingi District hospitals of Kitui County Kenya. Kitui County is located in the South of the former Eastern Province. It is a semi-arid region with sporadic rainfall, which impacts negatively on subsistence farming, which is the major economic activity. This county was selected for this study because none of the studies reviewed have been conducted in this region on risk factors for preterm birth. It was also important because the cultural practices of the people in this region include use of herbal remedies. It has two major urban centres namely, Kitui and Mwingi. Kitui and Mwingi District hospitals are the two largest public hospitals in the county.

2.3 Study population: The cases were immediate post-partum mothers who presented to Kitui and Mwingi District Hospitals within the study period between May and August, 2014, had a PTB (delivery at less than 37 completed weeks of gestation). Controls immediate post-partum mothers who presented to Kitui and Mwingi District Hospitals and had a term live delivery (delivery more or equal to 37 completed weeks of gestation). Very sick or unconscious mothers or those who did not give informed consent as well as those who could not communicate either in Kiswahili or English were excluded from the study. Mothers of postmature infants (more or equal to 42 weeks gestation) were also excluded from the control group.

2.4 Sample Size, Sampling Procedure and Participant recruitment

The study was designed to detect an Odds Ratio of two or more, with 80% or greater statistical power, exposure prevalence of 15% at 95% confidence level. A sample size of cases (n) = 115 and that of controls (n) =460 was adequate for this purpose (Brian et al. 2012).

Participants were recruited on a daily bases as they attended the hospitals over a period of three months. To recruit the participants took place in the postnatal wards, Assessment eligibility and informed consent sought for the study. All eligible participants were interviewed and prescription drug information extracted from the Mother and Child Booklet.

2.5 Data Variables

The level of education of the mothers was classified in to four categories depending on the highest level of education attained by individual participant, none (for those who had had no education), primary, secondary and tertiary.

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Table 1: Baseline characteristics of the mothers who had preterm birth (cases) and those who had term birth (controls) in Kitui County (2014)

Maternal Characteristics	Cases n=107 (%)	Controls n=453 (%)	Total (%)	p value
Mean age [SD]	25.4 [7.1]	24.4 [5.4]	25.2 [5.8]	0.116
Level of education				
None	7 (6.5)	23 (5.1)	30 (5.4)	0.168
Primary	63 (58.9)	222 (49)	285 (50.9)	
Secondary	29 (27.1)	174 (38.4)	203 (36.3)	
Tertiary	8 (7.5)	34 (7.5)	42 (7.5)	
Residence				
Rural	105 (98.1)	406 (89.6)	511 (91.3)	**0.005**
Urban	2 (1.9)	47 (10.4)	49 (8.8)	
Housing				
Stone house	8 (7.5)	45 (9.9)	53 (9.5)	**0.033**
Tin roof with brick wall	51 (47.7)	272 (60.0)	323 (57.7)	
Tin roof with mud wall	41 (38.3)	114 (25.2)	155 (27.7)	
Thatched house	7 (6.5)	22 (4.9)	29 (5.2)	
Previous pregnancies				
0	36 (33.6)	142 (31.4)	178 (31.8)	**0.04**
1	27 (25.2)	112 (24.7)	139 (24.8)	
2	18 (16.8)	127 (28.0)	145 (25.9)	
3	12 (11.2)	44 (9.7)	56 (10.0)	
> 3	14 (13.1)	28 (6.2)	42 (7.5)	
Number of ANC visits				
0	9 (8.4)	3 (0.7)	12 (2.1)	0.085
1	11 (10.3)	23 (5.1)	34 (6.1)	
2	37 (34.6)	44 (9.7)	81 (14.5)	
3	42 (39.3)	129 (28.5)	171 (30.5)	
4	5 (4.7)	180 (39.7)	185 (33.0)	
>4	3 (2.8)	74 (16.3)	77 (13.8)	
Tobacco use				
No	106 (99.1)	452 (99.8)	558 (99.6)	0.266
Yes	1 (0.9)	1 (0.2)	2 (0.4)	
Alcohol use				
No	96 (89.7)	430 (94.9)	526 (93.9)	**0.043**
Yes	11 (10.3)	23 (5.1)	34 (6.1)	
Prior PTB, miscarriage or pregnancy termination				
No	95 (88.8)	447 (98.7)	542 (96.8)	**<0.001**
Yes	12 (11.2)	6 (1.3)	18 (3.2)	
Preeclampsia				
No	97 (90.7)	448 (98.9)	545 (97.3)	**<0.001**
Yes	10 (9.4)	5 (1.1)	15 (2.7)	
Vaginal candidiasis				
No	97 (90.7)	410 (90.5)	507 (90.5)	0.963
Yes	10 (9.4)	43 (9.5)	53 (9.5)	

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Type of housing was used as a surrogate indicator for socio-economic status. Mothers who had had a previous preterm birth, miscarriage or termination of pregnancy were classified together. For all medications and herbal remedies, trimester in which the first dose was taken and the duration for which the medication was taken were combined to make one composite variable. Timing of medication use was classified as first trimester (one to 13 weeks), second trimester (14 to 27 weeks) or third trimester (after 27 weeks). Duration of use was classified as "once to 1 day", "2 to 5 days", "6 to 10 days", "11-30 days" or "more than 31 days".

2.6 Data Collection and Management

A structured questionnaire was administered to participants to collect data to determine maternal baseline characteristics and exposure to herbal remedies, every participant underwent a structured interview with the use of a questionnaire. Prescription medication data was abstracted from the Mother and Child booklet. Data variables were entered into Microsoft Excel 2010 spread sheet using the participant number as the identification (ID) number. De-identified data was exported to STATA version 12 for analysis.

2.7 Data analysis

Descriptive data analysis was done for socio-demographic variables. Mean and standard deviation were determined for age of the mothers. Counts and percentages were used to summarize categorical variables. Logistic regression was done to determine significant medication-related risk factors for preterm birth. To control for confounding, a multivariate analysis was done by manual forward stepwise model building until a parsimonious model was achieved. Odds ratios and 95% confidence intervals were reported and p-values of 0.05 and less were considered statistically significant.

2.8 Ethical considerations

The Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) gave ethical approval for the study (Reference No. P77/02/2014) and permission to carry out the study were sort from Kitui and Mwingi District Hospitals. Written informed consent was obtained from each participant. All the filled questionnaires were safely by the Principal investigator and electronic data were pass word protected. Only de-identified data was analysed.

3. Results

3.1 Sample baseline characteristics

The baseline characteristics are summarized in **Table 1**. The mean age of the participants in this study was 25.2 (±5.8) years. The cases had a mean age of 25.4 (±7.1) years and the controls 24.4 (±5.4) years. There was no significant difference in mean age across the two groups. Diagnosis of preeclampsia was significantly higher among the cases 9.4% (10/107) compared to controls 1.1% (5/453) [p<0.001]; previous PTB, pregnancy termination or miscarriage were higher in cases 11.2% (12/107) compared to controls 1.3% 6/453 [p<0.001]; The cases were more likely to belong to the two lowest socio-economic status 44.8% (48/107) than the controls 30.0%) (136/453) [p=0.033]. Parity of more than three was significantly more common among the cases 24.3% (26/107) compared to controls 15.9% (72/4530 [p=0.04]. There was no statistically significant difference between the two groups on the level of education. Most of the cases 98.1% (105/107) were drawn from rural areas compared to 89.6% (406/43) of controls [p=0.005].

The controls were more likely to have met the recommended at least four antenatal clinic visits 56.0% (254/453) compared to 7.5% (8/107 of the cases [p=0.085], although there was no significant difference across the two groups. Cases had a significantly higher proportion of alcohol users 10.3% (11/107) compared to controls 5.1% [23/453] [p=0.043].

3.2 Herbal remedy use in pregnancy

From **Table 2**, the cases were 16 times likely to have used herbal remedies at all in pregnancy than the controls (OR=16.2; 95% CI [6.52-35.6]). Cases were 15 times more likely to have used herbal remedies in the first trimester compared to the controls (OR=15.7; 95% CI [7.34-33.6]). Herbal use in the first trimester for two to five days had a 12 times higher risk of preterm birth (OR=12.01; 95% CI [5.1-28.3]) while use for six to 10 days increased the risk to 36 times (OR=36.53; 95% CI [4.52-295.36]). Finally, cases were 10 times more likely to have used herbal remedies in the second trimester for six to 10 days (OR=10.31; 95% CI [3.11-34.15])

Although this study was not intended to identify individual herbal remedies, some herbal remedies were frequently mentioned. These included "Mwarubaine" (*Azadirachta indica)* leaves and bark extracts "muembe" (*Mangifera indica)* leaves and bark extracts, and leaves of "mukawa" (*Carissa edulis*) and "kiluma" (*Aloe vera*). The following reasons were given for taking herbal remedies: prescribed by a relative including a parent, herbal remedy was considered safe for use in pregnancy, lack of alternative due to inaccessibility of health facilities, to strengthen the pregnancy, to reduce length of labour, and because it was recommended by other persons in the community. Other reasons given included recommendation by a traditional healer and adherence to cultural practices.

3.3 Multivariate analysis of risk factors for PTB

Diagnosis of preeclampsia was associated with more than 9 times higher risk for PTB OR=9.06 (p=0.001; 95% CI: 2.60-31.63), as was report of previous preterm birth OR=9.31 (p<0.001: 95% CI: 2.82-30.68). Low socioeconomic status was associated with a 51% higher risk for PTB OR=1.51 (p=0.03; 95%CI: 1.05-2.16). Herbal use in first trimester for 2-5 days was associated with 11 times higher risk OR=11.10 (p<0.001: 95% CI: 4.34-28.41), herbal use in first trimester for 6-10 days nearly 45 times higher risk OR=44.87 (p=0.001;95%CI: 4.99-403.87), and herbal use in second trimester for 6-10 days more than 16 times higher risk for PTB OR=16.43(p<0.001; 95% CI: 4.53-59.57). Prescribed folic acid in second trimester for more than 31 days was associated with 80% lower risk of PTB (OR=0.20, p<0.001; 95% CI: 0.12-0.34), **Table 3** and **Figure 1**.

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Table 2: Herbal remedy use in mothers who had preterm birth (cases) and those who had term birth (controls) in Kitui County (2014)

Composite Variable	Cases n=107(%)	Controls n=453 (%)	OR (95%CI)	p-Value
Herbal use, first trimester for one day	1(0.9)	1(0.2)	4.26(0.26-68.72)	0.307
Herbal use, first trimester for 2-5 days	19(17.8)	8(1.8)	12.01(5.1-28.3)	**<0.001**
Herbal use, first trimester six to 10 days	8(7.5)	1(0.2)	36.53(4.52-295.36)	**0.001**
Herbal use, second trimester for 6-10 days	9(8.4)	4(0.9)	10.31(3.11-34.15)	**<0.001**
Report of herbal use in the first trimester	28(26.2)	10(2.2)	15.7(7.34-33.6)	**<0.001**
Report of herbal use in pregnancy	37(34.6)	14(3.1)	16.2 (6.52-35.6)	**<0.001**

Significant p-values in **bold; CI confidence interval*

Table 3: Multivariate analysis of factors associated with preterm birth in mothers who had preterm birth (cases) and those who had term birth (controls) in Kitui County (2014)

Variable	Crude OR (95%CI)	p-value	Adjusted OR (95%C)*	p-value
Preeclampsia	9.21 (3.09-27.63)	**0.000**	9.06 (2.60-31.63)	**0.001**
Previous preterm birth	9.41 (3.45-25.69)	**0.000**	9.31 (2.82-30.68)	**0.000**
Housing	1.45 (1.08-1.95)	**0.013**	1.51 (1.05-2.16)	**0.03**
Residence	0.16 (0.04-0.72)	**0.013**	-	**-**
Alcohol use	2.14 (1.11-4.54)	**0.047**	-	-
Tobacco use	4.26 (0.26-68.72)	0.307	-	**-**
Number of Previous pregnancies	1.07 (0.90-1.26)	0.445	-	**-**
Herbal use in first trimester for 2-5 days	12.01 (5.10-28.30)	**0.000**	11.10 (4.34-28.41)	**0.000**
Herbal use in second trimester for 6-10 days	10.31 (3.11-34.16)	**0.000**	16.43 (4.53-59.57)	**0.000**
Herbal use in first trimester for 6-10 days	36.53 (4.52-295.30)	**0.001**	44.87 (4.99-403.87)	**0.001**
Herbal use in the first trimester once	4.26 (0.26-68.72)	0.307	-	**-**
Prescribed ferrous sulphate 2nd trimester for >31 days	0.19 (0.12-0.30)	**0.000**	-	**-**
Prescribed Folic acid, 2nd trimester > 31 days	0.18 (0.12-0.28)	**0.000**	0.20 (0.12-0.34)	**0.000**
Prescribed metronidazole 2nd trimester 2-5 days	6.57 (2.44-17.67)	**0.000**	-	-
Prescribed amoxicillin 1st trimester 2-5 days	0.09 (0.01-0.66)	**0.018**	-	**-**
Prescribed omeprazole 2nd trimester 6-10 days	6.51 (2.03-39.41)	**0.042**	-	-
Self-medication amoxicillin first trimester 2-5 days	4.42 (1.40-14.00)	**0.011**	-	-
Self-medication chlorpheniramine 1st trimester 2-5 days	4.36 (2.01-17.73)	**0.040**	-	-
Self-medication magnesium trisilicate 1st trimester 2-5 days	8.91 (2.19-36.23)	**0.002**	-	-
Self-medication paracetamol 1st trimester 2-5 days	3.78 (1.24-11.51)	**0.019**	-	-

Pseudo R2=0.2768, Significant p-values in **bold, CI confidence interval*

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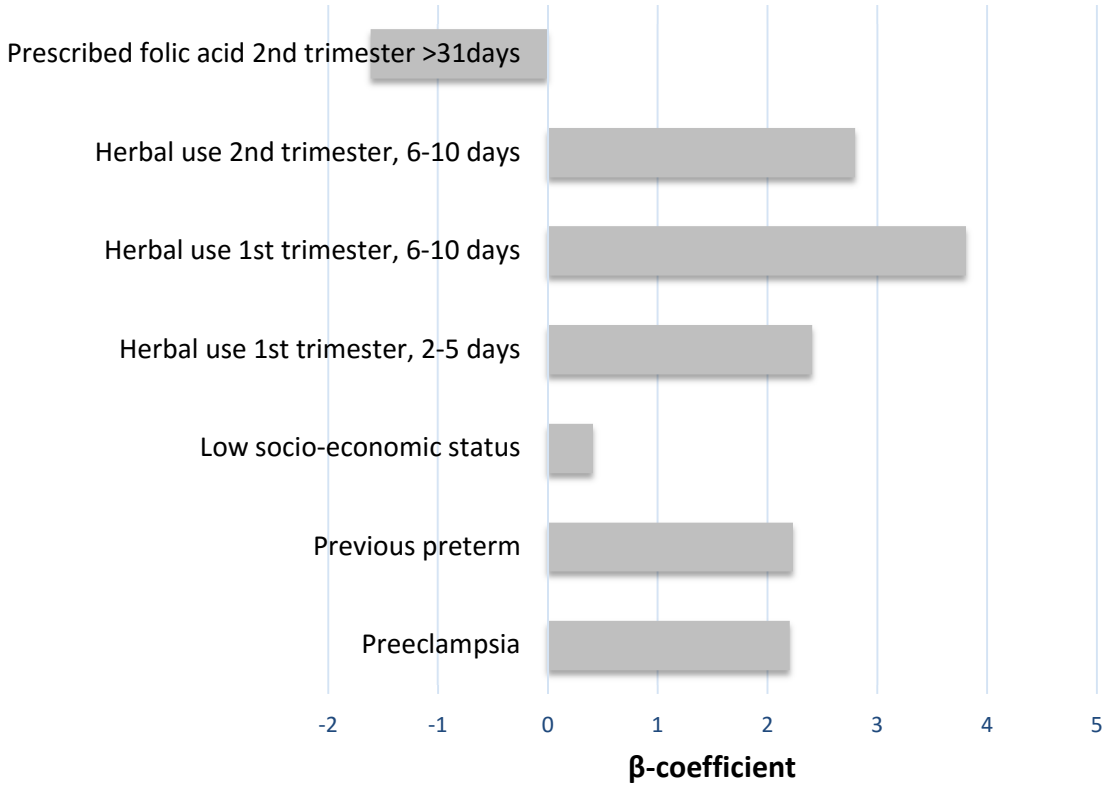

Figure 1: Summary of factors associated to preterm birth in Kitui County, Kenya (2014)

4. Discussion

The main findings of this study are that previous preterm birth, low socio-economic status and herbal use in pregnancy regardless of gestation are associated with a higher likelihood of preterm birth among pregnant women in Kitui County.

Diagnosis of preeclampsia was associated with more than nine times higher risk of preterm birth compared to mothers who did not have preeclampsia. This is more than twice the risk reported from Ardabil, Iran (Alijahan et al. 2014). Another study by Bilano et al in low and middle income countries found out that preeclampsia was a significant risk factor for PTB (Bilano et al. 2014).

Over 11% of the mothers with PTB had had either a previous PTB, pregnancy termination or miscarriage compared to only 1 % of the control mothers. Prior preterm, pregnancy termination or miscarriage was a significant risk factor for PTB in this study. This corroborates findings of a Brazilian study that found that previous abortion carried a 39% more risk for PTB (Passini et al. 2014). A study in Scotland found that previous abortion was associated with 12% risk in preterm birth (Oliver-Williams et al. 2013). Di Renzo et al reported nearly a doubling of risk for PTB by previous abortion (Di Renzo et al. 2011). Both abortion and previous PTB were reported to be significantly more frequent for mothers with PTB (16.3%) than mothers with term birth (11.5%) (Winer et al. 2009).

Mothers with three or more previous pregnancies in this study were 24% among the cases compared to 16% among the controls. Though number of previous pregnancies was not statistically significant after multivariate analysis, multiparity has been reported as a risk factor for preterm birth. An Iranian study found that there was a 56% increase in the risk for PTB for every increase in the number of gravidities (Poorolajal et al. 2014).

Low socio-economic was associated with significantly higher risk for PTB. Nearly 45% of the cases belonged to the lower two tiers of the socio-economic status compared to about a third of the controls. Low socio-economic status is a risk factor for PTB probably because other risk factors are linked to poor income. Inadequate maternal nutrition, low body mass index and manual labour as well as mental and physical stress, among others, are higher in poor populations. These are known independent risk factors for PTB (Rayco-Solon et al. 2005, Dole et al. 2004).

Among the cases, 10% reported use of alcohol compared to 5% among the controls. On multivariate analysis, this association ceased to be significant. However, a British cohort study found that women who used alcohol had a two and a half times higher risk for PTB than non-drinkers (Srikartika and O'Leary 2014).

Prescription medications, such as ferrous sulphate, metronidazole, omeprazole and amoxicillin were significant risk factors on bivariate analysis, though they were not significant on multivariate analysis. This also applied to self-medications, such as amoxicillin, chlorpheniramine and magnesium trisilicate.

Prescribed folic acid from the second trimester for more than 31 days was associated with lower risk for PTB. On multivariate analysis, this study found that others on folic acid were 80% less likely to have PTB compared to mothers not on folic acid. Mothers needed to use it for more than 31 days for any advantage to be noted. This

corroborated findings of other studies that concluded that folic acid use in pregnancy appeared to be protective against PTB (Verstappen et al. 2013), (Lupattelli et al. 2014). A Chinese study also reported a 14% risk reduction with use of folic acid (Li et al. 2014).

The main finding of this study are that herbal remedy use was associated with a higher risk of PTB in Kitui County. The use of herbal remedies in pregnancy in Kitui County is common and deleterious. Exposure to herbal remedies in the first trimester was associated with very high risk for PTB. Longer use of herbal remedies was associated with higher risk. It was observed that herbal decoctions prepared at home and herbal remedies acquired from herbal clinics were the most commonly used by the mothers. Clearly then, herbal remedy use in pregnancy is a significant risk factor for PTB, especially in the first and second trimesters. Herbal remedies contain many unstandardized bioactive xenobiotics and secondary plant metabolites many of which may have toxic effects to the developing foetus. In addition, herbal decoctions preparation at home may not adhere to stringent good manufacturing practices. Microbial contamination may occur during extraction, packaging and while dispensing, exposing the mother to dangerous infections. In addition, herbal preparations may also have contamination with heavy metals such as lead and mercury, depending on the source (Karri, Saper, and Kales 2008).

The results of this study corroborates findings of an Italian study that showed herbal remedy use is associated with increased adverse pregnancy outcomes, including PTB (Cuzzolin et al, 2010). Another study on use of Chinese herbal medicines in pregnancy among the Taiwanese reported that pregnant women with threatened abortion were more likely to have used herbal remedies than other pregnant women (Chuang et al, 2007). A multicentre study on herbal supplements in pregnancy also found that mother's length of gestation was affected by herbal use. Mothers using herbal remedies were twice as likely to have PTB as non-users (Facchinetti et al. 2012). It is therefore important for health providers to be sensitized on local herbs and their use in pregnancy.

5. Conclusion

Herbal use in pregnancy regardless of gestation, previous preterm birth and low socio-economic status and are risk factors for PTB in Kitui County Kenya. Interventions targeted to reduction of these risk factors will be an important additional prong in the reduction of PTB.

Conflict of Interest declaration

The authors declare no conflict of interest.

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