

Prevalence and Factors Associated With Histological Chorioamnionitis among Term Women Delivering From Mbarara Regional Referral Hospital

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Abstract

Background: Chorioamnionitis (CAM), is an acute inflammation of the membrane and chorion of the placenta which can either be clinical or histological. At Mbarara Regional Referral Hospital the prevalence and factors associated with histological chorioamnionitis are widely unknown.

Objective: To assess the prevalence and factors associated with histological chorioamnionitis in term pregnancy among mothers delivering from Mbarara Regional Referral Hospital.

Methods: At inclusion in a cross-section, from December 2015 to February 2016, 136 women at term were interviewed. The placentas were evaluated, and diagnosis was based on histologic examination of the placenta. Placentas with microscopic evidence of inflammation of the membranes (infiltration of polymorphonuclear leukocytes and other immunocytes, such as macrophages and T cells) were considered positive for histological chorioamnionitis (HCA). Placental positive for HCA were scored and categorized as: Grade 1 (mild to moderate chorioamnionitis) or Grade 2 (severe chorioamnionitis- three or more chorionic microabscesses). Logistic regression was used to determine factors associated with chorioamnionitis. The significant level of 5% was used. Odds ratios and their corresponding 95% CI were provided at both bivariate and multivariate analysis.

Results: Among the 129 placentas of mothers at term that were examined, histological chorioamnionitis was diagnosed (HCA-positive) in 34.1% of women. Duration of labor more than 18 hours was found to be associated with HCA (aOR=4.0, 95%CI:1.30-12.39, $p=0.0267$). There were 34 cases of HCA grade 1 among cases positive for HCA (81.8%).

Conclusions: In our study, the prevalence of HCA was found to be high and duration of labor more than 18 hours was found to be significantly associated with HCA. The proportion of grade 1 HCA among term women with HCA at MRRH is 81.8%.

Background

Chorioamnionitis (CAM), an acute inflammation of the membrane and chorion of the placenta (Eschenbach et al., 1993) is a major cause of maternal and perinatal morbidity and mortality (Nasef et al., 2012). The diagnosis can either be clinical or histological. The gold standard for diagnosing chorioamnionitis is placental histological examination (Redline et al., 2003).

Clinically, it's defined by the presence of maternal symptoms and signs which include fever ($>37.5^{\circ}\text{C}$), with fundal tenderness, foul smelling vaginal discharge, maternal tachycardia (>100 beats per minute) or fetal tachycardia (>160 beats per minute) and leucocytosis ($>15000\text{cells}/\text{mm}^3$) (Menon et al., 2010). Histologically it is defined by presence of inflammation and necrosis in the chorion and amnion (Redline et al., 2003).

Rovira and colleagues in Sant Joan de Deu hospital in Spain, found the prevalence of chorioamnionitis to be 49%, while a study in Kenya by Musana and collaborators was found to be at 16.8%. The prevalence of chorioamnionitis shows a clear strong relationship with gestational age, with about 10% of deliveries at term (Sebire et al., 2001). Risk factors for chorioamnionitis includes longer duration of membrane rupture, prolonged labor, nulliparity, African American ethnicity, internal monitoring of labor, multiple vaginal exams, meconium-stained amniotic fluid, smoking, alcohol or drug abuse, immune-compromised states, epidural anesthesia, colonization with group B Streptococcus, bacterial vaginosis, sexually transmissible genital infections and vaginal colonization with ureaplasma (Soper et al, 1989). Fetal inflammatory response syndrome (FIRS), periventricular leucomalacia and cerebral palsy have been associated with severe histological chorioamnionitis

(HCA) (Lee et al, 2007). Other factors that have been associated with HCA include early onset neonatal sepsis (EONS) (Ibrahim and Manan, 2014) and puerperal sepsis (Gravett, 2016).

There is very sparse literature on chorioamnionitis in Uganda. Therefore this study is aimed to determine the prevalence and factors associated with histological chorioamnionitis in term mothers delivering from Mbarara Regional Referral Hospital (MRRH).

Chorioamnionitis is a known cause of puerperal sepsis (Mark et al., 2000) and Early Onset of Neonatal Sepsis (EONS) (Mohamed et al., 2014) which are the leading causes of maternal and neonatal morbidity and mortality at Mbarara Regional Referral Hospital. Much as puerperal sepsis accounts for 30.9% of maternal deaths in MRRH (Ngonzi, 2016), the proportion that is due to HCA is not known. Much as prevalence is high in Kenya (16.8%) (Musana et al., 2009), the Ugandan prevalence is not known. Therefore it is for the above reasons that the study was done to answer the above problem.

Objectives

Prevalence and factors associated with histological chorioamnionitis in term women delivering from Mbarara Regional Referral Hospital.

Materials and Methods

This was a cross-sectional study where histopathological examination of placentas was carried out to determine the prevalence, factors associated and commonest grade of histological chorioamnionitis among term mothers delivering from MRRH.

The study was conducted at MRRH, in the departments of Obstetrics and Gynaecology, on postnatal ward, labor ward and the operating theatre. Histology examinations were carried out at the histopathology lab of Mbarara University of Science and Technology (MUST).

Study population included all mothers delivering from MRRH from December 2015 to February 2016.

Inclusion Criteria: All women at term delivering from MRRH from December 2015 to February 2016 and consented to have their placentas studied.

Dependent Variable: Presence of HCA and its corresponding grades.

Independent Variables: Demographics of the patient: age, tribe, religion, district of residence, level of education, marital status, occupation, use of alcohol or tobacco and level of income. Obstetrics factors: Number of digital vaginal examinations (DVE), duration of labor, meconium stained amniotic fluid, antenatal attendance, duration of membrane rupture, parity, and history of PROM. Medical factors: HIV infection, urinary tract infection, sexually transmitted infection, history of vaginitis and use of antibiotics.

The sample size for the study was calculated using the Kish and Leslie formula (Kish L. 1965), $S = 136$

Study Procedure: Gestation age was estimated using the naegele's rule or first trimester ultrasound scan to determine mother at term. After the eligible mothers delivered the placenta, the placenta was placed in a bucket with 10% buffered formalin. This was performed by the principal investigator or the research assistant.

The mothers were given information while in labor and verbal consent sought. After the mothers were stabilized after delivery, the principal investigator or a trained research assistant obtained the written consent from mothers to include their placentas in the study. The placentas of mothers who declined to participate in the study were discarded thereafter as is the routine. The questionnaire was filled to completeness through interview or data from the patient file for all consented participants by the principal investigator or the research assistant. The collected placentas were sent to the histopathology laboratory of MUST for processing by the lab technicians and examination by a Pathologist.

The laboratory technician processed the tissues by passing them through ascending grades of alcohol that is 70 and 90% alcohol and finally absolute alcohol (dehydration), and then were passed through xylene for clearing. After clearing, the tissues were passed through one to three changes of paraffin wax and then embedded in fresh wax by filling a mould of suitable size with molten paraffin wax and orienting the specimen in the mould to ensure its cut in the right plane and finally cooling the mass to ensure solidification. Tissues were section on a microtome and put on a slide. The tissues were finally stained using the haematoxylin and eosin technique.

The slides were read by a pathologist together with the principal investigator and based on microscopic evidence of inflammation of the placenta, umbilical cord, and membrane (infiltration of polymorphonuclear leukocytes and other immunocytes, such as macrophages and T cells) diagnosis of HCA was made. For histologic grading whether maternal or fetal inflammatory response, it was divided as grade 1 (mild – moderate) or 2 (severe). For maternal inflammation, grade 1 (mild–moderate) was made if individual or small clusters of maternal neutrophils diffusely infiltrated amnion, chorionic plate, chorion laevae, and/or subchorionic. Grade 2 (severe) was made in the presence of three or more chorionic microabscesses between chorion and decidua in the membranes and/or under the chorionic plate or a continuous band of confluent chorionic polymorphonuclear leukocyte (PMN) more than 10 cells in width occupying more than half of the subchorionic fibrin or one revolution of the membrane role

For fetal inflammation, grade 1 (mild–moderate) was made where scattered neutrophilic infiltrate in the subendothelial or intramural portions of any chorionic (or umbilical) vessel were present. Grade 2 (severe) was made with presence of chorionic plate (or umbilical) vessels with near confluent neutrophils plus attenuation and/or degeneration of vascular smooth muscle cells on the side facing the amniotic cavity.

Data Entry and Analysis: The data was coded and entered into a computer software EPI-DATA version 3.1 thereafter exported to STATA version 11 for analysis. Description of participants’ baseline characteristics was done using median for continuous variables and proportions for categorical variables. The prevalence of HCA was calculated as proportion of all histologically confirmed HCA of the total number of evaluated participants. Chi-square and logistic regression was used to determine factors associated with chorioamnionitis. All significant factors at bivariate were incorporated into analysis using manual backward stepwise selection method. The significant level of 5% was used. Odds ratios and their corresponding 95% CI were provided at both bivariate and multivariate analysis.

Ethical Considerations: The approval was obtained from the Faculty of Medicine Research Committee and MUST Research Ethics Committee.

Study Limitations: One of the limitations was confirming the gestation age since some mothers were not sure of their last normal menstrual period. This was overcome by comparing the dates on their antenatal cards or by use of first trimester ultrasound scan.

Results

Socio-Demographics Characteristics

The mean age of the participants was 25 years with most below 35 years (91%). Majority were Banyankole (85.3%), in monogamous marriage (86.8%), Christians (93.4%), with at least primary education (95.4%) (Table 1).

Table 4: Showing Socio-Demographics Characteristics (N=136)

Characteristic	n (%)
Median age in years (IQR)	25 [22-29]
Age categories in years	
<20	12 (8.8)
20-24	55 (40.4)
25-34	57 (41.9)
≥35	12 (8.8)
Tribe, n (%)	
Banyankole	116 (85.3)
Bakiga	6 (4.4)
Others	14 (10.3)
District of Residence	
Mbarara	97 (71.3)
Isingiro	26 (19.1)
Kiruhura	4 (2.9)
Others	9 (6.6)
Religion	
Christian	127 (93.4)
Islam	9 (6.6)
Level of Education	
No Formal Education	9 (6.6)
Primary Education	75 (55.2)
Secondary Education	41 (30.2)
Tertiary Education	11 (8.1)
Marital Status	
Single/Cohabiting	10 (7.4)
Married – Monogamous	118 (86.8)
Married – Polygamous	8 (5.9)
Occupation	
Civil Servant	20 (14.7)
Peasant	34 (25.0)
Business	48 (35.3)
Unemployed	34 (25.0)
Income Categories in Uganda shillings	
<100,000/=	
100,000-200,000/=	46 (34.1)
>200,000/=	49 (36.3)
	40 (29.6)
Alcohol use	25 (18.4)
Tobacco Use	1 (0.7)

Obstetric and Medical Characteristics

Para-one mothers comprised of 36.8 of the participants and 93.4% had attended at least 3 antenatal visits. Those who had laboured for more than 18 hours were 16.9%. Majority had clear liquor (60.3%), non-foul smelling liquor (92.7%), HIV negative (91.5%), and without history of antibiotic use prior to admission (76.4%). There were only 26 patients who had vaginitis (Table 2)

Table 5: Showing Obstetric and Medical Characteristics (n=136)

Characteristic	n(%)
Parity	
1	50 (36.8)
>1	86 (63.2)
Number of Antenatal Visits	
<3	9 (6.6)
3	57 (41.9)
≥4	70 (51.5)
PROM	6 (4.5)
Duration of membrane rupture in hours	
< 6	66 (48.5)
≥6	13 (9.6)
Unknown	57 (41.9)
Duration of labor in hrs	
<12	54 (39.7)
12-18	44 (32.4)
> 18	23 (16.9)
Unknown	15 (11.03)
Number of DVE	
<5	92 (69.2)
≥5	41 (30.8)
Nature of Liquor	
Clear	82 (60.3)
Meconium grade 1	38 (27.9)
Meconium grade 2	11 (8.1)
Meconium grade 3	4 (3.7)
Foul smelling liquor	10 (7.4)
HIV testing	130 (95.6)
Duration since last HIV Test in months	
< 6	33 (25.38)
≥ 6	2 (1.54)
Unknown	95 (73.1)
HIV positive	11 (8.5)
Use of antibiotic prior to admission	
Never	
<1 month	104 (76.4)
≥ month	22 (16.2)
Unknown	10 (7.4)
History of Malaria	4 (2.9)
History of UTI	10 (7.4)
History of Vaginitis	26 (19.1)
History of STI	2 (1.5)

Socio-Demographics Characteristics at Bivariate Analysis

At bivariate analysis socio-demographics had no significant p value (Table 3)

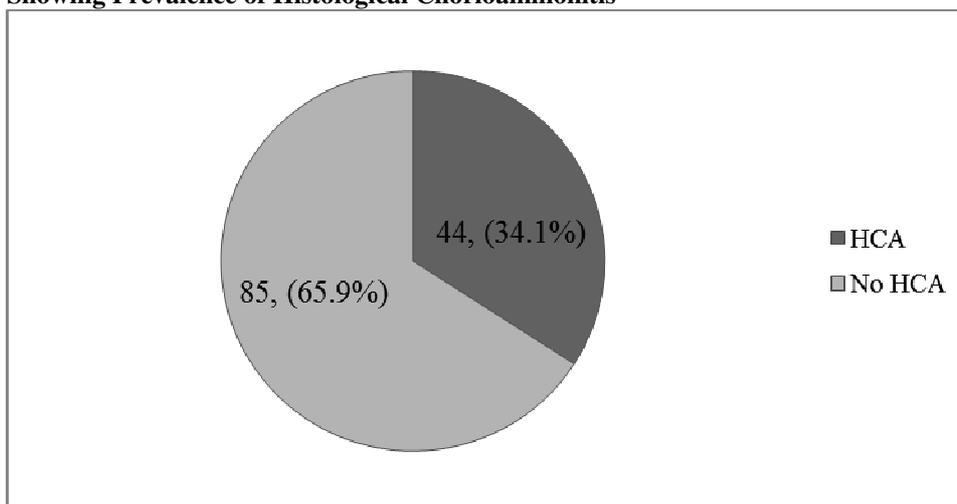
Table 3: Showing Socio-Demographics Characteristics at Bivariate Analysis

Variable	No Chorio n (%)	Chorio n (%)	OR [95% CI]	P value
Age categories in years				
<20	4 (36.4)	7 (63.6)	8.8 [1.25-61.68]	0.0743
20-24	31 (62.0)	19 (38.0)	3.1 [0.61-15.52]	
25-34	40 (71.4)	16 (28.6)	2.0 [0.39-10.16]	
≥35	10 (83.3)	2 (16.7)	1.0	
Tribe				
Banyankole	75 (68.2)	35 (31.8)	1.0	0.2228
Bakiga	2 (33.3)	4 (66.7)	4.3 [0.75-24.52]	
Others	8 (61.5)	5 (38.5)	1.3 [0.41-4.39]	
District of Residence				
Mbarara	61 (65.6)	32 (34.4)	1.0	0.9494
Isingiro	16 (64.0)	9 (36.0)	1.2 [0.43-2.70]	
Kiruhura	2 (66.7)	1 (33.3)	0.9 [0.08-10.91]	
Others	6 (75.0)	2 (25.0)	0.6 [0.12-3.33]	
Religion				
Christian	78 (65.0)	42 (35.0)	1.0	0.4200
Islam	7 (77.8)	2 (22.2)	0.5 [0.11-2.67]	
Level of Education				
No Formal Education	4 (50.0)	4 (50.0)	1.0	0.4977
Primary Education	45 (63.3)	26 (36.6)	0.6 [0.13-2.51]	
Secondary Education	29 (74.4)	10 (25.6)	0.3 [0.07-1.64]	
Tertiary Education	7 (63.6)	4 (36.4)	0.6 [0.09-4.00]	
Marital Status				
Single/Cohabiting	6 (66.7)	3 (33.3)	1.0	0.4721
Married – Monogamous	73 (64.6)	40 (35.4)	1.1 [0.26-4.62]	
Married – Polygamous	6 (85.7)	1 (14.3)	0.3 [0.03-2.00]	
Occupation				
Civil Servant	12 (63.2)	7 (36.8)	1.0	0.5256
Peasant	24 (72.7)	9 (27.3)	0.6 [0.19-2.15]	
Business	31 (68.9)	14 (31.1)	0.8 [0.25-2.39]	
Unemployed	18 (56.3)	14 (43.8)	1.3 [0.42-4.27]	
Income Categories in Uganda shillings				
<100,000/=	29 (70.7)	12 (29.3)	1.0	0.7131
100,000-200,000/=	31 (64.6)	17 (35.4)	1.3 [0.54-3.25]	
>200,000/=	25 (62.5)	15 (37.5)	1.5 [0.57-3.67]	
Alcohol use				
Yes	16 (69.6)	7 (30.4)	0.8 [0.31-2.16]	0.6796
No	69 (65.1)	37 (34.9)	1.0	

Prevalence of Chorioamniotitis

The prevalence of histological chorioamniotitis among term women delivering from MRRH is 34.1 % (Figure 1).

Figure 1: Showing Prevalence of Histological Chorioamnionitis



Obstetrics and Medical Characteristics at Bivariate Analysis

Parity and duration of labor (>18 hours) had a significant p value HCA. Mothers reporting to have been in labor for more than 18 hours had a 4.2 times more likely to have HCA compared to those below 12 hours, $p=0.019$. Para one mothers were 2.3 times more likely to develop histological chorioamnionitis compared to multi parous mothers $p=0.0289$ (Table 4)

Table 4: Showing Obstetrics and Medical Characteristics at Bivariate Analysis

Variable	No Chorio	Chorio	OR [95% CI]	P value
Gravidity				
1	24 (53.3)	21 (46.7)	2.3 [1.09-4.95]	0.0289
>1	61 (72.62)	23 (27.4)	1.0	
Number of Antenatal Visits				
<3				0.4057
3	5 (55.6)	4 (44.4)	1.0	
≥4	33 (61.1)	21 (38.9)	0.8 [0.19-3.30]	
PROM				
Duration of membrane rupture				0.7994
< 6	3 (60.0)	2 (40.0)	1.3 [0.20-7.90]	
≥6	40 (66.67)	20 (33.3)	1.0	
Unknown	7 (58.3)	5 (41.7)	1.4 [0.40-5.07]	0.8491
Unknown	38 (66.7)	19 (33.3)	1.0 [0.46-2.16]	
Duration of labor				
<12	36 (70.6)	15 (29.4)	1.0	0.0196
12-18	31 (73.8)	11 (26.2)	0.9 [0.34-2.12]	
> 18	8 (36.4)	14 (63.6)	4.2 [1.46-12.09]	
Unknown	10 (71.4)	4 (28.6)	1.0 [0.26-3.55]	
Number of DVE				
<5	62 (70.5)	26 (29.6)	1.0	0.1740
≥5	22 (57.9)	16 (42.1)	1.7 [0.79-3.82]	
Nature of Liquor,				
Clear	53 (69.7)	23 (30.3)	1.0	0.7502
Meconium grade 1	23 (60.5)	15 (39.5)	1.5 [0.67-3.39]	
Meconium grade 2	6 (60.0)	4 (40.0)	1.5 [0.40-5.96]	
Meconium grade 3	3 (60.0)	2 (40.0)	1.5 [0.24-9.81]	
Foul smelling liquor	8 (80.0)	2 (20.0)	0.5 [0.09-2.26]	0.3071
History of UTI	5 (55.6)	4 (44.4)	1.6 [0.41-6.29]	0.5054
History of Vaginitis	12 (50.0)	12 (50.0)	2.3 [0.93-5.62]	0.0744

Multivariate Analysis

Only duration of labor (>18 hours) is independently associated with HCA (Table 5)

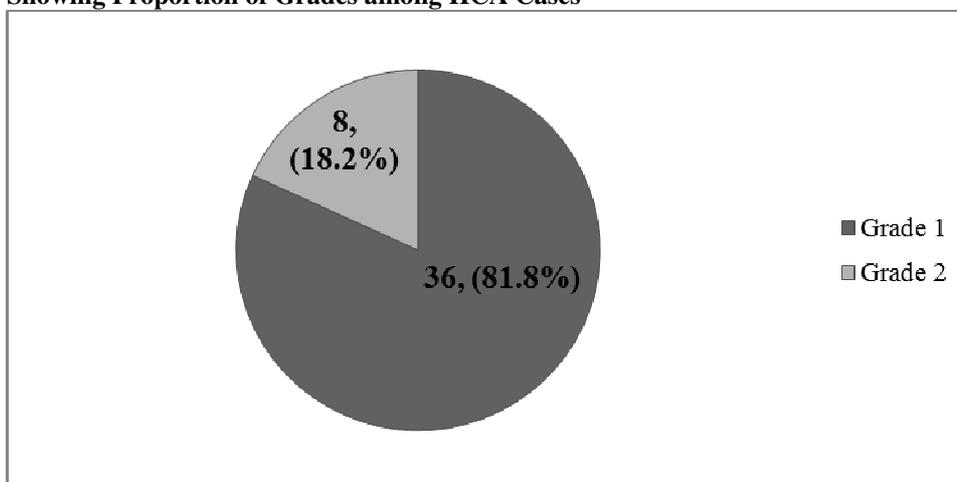
Table 5: Showing Multivariate Analysis

Variable	aOR [95% CI]	P-value
Age categories in years		
<20	11.1 [1.36-90.44]	0.0801
20-24	4.0 [0.69-23.27]	
25-34	2.8 [0.47-16.18]	
≥35	1.0	
Duration of labor		
<12	1.0	0.0267
12-18	0.8 [0.29-1.98]	
> 18	4.0 [1.30-12.39]	
Unknown	0.8 [0.93-3.32]	

Proportion of Grades among HCA Cases

The proportion of grade 1 HCA among term women with HCA at MRRH is 81.8%. (Figure 2)

Figure 2: Showing Proportion of Grades among HCA Cases



Discussion

Prevalence of Chorioamnionitis

Prevalence of HCA at MRRH is 34.1%, which is similar to a study by Roberts and collaborators in 2012, conducted in the Massachusetts USA. This prevalence was higher compared to a study done in Siena Italy by Torricelli and colleagues in 2013 where they found prevalence of HCA at term to be 28.7%. A study done in Kenya by Musana et al in 2009, found prevalence of HCA to be at 16% although this study included both term and preterm pregnancies. This prevalence was lower than that found by Rovira et al and collaborators in 2011 where they looked at prevalence of HCA in preterm labor and found it to be 49%. Prevalence of HCA is inversely correlated with gestational age, occurring in 50% of preterm birth and in up to 20% of deliveries at term (Conti et al., 2015). These differences could have been due to the fact that apart from study by Roberts, the rest were not gestation specific.

Factors Associated with Chorioamnionitis

Durations of labor (>18 hours) was found to be significant where participants with more that 18 hours of labor duration had 4 times higher odds of developing HC

A compared to those with less than 12 hours. Prolonged labor has been implicated as a risk factor for developing chorioamnionitis. Labor lasting 12 hrs or more has been associated with a four-fold increase in risk of chorioamnionitis (Galinsky et al., 2013).

Although maternal age did not have a significant p value, mothers with less than 20 years, had 11times higher odds of developing HCA compared to those above 35 years. This study is consistent with another study where it was found women with chorioamnionitis tend to be younger than those without chorioamnionitis (Fassett et al

2013). This be due to the fact that younger mothers are mostly prime-gravida who are associated with longer duration of labor making them prone to other risk conditions like increased durations of rupture of membranes, multiple DVE which may contribute to the development of HCA.

This study also did not show any relationship between parity and the presence of HCA. This is similar to the findings of Mwanyumba and collaborators in 2002 and Smulian and collaborators in 1999 where parity did not significantly affect the presence of HCA. However, nulliparity has been associated with the development of Histological chorioamnionitis in other studies (Torricelli et al., 2013). This could be due to the fact than prime-gravid labor longer that multigravida mothers which put them at risk of increased number of DVE as well and increased labor duration.

PROM has been implicated as a major factor in the causation of HCA and this has been reported to occur twice as frequent in membranes that ruptured before the onset of labor as those that ruptured after labor has started (Naeye, 1982). Roberts, 2012 also found that rupture of membrane for more than 12 hours was a significant factor for developing HCA. In our study, PROM had no effect on HCA. This could be due to the few cases of participants with rupture of membranes. However this finding is similar to other reported study (Mwanyumba et al., 2002). However PROM may lead to an abnormal inflammatory reaction and it's known that a prolonged duration of rupture of membranes enhances the occurrence of an excess of intrauterine inflammatory *milieu* where other risk conditions may contribute to the development of HCA

Only 22 participants on this study had been on antibiotics in the last one-month prior to delivery and there was no correlation to presence of HCA. The study by Smulian and collaborators, did not show any correlation with the use of antibiotics and HCA. However this number of participant and the duration of use of antibiotics were too few to make meaningful comparison with other studies. Use of antibiotic suggest treatment of bacterial infection in pregnancy which include but not limited to urinary tract infection, sexually transmitted infection, and bacterial vaginosis which are known to be risk factors for developing HCA

In our study history of vaginitis was associated with a 2.5 higher odds of having HCA although p value was not significant. A finding that is consistent with other studies (Yudin, 2005). However in our study this relationship was not significant potentially due to the low number of cases of vaginitis. On other hand, as a limitation of this study the diagnosis of vaginitis was based on clinical suspicion without laboratory confirmation and so could not be classified as bacterial vaginitis as reported by Yudin.

Grades of Histological Chorioamnionitis

The grade specific among the cases of HCA, majority had grade 1 HCA (81.8%). Roberts et al., 2012, in a study conducted in the Massachusetts USA had similar findings with grade specific of grade 1 (78%) higher than grade 2.

Conclusion

Prevalence of HCA in MRRH is high. Duration of labor of more than 18 hours is independently associated with HCA. Grade 1 is the commonest form of histological chorioamnionitis

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