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Antibiotic Use for Prolongation of Pregnancy in Women With Preterm Labour or Premature Rupture of Membranes

by

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ABSTRACT

Objective: To determine and compare the frequency of antibiotic use for prolongation of pregnancy (POP) between 1996 and 1999 in women admitted for preterm labour (PTL) or preterm premature rupture of membrane (PPROM) and to examine the effect of antibiotic use on POP.

Design: A cross-sectional study design was used.

Results: Results showed an overall increase in antepartum antibiotic use from 1996 to 1999. Trend for increased antibiotic use was observed at all sites with FMC having the most significant increase. Women with PPROM who received antibiotics had a mean POP (admission to delivery) of 13.3 days compared to 11.4 days in those with no-antibiotics. Women with PTL who received antibiotics had a shorter POP than those who did not receive any antibiotics.

Conclusion: Antepartum antibiotic use increased from 1996 to 1999 in CRHA. Women with PTL did not seem to benefit from antibiotic use for prolongation. Pregnancy was prolonged by 48hr in women with PPROM who received antibiotics compared to those who did not.

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CHAPTER ONE: INTRODUCTION AND PURPOSE

1.1 Introduction to the Research Problem

Worldwide, preterm labour and preterm premature rupture of membranes both remain leading problems in health care. Preterm birth (before 37 weeks of gestation) complicates about 10% of pregnancies and is responsible for 75% to 80% of perinatal morbidity and mortality (Mercer et al. 1997a). It is estimated that in the United States, the national health care cost of prematurity is more than $4 billion annually (Mercer et al. 1997a). Unfortunately, over the past two decades the incidence of preterm birth has risen despite improvements in perinatal care and the introduction and use of therapeutic and prophylactic agents (Sawdy et al. 1999; Goldenberg et al. 1998).

Spontaneous preterm labour with intact membranes (PTL) and preterm premature rupture of membranes (PPROM) are each responsible for about 25 to 40 % of preterm births (Chaim et al. 1998; Romero et al. 1993). PPROM is defined as rupture of membranes before 37 completed weeks of gestation and before the onset of contractions.

A wide range of medical complications, demographic, socioeconomic and obstetric factors have been implicated in causing preterm labour and premature rupture of membranes (Mercer et al. 1997a). About 20% of preterm births are related to obstetric complications, which result in immediate delivery. The Preterm Prediction Study has also identified an increased risk of preterm birth associated with other factors such as previous preterm birth, black ethnicity, and age greater than 30 years. However, about one-half of the preterm births have an unknown etiology (Svare et al. 1997). It has been strongly suggested that infection (e.g. urinary tract, lower and upper genital tract) is

an important risk factor for initiation of PTL or PPROM (Andrews et al. 1995; Mercer et al. 1996).

The ultimate goal of prolongation of pregnancy, in cases where it is advantageous to the fetus, is to reduce gestational age-dependent neonatal complications related to prematurity such as low birth weight. Infants with birth weight less than 1500g account for 65% of neonatal mortality. During the interval from 24 to 32 weeks gestation, an additional week in utero significantly increases perinatal survival. At 24 weeks, neonatal survival is estimated to be about 17%, at 26 weeks 50%, and rising to 95% at about 32 weeks gestation (Higby et al. 1993).

Treatments used for prolongation of pregnancy include therapeutic tocolysis, maternal corticosteroids administration and maternal antepartum antibiotics treatment (Mercer et al. 1997a).

The potential theoretical benefits of antibiotic use in the setting of premature rupture of membranes or preterm labour include the treatment of subclinical intrauterine infections that may be responsible for membrane rupture or initiation of preterm labour, and the prevention of ascending infection subsequent to the preterm premature rupture of membranes (Mercer et al. 1998).

However, the use of antibiotic therapy for prolongation of pregnancy in case of PPROM or PTL has been a controversial strategy. The Cochrane Database of Systematic Reviews has concluded that, no overall benefit from antibiotic treatment of preterm labour with intact membranes was observed in maternal outcomes, but the results raised concerns about an increase in perinatal mortality (King et al. 2000).

On the other hand, the Cochrane Database has concluded that antibiotic treatment following preterm premature rupture of membranes is effective in prolonging pregnancy as well as in reducing maternal and neonatal infectious morbidity (Kenyon et al. 1999).

Consequently, despite controversies with respect to its effectiveness, antibiotic treatment has become a significant option in the therapeutic management of preterm labour and PPROM for prolongation of pregnancy and reduction of neonatal complications related to infection and prematurity (Lamnot 1998; Keirse et al. 1995; Goldenberg 1998).

It has been speculated that the frequency of antibiotic use has also increased in the Calgary region as a result of the published evidence for benefits of this treatment strategy (Personal communication; Dr. Wood, November 1999).

However, the efficacy of this practice in all populations of women with PPROM or preterm labour is still unknown. In addition, increased use of antibiotics in mothers may pose problems to the health of both the mother and the infant by selecting for antibiotic-resistant microorganisms and causing an increase of adverse reactions (Towers et al. 1998; Gibbs et al. 1997).

Therefore, it is important to examine the changes and current practices of antibiotic treatment and its impact on the prolongation of pregnancy in the Calgary region as a first step towards establishing and implementing guidelines and standards of care for women with PTL or PPROM.

1.2 Study Objectives

The specific objectives of this study are:

1) To determine the frequency of antibiotic use for prolongation of pregnancy in women admitted to the hospital with preterm labour and intact membranes or with preterm premature rupture of membranes (PPROM) greater than 12 hours, within the Calgary Regional Health Authority (hereafter referred to as CRHA) in 1999.
2) To compare the frequency of antibiotic use for prolongation of pregnancy during the year 1996 (January 1st to December 31st) with the year 1999 (January 1st to December 31st).
3) To examine the association between antibiotic use and prolongation of pregnancy (days) in women admitted to the hospital with preterm labour and intact membranes or with preterm premature rupture of membranes (PPROM) greater than 12hours, within the CRHA.

1.3 Study Questions

1) What proportion of women in preterm labour and intact membranes or with PPROM greater than 12 hours received antibiotic treatment for prolongation of pregnancy between January 1st, 1999 and December 31st , 1999?
2) Is there a difference in the proportion of antibiotic use for prolongation of pregnancy in women with preterm labour and intact membranes or with PPROM greater than 12 hours, between January 1st to December 31st , 1996 and January 1st to December 31st, 1999?

3) Is there an association between antibiotic use and prolongation of pregnancy among the women admitted to the hospital with preterm labour and intact membranes or with PPROM greater than 12 hours, within the CRHA?

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter first provides an overview of preterm labour and premature rupture of membranes, the risk factors, their relationship with infection and their management. Then, it reviews the available literature on antibiotic use for treatment of preterm labour and premature rupture of membranes and its effect on prolongation of pregnancy.

2.2 Preterm Labour

Preterm labour is defined as labour occurring after 20 weeks but before 37 weeks of gestation and it complicates 5% to 15% of all pregnancies (Pernoll. 1991). It has been estimated that approximately 25% to 40% of all preterm births resulted from spontaneous preterm labour. If not prevented, preterm labour results in preterm delivery. Diagnosis of preterm labour is not easy. It is based on clinical observations. However, in order to initiate appropriate treatment. it is very important to differentiate "true" preterm labour from "false" preterm labour. The diagnosis of preterm labour maybe in error in about 40% to 70% of cases if uterine contraction is used as the sole criteria for diagnosis (Higby et al. 1993). The presence of uterine contractions occurring at least twice every 10 minutes, accompanied by cervical dilation of $\geq$ 2 cm or effacement of $\geq$ 80% or documented cervical changes over 1 hour in the presence of uterine activity or bulging membranes are all diagnostic signs of preterm labour with intact membranes.

The etiology of preterm labour is multi-factorial. There are certain risk factors that are strongly associated with an increased incidence of preterm labour. Among the risk factors known to predispose pregnant women to preterm labour are: 1) previous

preterm labour, 2) uterine anomalies, 3) placenta abnormalities, 4) incompetent cervix, 5) multiple gestation, 6) maternal age below 16 years or above 35 years, 7) preterm rupture of membranes and 8) infection such as pyelonephritis (Pernoll, 1991; Roberts et al. 1990). Also associated with preterm labour and birth are low socioeconomic class, cigarette smoking, poor nutrition and low body-weight during pregnancy (Steer et al. 1999).

2.3 Preterm Premature Rupture of Membranes

Premature rupture of membrane (PROM) is defined as the rupture of membrane at any time prior to the onset of labour (or at least one hour prior to labour). Preterm premature rupture of membranes (PPROM) is defined as premature rupture of membranes which occurs before 37 weeks of gestation (Gabbe et al. 1991). PPROM occurs in about 2% to 3% of all pregnancies and is responsible for about one third of preterm births (Mercer et al.1998). PPROM is associated with perinatal morbidity and mortality directly related to prematurity. Approximately 70% to 80% of women with PPROM deliver within one week of membrane rupture (Mercer et al. 1998) but it can happen anywhere from one hour to several weeks or months prior to labour (Dunnihoo 1992).

As in preterm labour, the etiology of preterm premature rupture of membranes is multi-factorial. A number of conditions such as: 1) increased intra-amniotic pressure, 2) placental abruption, 3) placenta previa, 4) multiple gestations and 5) trauma, may predispose women to development of PPROM. Other risk factors such as smoking and

nutritional deficiencies, genetic abnormalities and intrauterine infection are also thought to be associated with PPROM (Maymon et al. 1998; Mercer et al. 1998).

The relationship between intrauterine infection and PPROM is thought to be particularly strong in the late second and early third trimesters of pregnancy (Mercer et al. 1997b).

2.4 Infection, Preterm Labour and Preterm Premature Rupture of Membranes

The role of infection in the development of preterm labour or premature rupture of membranes has been the focus of many investigations. The first study conducted 40 years ago, supported the role of infection in preterm delivery (Yost et al. 2000). Since then, there has been an increasing body of evidence supporting the association between urinary tract infections, intrauterine infections and vaginal microflora such as bacterial vaginosis (BV) and an increased risk of preterm birth (Yos et al. 2000).

Evidence over the past 20 years has revealed that the infection-inflammation response may cause from 20% to 40% of preterm births (Gibbs et al. 1997; Keirse 1995).

Infection is believed to contribute to the initiation of preterm labour through inflammation and stimulation of the cytokine cascade (Keirse 1995). Microorganisms can ascend through the cervical mucous plug into the uterus and initiate an inflammatory response in the placenta, fetal membranes or in maternal decidua, which leads to the release of cytokines. These cytokines initiate a cascade of prostaglandins, which in turn will produce uterine contractions (Steer et al. 1999).

Numerous studies have provided evidence of an association between the presence of bacterial vaginosis, a common infection of the female genital tract, and preterm labour and delivery (Gibbs et al. 1997; Meis et al. 1995).

Bacterial vaginosis is caused by the alteration of the vaginal normal flora by a reduction in vaginal lactobacilli and an increase in gram negative and anaerobic bacteria (*Gardnerella vaginalis*, *Bacteroids* sp, *Prevotella* sp, *Mobiluncus* sp. *Group B Streptococcus* and *Peptostreptococcus* sp) and genital mycoplasmas (*U.urealyticum* and *M. hominis*) (Brocklehurst 1999).

Bacterial vaginosis (BV) is often asymptomatic and it is thought to be present in approximately 16-20% of pregnant women (Yost et al., 2000; Brocklehurst et al., 1999). The estimated odds-ratio for preterm birth, in the presence of bacterial vaginosis, has been reported to be at least in the range of 1.5-2.0 (Andrews et al., 1995) and 5 to 5.7 in women with BV at less than 16 weeks gestation (Lamnot 2000).

In 1995, Hiller et al. published results of a large study of 10,000 women. The results showed that independent of other risk factors, those women diagnosed with BV during the second trimester were 40% more likely to have a premature low birth weight baby than those without BV. In addition, the results of a clinical trial published in 1995 concluded that women with BV diagnosis and subsequent treatment with metronidazole and erythromycin had a significant reduction from 49% to 31% in preterm delivery compared to those with untreated BV. The association between treatment and a lower rate of preterm birth was only observed in women who had bacterial vaginosis and who were more at risk for preterm delivery (Hauth et al. 1995; Morales et al. 1994). In contrast, in 1996, Goldenberg et al. hypothesized that "bacterial vaginosis may just serve

as a marker for women who have a chronic endometrial infection, yet is of little consequence as long as the uterus is free of organisms. The underlying disease is chronic colonization of the endometrium and a symptom of that underlying disease is spontaneous preterm labour". In addition in a study by Carey & Klebanoff et al. 2000, results revealed that treatment with metronidazole of women with asymptomatic bacterial vaginosis did not reduce the occurrence of preterm delivery or other adverse perinatal outcomes.

The presence of BV is also associated with an increased risk of chorioamnionitis and postpartum endometritis. Hillier et al. found that women with BV are twice as likely to have bacteria isolated from their amniotic fluid compared to those without BV (Hiller et al. 1995).

In 1998, both the American College of Obstetricians and Gynecologists and the Center for Disease Control and Prevention made recommendations for treatment of BV during pregnancy. They recommended the use of oral metronidazole or clindamycin (Yost et al. 2000).

Lower Genital tract infections such as *Syphilis, Trichomonas vaginalis, Neisseria gonorrhoeae, Ureaplasma urealyticum* and *Chlamydia trachomatis* are associated with increased risk for preterm labour and delivery (Gibbs et al. 1997). However, the available evidence is inconsistent primarily because the studies used insensitive screening tests or did not control for other potential confounding variables.

Where some studies have shown as much as a two fold increased risk of preterm birth in women with *Chlamydia*, other studies have shown no significant association between *Chlamydia* infection and preterm birth (Yost et al. 2000). The Preterm

Prediction Study of the National Institute of Child Health and Human Development Maternal Fetal Medicine Units network recently examined the association between genitourinary chlamydia infection and preterm birth (Andrews et al. 2000). This study is one of the few which adjusted for other risk factors of preterm birth. The overall prevalence of *C. trachomatis* was 11.1% at 24 weeks and 11.9% at 28 weeks gestation.

One hundred ninety women with preterm delivery (<37 weeks) and 190 matched controls with delivery greater than 37 weeks were assessed. In general, genitourinary C. trachomatis infection at 24 week gestation was associated with a 2 to 3 fold increase in the risk of subsequent preterm birth (Andrews et al. 2000).

The role of *Ureaplasma urealyticum* in preterm birth is also not fully understood. *Ureaplasma urealyticum* is indigenous to the vaginal flora. A higher percentage of cervicovaginal culture positive for *Ureaplasma urealyticum* has been identified in women who delivered preterm between 26 to 33 weeks gestation than those who did not deliver preterm (Lamnot et al. 1987). However, others have shown that vaginal colonization with *U. urealyticum* is not associated with preterm labour or preterm birth (Carey et al. 1991).

Other studies have focused on the role of clinical and histologic chorioamnionitis, and infection of amniotic fluid in preterm birth. In general, microbial colonization of the chorioamnion is more prevalent in women with lower gestation age and therefore smaller birth weight babies. It is estimated that as many as 80% of women who deliver before 30 weeks of gestation have histologic chorioamnionitis (Goldenberg et al. 1996).

There is also some evidence that when organisms are present in amniotic fluid prior to 20 weeks, the pregnancy generally terminates in the next 4 to 8 weeks

(Goldenberg et al. 1996). There is data available which links the presence of microorganisms in the amniotic fluid and chorioamnion to spontaneous preterm labor and birth in women who otherwise do not have any signs or symptoms of infection (Gibbs et al. 1992b). It has been proposed that up to 15% of preterm labour with intact membrane may be due to chorioamniotic infection (Dodson et al. 1988).

Researchers have also investigated the relationship between levels of IL-6, a cytokine that stimulates prostaglandin release by amnion and decidua, and chorioamnion infection. It is hypothesized that inflammation in the upper genital tract area which leads to production of IL-6 cytokine and as the result a higher level of IL-6 is observed in those women with amniotic fluid or chorioamnion infection (Yost et al. 2000). Andrews et al. 1995, found that IL-6 levels are significantly higher in women with preterm labour as well as the level appears to increase at lower gestation age. Therefore, concluding from available data, some suggest that IL-6 could act as a marker for upper genital tract infection (Yost et al. 2000).

Similarly, intrauterine infection is strongly associated with the development of PPROM, particularly in the late second and early third trimester of pregnancy (Mercer et al. 1997a). A broad spectrum of aerobic and anaerobic, gram positive and gram-negative organisms as well as genital mycoplasma are obtained from amniotic fluid after PPROM (Maymon et al. 1998a). Positive amniotic fluid culture is identified in 14% to 37% of specimens after PPROM (Mercer et al. 1998).

Ascending intrauterine infection may also lead to membrane rupture through protease-induced membrane weakening, cytokine induced local prostaglandin production, and asymptomatic contractions (Mercer et al. 1996). Infection may occur during or after

the rupture of membranes and can lead to subclinical and clinical amnionitis and fetal infection (Mercer et al. 1996).

Genital *Group B Streptococcus* (GBS) colonization has been implicated as a risk factor for preterm birth. In 1999, Allen et al. has demonstrated that women who were colonized with GBS were more than twice as likely to deliver prematurely (OR=2.43; 95%CI 1.39 to 4.23). However, the main concern with GBS is still the vertical transmission of this infection from mother to the new born leading to neonatal sepsis. Therefore, a protocol for prevention of GBS disease in pregnant women and in their newborns was implemented by the Center for Disease Control in 1996. These recommendations suggest the use of intrapartum antimicrobial prophylaxis in those with preterm labour or with a duration of PROM greater than 18 hours or body temperature greater than 100.4 F.

Urinary tract infections are also one of the most common infections during pregnancy. About one third to one half of women with untreated asymptomatic bacteriuria will eventually develop pyelonephritis (Yost et al. 2000).

Before the antibiotic era, about 21-50% of women with pyelonephritis would deliver prematurely. Even though untreated pyelonephritis seems to be associated with an increased risk of preterm birth, the association between asymptomatic bacteriuria and preterm birth is still controversial. Dodson et al. has summarized the literature and the available meta analyses in regards to bacteriuria and preterm delivery. One of the meta analyses included 3,600 bacteriuria patients from 19 studies. The rate of prematurity in women with bacteriuria was 10.9% compared to 8.6% in 31,000 controls (Dodson et al. 1988).

Another study by Gibbs et al., in 1985, compared the prematurity rates between women with untreated bacteriuria, treated bacteriuria and also women with sterile urine by combining data from eight studies. The prematurity rates were significantly different between the groups: 6.8% in treated group, 18% in untreated group and 10.1% in women with sterile urine ($p<0.001$).

Despite the discrepancies presented in the available research related to bacteriuria and prematurity, Dodson et al. concludes that "women with asymptomatic bacteriuria have a high risk of developing pyelonephritis and data on asymptomatic bacteriuria is at least suggestive of an association with preterm labour"(Dodson et al. 1988).

2.5 Management of Preterm Labour and Preterm Premature Rupture of Membranes

The management decisions for preterm labour depend on the presence of uterine contractions, cervical dilation and effacement and absence of contraindications for continuation of pregnancy (Pernoll 1991; Mercer et al. 1997a). In cases of suspected amnionitis, cervical dilation above 4 to 5 cm, persistent abnormal fetal heart rate testing, vaginal bleeding suggestive of placenta abruption, positive amniotic fluid culture at any gestation, preterm labour is allowed to continue to delivery (Mercer et al.1997a).

Otherwise, the immediate goal of management of preterm labour is cessation of uterine contractions (tocolysis) to prolong pregnancy in order to allow adequate time for other interventions (i.e. corticosteroids) that could reduce gestational age dependent morbidity (Keirse et al., 1995). In about 30% of the patients in preterm labour, uterine contractions cease spontaneously without treatment (Higby et al. 1993). Otherwise, the

betamimetics, particularly ritodrine and magnesium sulfate, are the most commonly used tocolytic therapies for prolongation of pregnancy. Indomethacin, an anti-inflammatory drug is also widely used as tocolysis for treatment of preterm labour.

Data from randomized trials have shown that tocolytics drugs can prolong pregnancy for up to 48 hours (Higby et al. 1993). The most benefit is observed in those with gestational age between 24 and 32 weeks (Macones et al. 1992).

It is estimated that only about 25% of women with preterm labour benefit from tocolysis (Pernoll 1991). There is some evidence that subclinical infections, particularly those of amniotic fluid, can be a cause of tocolytics failure (Newton et al. 1991).

Glucocorticoid therapy is also used in the management of preterm labour. The most commonly used glucocorticoid is betamethsone. Glucocorticoids significantly reduce the incidence of neonatal respiratory distress syndrome, intravascular hemorrhage, and mortality (Crowley et al. 1995). Steroids administered within 24 to 48 hours before birth may reduce by one half the incidence and severity of respiratory distress syndrome and mortality in newborn infants (Steer et al. 1999). However, a recent meta-analysis of studies among patients where antibiotics were given either alone or in combination with glucocorticoids following PPROM, showed that the advantages of antibiotic treatment (ie. reduction of chorioamnionitis, postpartum endometritis and neonatal sepsis) are diminished in presence of glucocorticoid therapy (Egarter et al. 1998).

The management of preterm premature rupture of membranes depends on gestational age, presence of infection and presence of other fetal maternal complications.

If women with PPROM have chorioamnionitis, vaginal bleeding, advanced labour, or complications related to the fetus, then delivery is necessary and is beneficial for both the mother and the fetus.

Women with membrane rupture near term (34 weeks of gestation) benefit from delivery, if pulmonary maturity is present in the fetus. Mercer et al.(1996), recommended that those women with gestational age greater than 32 weeks and fetal pulmonary maturity are better served with expeditious delivery rather than by expectant management (Mercer et al. 1996). Currently within the CRHA, women with PPROM are induced at 34 weeks gestation (Personal communication; Dr. Wood, November 1999).

Where rupture of membranes occurs remote from term and there is no indication for delivery, prolongation of pregnancy can have significant benefits for the fetus by reducing gestational age-dependent perinatal morbidity (Mercer et al. 1998).

2.6 Antibiotic Treatment During Pregnancy

Following the evidence of numerous studies for presence of an association between preterm birth and infection during pregnancy, it was postulated that antimicrobial therapy might be useful in treating intrauterine infections and, therefore, in prolonging pregnancy after the onset of PTL or PPROM. Several randomized clinical trials have been carried out to investigate the effects of antibiotic therapy on prolongation of pregnancy in such cases (Appendix A. Tables I, II, III). Conclusions regarding the benefits of antibiotic treatment for prolonging pregnancy are inconsistent and remain a controversy.

Even though some studies, particularly those evaluating antibiotic treatment for prolongation of pregnancy after PPROM, have demonstrated significant prolongation, there are some concerns with respect to the lack of evidence for reduction of maternal and neonatal morbidity in these studies and for the potential ramifications of the increasing use of antibiotics.

Some recent studies have shown that antibiotic use, both antepartum and intrapartum, can lead to the selection of resistant microorganisms by altering the cervical microflora and increasing the risk for antibiotic resistant neonatal sepsis when infection occurs (Mercer et al. 1999 and Tower et al. 1998). These studies have both shown the association between maternal antibiotic treatment and neonatal sepsis by organisms resistant to Ampicillin and to previously administered maternal antibiotics (Mercer et al. 1999 and Towers et al. 1998).

Mercer et al. (1999) demonstrated that ampicillin resistance increased with antepartum antibiotics (57% vs. 34%; $p=0.03$), intrapartum antibiotics (55% vs. 28%; $p<0.01$) and any prenatal antibiotic exposure (52% vs. 22%; $p=0.01$) in babies whose mother received antibiotics compared to those who did not. In this study, 96 infants were identified with confirmed sepsis. Ampicillin resistance was identified in at least one isolate in 45% of these infants.

Furthermore, in a prospective cohort study performed during the years 1991-1996, Tower et al. (1998) identified an association between the increased administration of antenatal ampicillin to pregnant women and increased incidence of early onset neonatal sepsis with non-group B streptococcal organisms that are resistant to ampicillin. During the 6 years, Towers et al. (1998) identified 27 confirmed non-group B streptococcal

cases. Fifteen mothers had received antenatal ampicillin and 13 of the 15 bacteria isolates from these neonates (87%) were resistant to ampicillin compared to 2 out of 12 (17%) neonates to whom no antenatal antibiotics were administered (p=0.004). Four out of the 27 neonates died of sepsis.

As such, antibiotic use during pregnancy remains a controversial issue. The following two sections of this chapter, (2.61 and 2.6.2), will review the available literature regarding antibiotic treatment for both PTL and PPROM and the effect of this treatment on the prolongation of pregnancy.

2.6.1 Antibiotic Treatment in Preterm Labour with Intact Membrane

An extensive search of literature using the key words 'antibiotic' and 'preterm labour' in the Medline database, showed eleven randomized control trials which used antibiotic treatment to prolong pregnancy in women with preterm labour and intact membranes (Appendix A,Tables I, II). A variety of antibiotic therapies including erythromycin, ampicillin, amoxicillin, clindamycin, metronidazole, sulbactam, calvulonic acid and ceftizoxime have been investigated.

The first study, in 1986, a randomized, double-blinded, placebo-controlled trial assessing the effect of erythromycin, was performed. Tocolytics were also used for treatment of preterm labour. This study showed a significant increase in the mean latency period in antibiotic group (32.5 ± 11.2 vs. 22.4± 7.2 days; p=0.027). The incidence of delivery at term between the two groups was also significant (7/8 vs. 3/9; p=0.039). This study concluded that oral erythromycin was a potentially useful adjunct in the prevention of preterm delivery (McGregor et al. 1986).

In 1991, McGregor et al. performed a similar study but using intravenous clindamycin for prolongation of pregnancy. Tocolytics were used in both groups. In this study, pregnancies continued longer in women treated with clindamycin than those receiving placebo (35.3 ± 24.1 vs. 25.4± 20.0 days; p=0.02). However, this study did not show any decrease in preterm delivery or increased gestational age at delivery among those mothers who received clindamycin (McGregor et al. 1991).

Morales et al. (1988) performed a study with ampicillin, erythromycin or placebo administered to individuals with diagnosis of preterm labour who also received tocolytics. In this study, women also received tocolytic therapy for preterm labour. Once again, a significant prolongation of pregnancy was demonstrated in those with either antibiotic regimen versus the control (31.7 ± 23.2 and 28.5 ± 19.0 vs. 16.6 ± 17.7 d; p=<0.01 and p<0.05 respectively). Morales et al. concluded that despite no decrease in neonatal or maternal morbidity, antibiotics were beneficial adjuncts in the treatment of preterm labour. In this study, women treated with ampicillin showed a decreased incidence of preterm delivery than those who received erythromycin or placebo when bacterial vaginosis was diagnosed.

In 1989, Newton et al. performed two randomized placebo-control trials to investigate the efficacy of antibiotic treatment in women with preterm labour and gestation age between 24 to 34 weeks. In the first study, ampicillin followed by erythromycin for one week was administered. Both tocolytics and corticosteroids were part of the protocol for treatment of preterm labour in this study. No statistically significant improvement was observed in preterm delivery or in prolongation of pregnancy (Newton et al. 1989) between the antibiotic group and placebo. In the second

study, the effect of ampicillin and sulbactam was evaluated in women with preterm labour and gestation age between 24 to 34 weeks. Again, no benefit of antibiotic use was observed. In this study, the effect of antibiotics on improving the effectiveness of magnesium sulfate tocolysis was assessed. Magnesium sulfate with or without antibiotics treatment delayed delivery a median of 26 days (Newton et al. 1991).

In 1993, Romero et al conducted a large multi-center clinical trial. Two hundred twenty-seven women in preterm labour received either intravenous ampicillin and erythromycin followed by oral amoxicillin/erythromycin base or matching placebo. Both tocolytics and corticosteroids were part of the protocol for treatment of preterm labour. This study did not demonstrate any improvement in prolongation of pregnancy or any decrease in maternal and neonatal morbidity rates in those with antibiotic therapy (Romero et al. 1993).

In a multicenter randomized, controlled clinical trial in, 1994, Norman et al., investigated the effects of ampicillin followed by metronidazole on preterm labour in 82 women also receiving corticosteroids and tocolytics (1994). Those receiving the antibiotics showed a significant prolongation of pregnancy compared to those receiving placebo (15d vs. 2.5; p=.04). Those women between 26 to 30 weeks gestation showed the greatest prolongation of pregnancy (25.5d vs. 2d).

In 1995, Gorden et al. published the results of a double blinded placebo controlled trial assessing the effect of ceftizoxime on preterm labour. One hundred and seventeen women in preterm labour with gestation age between 24 and 35 weeks were assigned to either antibiotic or placebo group. Both groups were also treated with tocolytics and corticosteroids during preterm labour. There was no difference in interval to delivery

(34.5±21.1 days vs. 34.6±24.5 days, p=0.99) between the antibiotic group and placebo group.

In another double-blind, placebo controlled trial, patients were randomized to receive ampicillin-sulbactam followed up by amoxicillin-clavulanic acid vs. placebo medications. Seventy eight women in preterm labour between the gestational age of 24 and 34 weeks were involved in the study. In this study neither tocolytics nor corticosteroid were used. There was no improvement observed in gestation age at delivery (34.2 ± 0.7 vs. 34.1 ± 0.6 wk) or improvement in birth weight or neonatal morbidity rates with antimicrobial therapy (Cox et al. 1996).

In 1997, Svare et al. examined the effect of ampicillin and metronidazole treatment in preterm labour with intact membrane. In this study patients were randomized to receive ampicillin and metronidazole or placebo regimen. One hundred and twelve women with preterm labour, who also received tocolytics and corticosteroids, participated. The authors concluded that a significant prolongation of pregnancy (47.5 d vs. 27 d; $p<0.05$), and a decreased incidence of preterm birth (42% vs. 65%; $p<0.05$) resulted. However, they did not show any improvement in maternal or neonatal infectious morbidity.

Oyarzun et al, assessed the effect of amoxicillin and erythromycin in 196 women in preterm labour. Women were randomly assigned to receive antibiotics or placebo. Both groups also received tocolytics and corticosteroids during preterm labour. There was no significant difference in prolongation of pregnancy or in the frequency of preterm delivery among the two groups (Oyarzun et al. 1998).

In summary, five of these twelve clinical trials, which examined antibiotic therapy for women with preterm labour and intact membranes, showed a significant prolongation of pregnancy due to the use of antibiotics (McGregor et al. 1986; Morales et al. 1988; McGregor et al. 1991; Norman et al. 1994; Svare et al. 1997). However, only two studies actually showed significant decreases in rates of preterm delivery (Morales et al. 1988; Svare et al. 1997).

There is conflicting evidence regarding the impact and benefit of antibiotic treatment on the prolongation of pregnancy in women with preterm labour and intact membrane and on the improvement of neonatal outcomes. The discrepancy in the study results may be due to many factors including:

1) Methodological differences among the studies
2) Small sample sizes
3) Differences in type (single agent vs. combination therapy) and dosage of antibiotics used
4) Differences in the characteristics of the study population
5) Differences in the causal role of infection in preterm labour among different populations
6) Discrepancies in criteria for diagnosis of "true" preterm labour

The overall lack of benefits from antibiotic treatment in women with preterm labour and intact membrane may be because only a subgroup of women who actually had subclinical intrauterine infection could benefit from antibiotic treatment (Chaim et al. 1998; Oyarzun et al. 1998). Most studies administered antibiotics to all patients with preterm labour without identifying the intrauterine infection status.

Reimer et al. (1999) suggests that antibiotics should not be used routinely to prolong pregnancy in women with preterm labour and intact membranes. Furthermore, Oyarzun et al., (1998) explained the antibiotics failure in the prevention of preterm delivery by stating that, "intrauterine infection is only one of the etiopathogenic conditions associated to preterm labour. Thus, antibiotic administration would not be effective in treating preterm delivery in patients without infection".

In addition, Lamont et al. (1998) suggested that preterm labour at gestations below 28 weeks is more likely to be due to an infective etiology than preterm labour at gestation age closer to 37 weeks, which is more likely to be physiological. Therefore, antibiotic interventions closer to 37 weeks of gestation are less likely to show any benefit. Similarly, Cassell et al. (1993) observed that 73% of women with a spontaneous preterm delivery (<30 weeks gestation) and 83% of those delivering infants weighing less than 1,000 gram at birth, had a chorioamnion culture positive for one or more organisms.

None of the individual clinical trials have shown a significant improvement in neonatal outcomes such as neonatal sepsis, respiratory distress syndrome or intravenous hemorrhage, as a result of antibiotic therapy with the exception of a significant reduction in necrotizing enterocolitis in one study (Norman et al. 1994).

In fact, a meta-analysis of seven studies published between 1989 and 1995 on adjunctive antibiotic treatment in preterm labour and neonatal morbidity, reported an increased risk of neonatal mortality with OR= 3.25, 95% CI 0.93-11.38 (Egarter et al. 1996).

The Cochrane Database of Systematic Reviews of clinical trails investigating antibiotics for preterm labour with intact membranes, concludes that there is no observed

overall benefit, from antibiotic treatment of preterm labour with intact membranes on outcomes for the mothers. The results, however, raise a concern about an increase in perinatal mortality. Consequently, antibiotic treatment is not recommended as a routine practice for all women presenting with preterm labour and intact membrane (King et al. 1999).

2.6.2 Antibiotic Treatment in Preterm Premature Rupture of Membranes (PPROM):

Similar to observations with respect to preterm labour, there is evidence that PPROM is also associated with the presence of intrauterine infections. Therefore, based on the theory that antibiotics could treat subclinical infections or prevent ascending infections subsequent to PPROM, an investigation on the effects of antibiotics on PPROM commenced. Prevention or treatment of infection could potentially reduce the maternal and neonatal infectious morbidity in addition to reducing the effects of neonatal prematurity.

The first prospective clinical trial to assess the effect of antibiotics on PPROM was done in 1963 by Lebherz et al. This study evaluated the effect of tetracycline after preterm and term PROM. The authors showed a significant reduction in maternal endometritis. However, prolongation of pregnancy or neonatal infectious morbidity were not addressed in this study.

Between 1963 and 1997, 29 prospective trials, including 17 randomized clinical trials on antibiotic therapy in PPROM, were performed using various forms of antibiotics. Four meta-analysis were published reviewing the available literature on this subject

(Mercer et al. 1996; Egarter et al. 1996; Mercer et al. 1998; Maymon et al 1998a).

Additionally, the Cochrane Database of Systematic Reviews has examined twelve randomized, placebo-control trials on the impact of antibiotic treatment on prolongation of pregnancy in women with preterm premature rupture of membranes.

The results of a meta-analysis conducted by Maymon et al. in 1998, based on 16 randomized clinical trial studies, suggested that patients who received antibiotic therapy had a significantly prolonged interval to delivery compared to those without treatment (42.3% vs. 24.1% respectively, $p<0.002$; OR= 2.35, 95% CI: 1.67-3.29). Furthermore, there was a significantly lower rate of chorioamnionitis and endometritis in patients who received antibiotics compared to those without therapy.

Mercer et al. (1996), summarized the results of 15 clinical trials which have compared the effect of systematic treatment with placebo or control group in patients with PPROM. In this review more than 18,000 women were included. Seven of the trials assessed pregnancy prolongation. This meta analysis also confirmed a significant improvement in pregnancy prolongation with antibiotic treatment.

Only one study, conducted by Blanco et al. (1993) did not show significant prolongation. The control group in this study had a long median latency period of 11.4 days. Mercer et al. (1996), suggested that the lack of significant benefit from antibiotic therapy in the Blanco et al. study, may be due to the selection criteria or the population evaluated with a lower risk for intrauterine infections and therefore, less benefit for antibioitc use. Also, in Mercer's review, it has been shown that from all the studies included there is enough evidence that chorioamnionitis was significantly reduced with antibiotic treatment.

There are many inconsistencies in the available studies on antibiotic therapy and PPROM related to the methodology used, inclusion/exclusion criteria for participants, antibiotic type and duration of therapy, gestation age on admission, and sample size. Such confounding variables may limit the validity of the conclusions and generalizability of these results in other populations.

Similar to the Cochrane Database of Systematic Reviews, Appendix A, Table III, presents only the randomized placebo-control trials reviewed for the purposes of this study. Four of the studies identified in the Cochrane database (Cox et al. 1995; Garcia et al. 1995; and Svare et al. 1997; Ovalle Salas et al.1997) were not included in the Appendix A, Table III, as one was in a different language, two were theses and one was only an abstract; therefore, the details of the studies were not available for further critical appraisal.

The Cochrane reviews concluded that antibiotic therapy following preterm premature rupture of membranes is effective in prolonging pregnancy as well as in reducing maternal and neonatal infectious morbidity (Kenyon et al. 1999).

The largest randomized double blind controlled study of antibiotic treatment in management of PPROM was done at the university hospitals of the National Institute of Child Health and Human Development Maternal Fetal Medicine Unit network (NICDH-MFMU) (Mercer et al. 1997b). A total of 614 women with PPROM and gestational age between 24 and 32 weeks, who had not received corticosteroids for fetal maturation or antibiotic therapy within 1 week of randomization, participated. In this study the antibiotic regimen assessed was ampicillin (2 g dose every 6 hours) and erythromycin

(250 mg every 6 hours) for 48 hours followed by oral amoxicillin (250mg dose every 8 hours) and erythromycin base (333 mg dose every 8 hours) for 5 days.

Group B streptococcus (GBS) cultures were taken on all participants. All GBS carriers (19.2%) were treated prior to and during labour in accordance with the suggested intrapartum GBS prophylaxis by the American Collage of Obstetricians and Gynecologists.

The results showed that antibiotic treatment in the GBS negative cohort significantly prolonged median time to delivery (6.1 vs. 2.9 days, $p<0.001$) and a significantly higher number of patients in the antibiotic group remained pregnant at each day between 2 days and 3 weeks compared to those who did not receive any antibiotics. In the positive GBS cohort, the additional antibiotic therapy had no significant effect on prolongation of pregnancy.

This multicenter randomized clinical trial suggested that antibiotic treatment could suppress or prevent clinically significant intrauterine infection and, therefore, result in prolongation of pregnancy and reduction of infant morbidity (such as respiratory distress). Based on the results of previous studies and this study, Mercer et al. (1997b) recommended that all women undergoing expectant management of PPROM, remote from term, should receive antibiotics prior to initiation of labour, regardless of GBS carrier status. Mercer et al. (1998) suggested that an initial treatment with an intravenous broad spectrum regimen, such as ampicillin plus erythromycin or an extended spectrum penicillin or cephalosporin, for 48 hours followed by oral therapy (amoxicillin and erythromycin) for an additional five days would be effective.

However, the application of Mercer's (1997b) recommendations in Canadian populations may have varying results. The majority of the population in this study were inner city residents with poor prenatal care with high rates of infection. For instance, in Mercer's study the rate of *Chlamydia trachomatis* was13.8% and 15.4% in the treatment and placebo group respectively. *Neisseria Gonorrhea* was approximately 8% in Mercer's study which is considerably higher than the rate in Canada (14.9 per 100,000 for the total population of Canada in 1998; estimated by Health Canada). Therefore, it is important to see if the same results can be obtained in other populations before the recommendations are included as part of the standard strategies for management of PPROM.

2.7 Prevalence of Antibiotic Use for Prolongation of Pregnancy

Although there are many studies evaluating the effect of antibiotic use on prolongation of pregnancy after preterm labour or premature rupture of membrane, there is a lack of knowledge about the current extent of antibiotic use during pregnancy in hospitals. In other words, it is not clear what impact these studies have had on current practices for antibiotic use and whether the results of these studies are generalizable to other populations.

In fact, there is only one population based study which has examined the frequency of antibiotics use in pregnancy (Mercer et al. 1999). This study, which was performed at six hospitals in metropolitan Memphis, Tennessee, reviewed maternal and neonatal records in 8,593 live born babies between July 1997 and February 1998. The rate of preterm birth in this population was 14.8%. Overall frequency of antibiotic use of the mother before delivery was 46.0%. Of the mothers receiving antibiotics, 30.4% of

the mothers received antepartum antibiotics and 24.9% received intrapartum antibiotics. In this study antibiotics were considered antepartum if they were given before the onset of labour or before a decision to proceed with cesarean delivery.

Antepartum antibiotics were used for a variety of reasons with the most common reason being urinary tract infection or asymptomatic bacteriuria. Six percent of the women were treated with antepartum antibiotics for bacterial vaginosis. Interestingly, despite the available data in the U.S. for use of antibiotic for prolongation of pregnancy in cases of PPROM, only 1.2% of women were treated just for the reason of having preterm premature rupture of membranes. The most common antibiotics used were ampicillin or amoxicillin. Of those women receiving antepartum antibiotics, 42.2% were given a penicillin or cephalosporin class of antibiotic.

CHAPTER THREE: METHODS

3.1 Introduction

This chapter describes the methodology of the study, including sampling procedure, data collection, data analysis and ethical considerations.

3.2 Overview of the Study Methodology

Data identification, collection and analysis were completed in multiple stages. The first stage was the identification of the sample. Information received from Corporate Data of the CRHA was examined and all hospitalizations that satisfied the inclusion criteria of the study were identified for review. Secondly, these admissions were reviewed on a case by case basis and data was collected for the study. Analysis of the data occurred during the last stage of the study.

3.3 The Study Design

A cross-sectional study design was used to compare the socio-demographic and obstetric characteristics, in addition to frequencies of antepartum antibiotics use for women admitted to three acute care hospitals in the CRHA with preterm labour and intact membranes or preterm premature rupture of membrane. Cross-sectional studies examine the relationship between disease (or other health related characteristics) and other variables of interest as they exist in a defined population at a particular time or period (Last 1995).

3.3.1 Study Population

Study population is defined as the group selected for investigation (Last 1995). The study population for this study was women admitted to the Foothills Medical Center (FMC), the Peter Lougheed Center (PLC) or the Rockyview General Hospital (RGH), in Calgary Regional Health Authority (CRHA), with preterm labour and intact membranes or preterm premature rupture of membranes for greater than 12 hours before delivery, between 22 and 34 weeks of gestation, during the periods of January 1st to Dec 1996 and January 1st to December 31st, 1999.

3.3.2 Sampling

The identification of the sample for this study will be described following an examination of the inclusion and exclusion criteria and the definitions of terms used in the study.

3.3.2.1 Inclusion and Exclusion criteria:

Women admitted to any of the three hospitals with preterm labour and intact membranes at 22 to 34 weeks of gestation who did not deliver within 12 hours of admission were included in the study sample.

The other group of women that were included in the study were those women admitted to hospital with preterm premature rupture of membranes between 22 to 34 weeks of gestation who did not go into labour within 12 hours of PPROM.

Excluded from the study were all women with preterm labour or PPROM who had a medical reason that contra-indicated prolongation of pregnancy as described in

Appendix B. All women with gestational age greater than 34 weeks were excluded as delivery is induced after 34 weeks gestation for women with ruptured membranes. All women who did not meet the diagnostic criteria for preterm premature rupture of membranes as well as for preterm labour were excluded (see section 3.3.3.1).

3.3.2.2 Definitions

The following are obstetrical terms as they are defined for the purposes of this study.

Preterm labour: Labour occurring between 22 and 34 weeks of gestation. The following International Classification of Disease (ICD-9) codes were used to identify these women (WHO, Pregnancy Childbirth and puerperium ICD-9; 1995).

644.0: Threatened premature labour (22-36wks) with no delivery

644.2: Early onset labour (22-36wks) with delivery

Premature rupture of membranes: Spontaneous rupture of membranes prior to onset of labour regardless of gestational age.

Preterm premature rupture of membranes (PPROM): Rupture of membranes before 37 completed weeks of gestation. The following ICD-9 coding were used:

658.1: Premature rupture of membranes (<24hr prior to onset of labour)

658.2: Delayed delivery after spontaneous or unspecified rupture of membranes (Prolonged rupture of membranes not otherwise specified or rupture of membranes >24 hr prior to onset of labour).

Intrapartum antibiotics include:

1) Antibiotics given to women who were admitted to Labour and Delivery with no hospital discharge before delivery, and delivered within 12hrs of admission.
2) Antibiotics given to women who were admitted to the Labour and Delivery unit with no discharge before delivery, and did not deliver within 12hrs from admission which were determined by an independent adjudicator to be intrapartum.
3) Antibiotics given to women during the final readmission to Labour and Delivery (i.e. the admission that results in delivery).

Antepartum antibiotics for prolongation of pregnancy: Antibiotics administered during the hospital stay, from admission for preterm labour to delivery or from the premature rupture of membranes to delivery for the purpose of prolonging pregnancy. This definition excludes intrapartum antibiotics.

Prolongation of pregnancy: Defined as an increased latent period (days) from admission to hospital to delivery or from premature rupture of membranes to delivery.

3.3.3 Variables Used in the Study

Information on the following variables were collected in this study.

Dates:

Admission date (for each admission)
Discharge date
Date of premature rupture of membrane
Date of delivery

Socio-Demographic variables:

a) Continuous
- Maternal age on admission

b) Categorical
- City of residence (Calgary vs. outside Calgary)
- Smoking during Pregnancy
- Alcohol consumption during Pregnancy

Obstetric variables:

a) Continuous
- Gestation age on admission
- Highest temperature 24 hr prior to delivery (indicator for infection)
- WBC count$x10^9$/L (indicator for infection)
- Total dose of antibiotics used
- Total length of hospital stay
- Neonate's birth weight

b) Categorical
- Admission reason (PTL vs. PPROM)
- Previous preterm birth
- Tocolytics during admission
- Corticosteroids during admission
- Antibiotic use prior to admission
- Antibiotic use during Hospital stay
- Types of antibiotics used
- History of infection during pregnancy
- Microbiological findings (*Chlamydia trachomatis*, Bacterial Vaginosis, Yeast sp., *Trichomonas vaginalis*, Group B streptococcus, *Neisseria gonorrhoeae*, Urine cultures)
- Delivery mode
- Admitted to Neonatal Intensive Care Unit
- 5 minute Apgar Score
- Gestation age at birth
- Neonate's gender

3.3.3.1 Operational Definitions

The following definitions were used as diagnostic criteria for preterm labour and preterm premature rupture of membrane.

Preterm labour:

Criteria: Admission to the hospital and one of the following:
1) Cervix ≥ 2cm.
or 2) Documented cervical change over a variable period of 1-6 hrs in the presence of uterine activity
or 3) Bulging of membranes
or 4) Tocolytics used for those women with < 33 weeks gestation

Preterm premature of membranes rupture:

Criteria: 1) Patient history consistent with PPROM
2) Pool of fluid seen on sterile speculum exam
3) Slide of vaginal discharge positive for ferning

3.3.4 Determination of Sample Size

Prior to initiation of the study, a sample size was calculated for comparing the proportions of women in preterm labour and those with PPROM who received antibiotics for prolongation of pregnancy during 1996 (p_1) and 1999 (p_2).

3.3.4.1 Sample Size Calculation

The sample size calculation was based on the assumption that overall, approximately 30-40% of all preterm births received antenatal antibiotics during 1993-96 (personal communication; Dr. Sauve, July 1999).

Fifteen percent was assumed to be a clinically significant increase in antibiotic use. Therefore, sample size calculation was based on the predicted proportion of antibiotic use in 1996 to detect a 15% increase in 1999 from the estimated frequency in 1996 (α =0.05; 1-β= 0.95). The formula used for sample size (n) was as follows:

$$n = \frac{f(\alpha, P)\,(p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

Where, p_1 = Estimated proportion of women in preterm labour and PROM who received antibiotic in the year 1996.

p_2 = Estimated proportion of women in preterm labour and PROM who received antibiotic in the year 1999.

1-β = 0.95, α= 0.05, two-sided

A total sample size of 286 women with preterm labour and PPROM for each year was found to be adequate for this study (Appendix D).

In order to calculate the sample size required for each stratum (preterm labour vs. preterm premature rupture of membranes) another assumption was considered. This assumption was that PTL with intact membranes is responsible for about 25% of preterm birth and PPROM is responsible for about 40% of preterm birth.

Weighted random sampling would have been required to provide adequate presentation of each stratum. Based on the above assumptions there was a 1 to 1.6 ratio

of preterm labour cases to preterm premature rupture of membrane cases. Therefore, out of 286 total sample size, about 179 cases of PPROM and 107 cases of PTL with intact membranes were required for each year. These cases were to be selected using a simple random sampling method from the total available number of cases in each stratum.

However, when the inclusion/exclusion criteria were applied to all eligible women from the three hospitals, the number of women eligible to be included in the analysis were smaller than the desired sample size (286 women from each year). Therefore, no weighted random sampling was performed. All women who met the inclusion criteria were included in the study.

3.3.5 Data Collection Procedures

Secondary data sources (existing data) were used to collect all information. Secondary data sources are defined as "data sources that were designed for administrative purposes or databases that were designed for ongoing epidemiologic surveillance of medical care" (Huston & Naylor. 1996). The secondary data sources used in this study were the first type, that is designed for administrative purposes.

Data was obtained from Corporate Data of CRHA. Data collection began with the identification of the sample. An overview of the data collection procedures will be divided into two sections. The first section is a description of the methods to identify the sample and the second section describes the data collection procedures for the study variables.

3.3.5.1 Identification of the Study Sample

Patients admitted to Foothills Medical Center (FMC), Peter Lougheed Center (PLC) and Rockyview General Hospital (RGH) were included in this study. Patients were selected in two stages as follows:

1) All women admitted to these three adult acute care hospitals in the Calgary region with one or more of the following ICD-9 diagnostic codes were identified by the Corporate Data of Calgary Regional Health Authority :

644.0: threatened premature labour (22-36 wk) with no delivery,

644.2: early onset labour (22-36 wk) with delivery,

658.1: premature rupture of membranes,

658.2: delayed delivery after spontaneous or unspecified rupture of membranes.

The resulting patient list was provided in a Microsoft Excel download. The following information was provided:

i) Hospital identification number

ii) Personal Health Number (PHN)

iii) Patient's date of birth

iv) Date and site of admission for preterm labour or PPROM

v) Date of delivery

vi) Date and site of discharge after delivery

vii) The ICD-9 coded diagnosis/complications of each admission

viii) Gestation age at birth (if available)

This information was used to detect and link possible readmissions of a patient to hospital within the CRHA, readmission to different hospitals and coding errors in PHN and hospital identification numbers (i.e. no PHN or one PHN assigned to two people).

Patients admitted with preterm labour or PPROM and a medical reason for immediate delivery, were identified and excluded by using the ICD-9 as listed in Appendix B.

For those admission with data available on gestation age at birth, gestation age on first admission was calculated using delivery dates and first admission dates. Those with a gestation week less than 22 or greater than 34 on first admission were identified and excluded.

Since the sampling unit is one woman, in cases of multiple admissions, the number of admissions was converted to number of women. For example, if one woman was admitted three times to FMC, in the analysis she would be counted only once (one unit of analysis).

Requests were made to the Health Records departments of each of the three hospitals to retrieve the charts of women who met the inclusion criteria.

2) The second stage of patient selection involved reviewing the charts to exclude those meeting any of the exclusion criteria that previously could not be identified by ICD-9 codes. In this stage the following women were excluded:

i) women with preterm premature rupture of membrane with duration <12hrs, or preterm labour with admission to delivery duration<12hrs

ii) women with gestational age less than 22 weeks or greater than 34 weeks on first admission (these were women whose gestation age at delivery was not available

from Corporate Data and therefore, gestation age on admission could not be calculated. Referring to the chart was necessary for determining admission gestation age)

iii) women with false PTL or PROM

The number of patients and reasons for exclusion were recorded from these charts.

3.3.5.2 Data Collection for the Study Variables

For the women meeting the inclusion criteria, the required data was collected using the data collection form (2) provided in Appendix C. This form was filled out for each woman. In cases of multiple admissions, extra copies of the form with information related to readmission were completed and attached to the first copy of the data collection form for that woman.

The charts of the initial twenty women were reviewed for the purpose of determining the feasibility of collecting the items on the data collection form. The variable "ethnic background" was deleted from the data collection form as there was no information on the charts for this variable. Based on these reviewed charts, the design and order of questions were also modified.

3.3.6 Data Management

The data was coded and entered in to the software package *Microsoft Excel*. Prior to analysis, the data were checked by focusing on (1) data entry errors (2) missing data, and (3) outlying values. Frequencies were generated to examine incorrect values for categorical data. For example, if antibiotic use was coded as one and two, the value

three would be identified as an incorrect value. The range of values for continuous data was also examined for potential errors. For example, an age of 92 would have indicated an error. Dates were checked to ensure that they were valid and were in a consistent format. In cases of missing data, charts were accessed a second time. Data was exported into the statistical program, Intercolled Stata 5.0, for the data analysis *(Stata Corporation, 1997).*

3.3.7 Data Analysis

Intercolled Stata 5.0 software program was used for analysis of data. Detailed descriptive univariate analyses were conducted for all variables. Counts and percentages were tabulated for each categorical variable. For the continuous variables, the mean and standard errors and 95% CI were calculated and presented in tables .The distribution of continuous variables were assessed using histograms and box-plots. In cases were the distribution of a continuous variable was not normal, an attempt was made to use appropriate transformation strategies to normalize the distribution.

For the analysis of the first two objectives, counts and percentages of soci-demographic and obstetric characteristics of women at each hospital site and for each year (1996 and 1999) were tabulated. Comparison of the categorical variables was done using chi-square test.

For continuous variables two-sample t-test was used when comparing the two years. In order to compare socio-demographic and obstetric results among the three sites, the analysis of variance test (ANOVA) was used. In each case, the assumption of

normality of distribution and equal variance among the groups were assesses before using ANOVA.

For analysis of the third objective, two-sample t-test was used for comparison of continuous variables and chi-square test for categorical variables between the antibiotic groups and no-antibiotics. The association between use of antibiotic (categorical) and increase in length of pregnancy (continuous) was assessed using two-sample t-test. To control for the influence of potential confounder on this association, stratified analysis was used. Stratifying the analysis of the results is defined as "separating a sample into several sub samples according to specific criteria such as age group" to control for effect of confounding variables (Last 1995).

Prevalence, defined as the number of events in a given population during a specific period divided by the total population at risk, was used to measure occurrence of different variables in the study population. Prevalence ratio was used to compare the prevalence of an event in the group of interest compared to the prevalence in the control group. Prevalence ratio was also used to determine effect of confounders on associations of interest.

3.3.8 Ethical Considerations

This was a quality assurance study done under the auspices of the Infection Prevention and Control department. In this study every effort was made to protect the patients' privacy and maintain confidentiality. The data collected for this study was gathered indirectly from all subjects. Privacy in research refers to limited access to a person (Beauchamp, 1996). The use of indirect methods such as the use of inpatient records did not result in risk of harm to subjects. The respect of participants' privacy was protected through ensuring their anonymity. All identifiable information was removed.

Confidentiality, defined as management of private information, was ensured by keeping all the data collected from patients' records, including the disk containing the prepared database, under lock and key at all times. In addition, the identifying information (Patient's name, PHN and date of birth) were recorded on a separate form attached to the data collection form. After the identifying information was used for the purpose of linking records of individuals from different sources (readmission to different hospitals) and in cases of missing PHN or duplicate identifying numbers, this information was detached from the data collection forms and purged. Furthermore, the study data has remained confidential; subject anonymity was maintained and results from the study was reported and/or published in such a way so that the individual patient's cannot be identified.

A study identification number was assigned to each record as the inpatient chart was reviewed. No information pertaining to physicians was collected from the chart.

CHAPTER FOUR: RESULTS - SITE SPECIFIC COMPARISONS OF SOCIO-DEMOGRAPHIC AND OBSTETRIC CHARACTERISTICS FOR THE YEARS 1996 AND 1999

4.1 Introduction

In this chapter the total sample size attained through the sample-selection procedure is described. Furthermore, the site specific, socio-demographic, and obstetric characteristics of women admitted for preterm labour or preterm premature rupture of membrane to any of the acute care hospitals in the CRHA during the years 1996 and 1999 are compared.

4.1.1 Selection of Study Sample and Total Sample Size for Year 1996 to 1999

For the study, a total of 2880 admissions from January to December 1996 and 3289 admissions from January to December 1999, with one or more of the requested ICD-9 codes (i.e. 644.0, 644.2, 658.1 and 658.2), were identified by the Corporate Data of the Calgary Regional Health Authority.

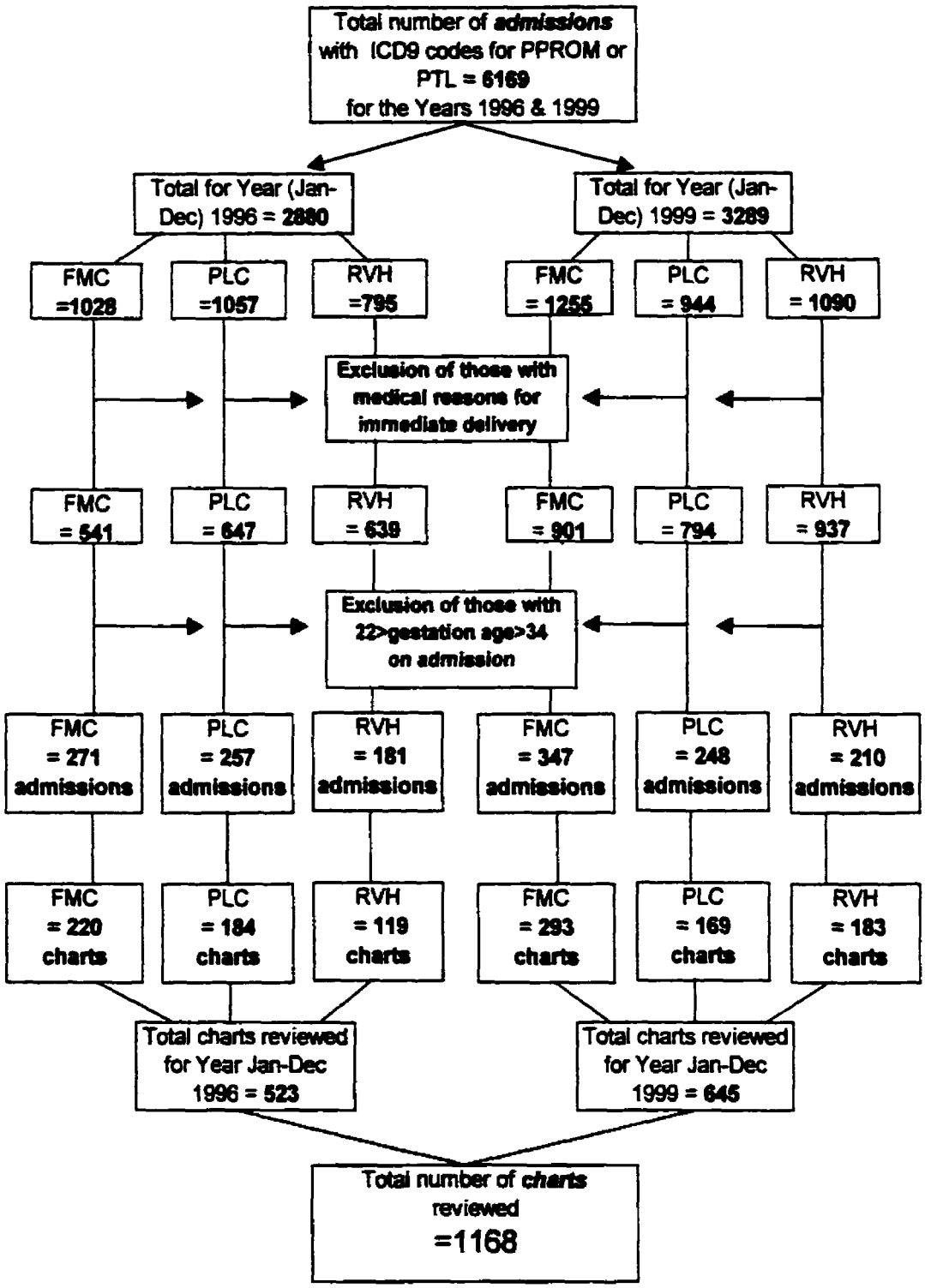
Women with an admission for preterm labour (PTL) or premature rupture of membranes (PPROM) and a medical reason for immediate delivery were identified and excluded from the study by using the ICD-9 codes of exclusion criteria listed in Appendix B. As a result, for the three hospitals a total of 1827 admissions from year 1996 and 2632 admissions from 1999 remained (Figure 4.1).

Of these admissions, those women with a gestation age between 22 to 34 weeks of pregnancy were identified. At this first stage of patient selection, 709 *admissions* for the year 1996 and 805 *admissions* for the year 1999 met all the inclusion criteria.

Since it was possible for one woman to have more than one admission, the number of admissions was translated into 523 eligible women with 709 admissions for 1996 and 645 women with 805 admissions for 1999. A flow chart of the steps involved in this first stage of patient selection is shown in Figure 4.1.

The list of these 1168 eligible women was given to the Health Records Department of each of the three hospitals and requests were made for their charts to be retrieved.

Figure 4.1 Flow Chart of the Selection of Patients' Records for Review



In the second stage of patient selection, a total of 1168 charts were reviewed for further exclusion of women (Figure 4.2):

(1) with PTL and duration of admission to delivery of <12hrs, or those with PPROM with duration of admission to delivery of <12hrs,

(2) with gestational age on first admission of less than 22 weeks or greater than 34 weeks,

(3) with false PTL or PPROM (using criteria mentioned in the methods section), and

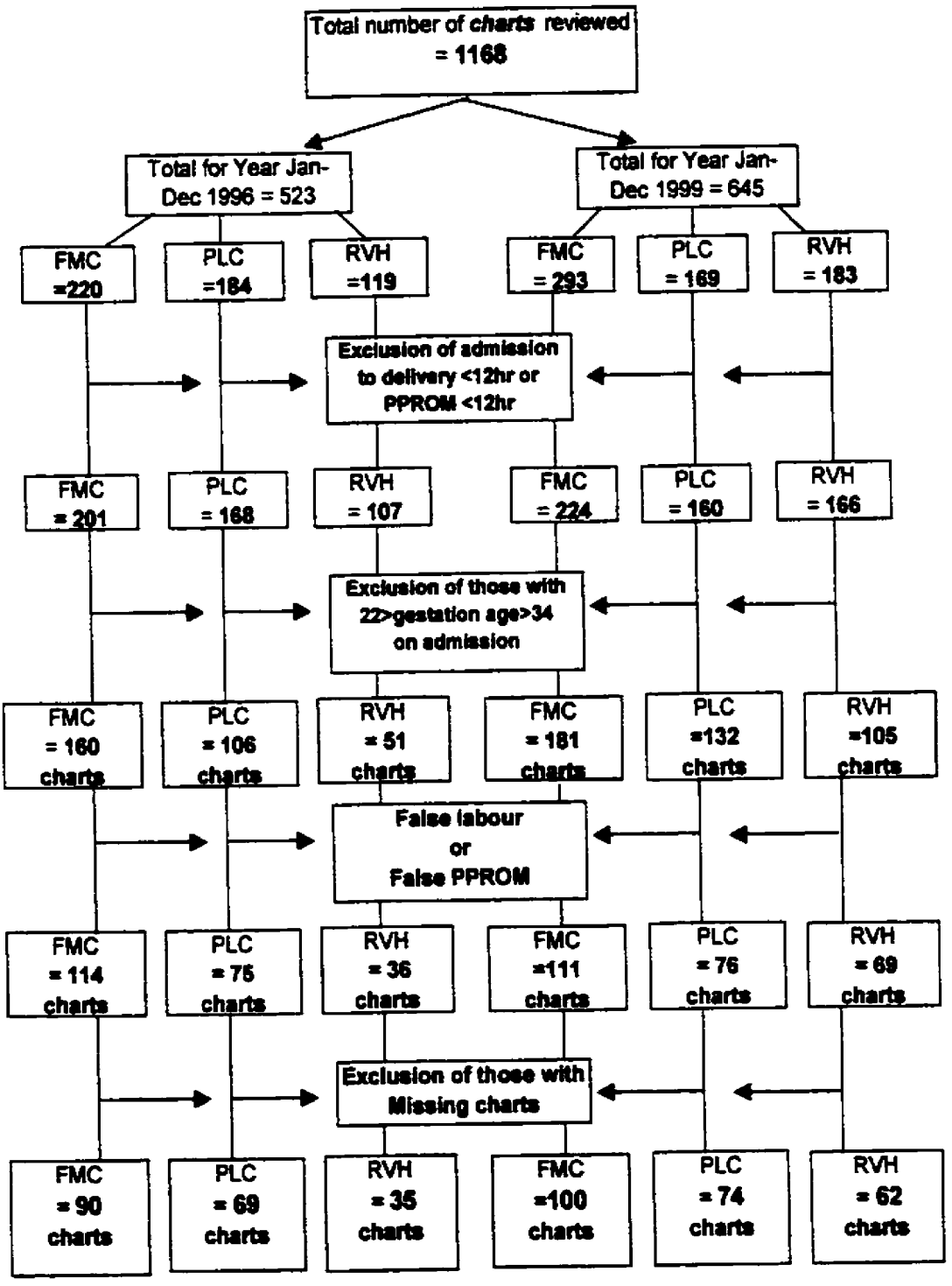
(4) with missing patients' records.

A total of 430 women, 194 from the year 1996 and 236 from the year 1999, met all the inclusion criteria and data was collected from their charts (Figure 4.2). The final sample size for each hospital for each year was as follow: 90 women from FMC, 69 from PLC and 35 from RGH during the year 1996 and, 100 women from FMC, 74 from PLC and 62 from RGH during the year 1999 (Table 4.1).

Table 4.1 Total Sample Size: Number of Eligible Women at Each Site

SITE	1996 (n)	1999 (n)
FMC	90	100
PLC	69	74
RGH	35	62
Total	194	236

Figure 4.2 Flow Chart of the Sample Selection from Reviewed Patients' Records



4.1.2 Missing Data

The following variables, used in the chapter four and five, had missing observations:

1. Neonatal Birth weight
   - 0 missing in 1996
   - 9 missing in 1999

2. Five minute Apgar score
   - 1 missing in 1996
   - 2 missing in 1999

3. Delivery mode
   - 2 missing in 1996
   - 0 missing in 1999

4. History of Infection during pregnancy
   - 64 missing in 1996
   - 165 missing in 1999

5. Reason for antibiotic use in hospital
   - 37 missing in 1996
   - 28 missing in 1999

4.2 Comparison of Site Specific Results in 1996: Socio-Demographic, Obstetric and Neonatal Characteristics

In the following section the socio-demographic, obstetric, and neonatal characteristics of women admitted to FMC, PLC or RGH for preterm labour or preterm premature rupture of membrane from January 1st to December 31st 1996 are compared using chi-square test for categorical variables and ANOVA for continuous variables.

4.2.1 Comparison of the Three Hospitals in 1996: Socio-Demographic Characteristics

Tables 4.2a and 4.2b describe the socio-demographic characteristics of women who met the inclusion criteria for 1996. Maternal age of the women from the three sites had both normal distributions and equal variance. As such, ANOVA was used to

compare these sites. The mean maternal age of women at RGH was 29.4 years compared to 26.8 years at PLC and 26.4 years at FMC. This difference was statistically but not clinically significant amongst the three sites.

At FMC, 27.8% of women admitted for PTL or PPROM resided outside the city of Calgary compared to only 7.2% and 5.7% at PLC and RGH respectively ($p<0.001$) (Table 4.2b).

Alcohol consumption during pregnancy was found to be significantly higher among those women admitted to PLC compared with the other two sites (23.2% vs. 6.7% at FMC and 2.9% at RGH; $p<0.001$). Thirty-one women (31%) at FMC, 26 (37.8%) at PLC, and 11 women (31.4%) at RGH smoked during their pregnancy. There was no significant difference in prevalence of smoking during pregnancy among the three sites (Table 4.2b).

Table 4.2 Comparison of Socio-Demographic Characteristics of Women at the Three Sites in 1996.

a) Continuous Variables:*

VARIABLES	FMC n=90 mean ±(95% CI)	PLC n=69 mean ±(95% CI)	RGH n=35 mean ±(95% CI)	*p* value
Age (years)	26.4 (25.2 to 27.8)	26.8 (25.3 to 28.3)	29.4 (27.1 to 31.7)	0.05

*ANOVA was used for comparison

Table 4.2 Continued

b) Categorical Variables:**

VARIABLES	FMC n=90 n (%)	PLC n=69 n (%)	RGH n=35 n (%)	*p* value
City of Residence				
Calgary	65 (72.2)	64 (92.8)	33 (94.4)	
Outside Calgary	25 (27.8)	5 (7.2)	2 (5.7)	<0.001
Smoking				
Yes	28 (31.1)	26 (37.8)	11 (31.4)	
No	57 (63.3)	40 (57.9)	23 (65.7)	0.87
Quit, before pregnancy	5 (5.6)	3 (4.3)	1 (2.9)	
Alcohol Consumption				
Yes	6 (6.7)	16 (23.2)	1 (2.9)	
No	84 (93.3)	53 (76.8)	34 (97.1)	0.001

** $\chi 2$ test was used for comparison

4.2.2 Comparison of the Three Hospitals in 1996: Obstetric Characteristics

Tables 4.3a and 4.3b describe the obstetric characteristics of women who were admitted to any of the three sites for PTL or PPROM during 1996. The mean gestation age of women on admission was very similar between FMC and PLC (29.6 and 29.7 weeks respectively). However, the mean gestational age on admission to RGH was 31.0 weeks (p=0.052). The box-plots of the distribution of gestation age on first admission of women admitted to the three sites are shown in Figure 4.3. The distribution at RGH was much more skewed than the other two sites. In fact, a closer look at the RGH data revealed that this skewness was due to two observations (women) with admission gestation ages of 23.0 and 23.1 weeks. Not including these two observations, gestation age on first admission at RGH would range from 28.0 to 34.0 weeks with a mean of 31.4 weeks (Figure 4.3).

In addition, the average total length of hospital stay (total inpatient days from first admission to delivery) for women admitted to FMC was longer than for women admitted to PLC or RGH (P<0.001).

Twenty-six women (28.9%) admitted to FMC had history of preterm birth. This number was significantly higher than the 11.6% at PLC and 11.5% at RGH (p=0.02). At all sites, a greater proportion of women were admitted for preterm labour than for PPROM, however, FMC had the most admissions due to PPROM than PLC and RGH (28.9% compared to 15.9% and 25.7% respectively). Sixty four women (71.1%) were admitted for PTL at FMC, of these 64 women 1 was admitted for PTL on first admission but on subsequent admissions had PPROM >12hr. Similarly, of the 58 (84.1%) and 24 (74.3%) women admitted for PTL, at PLC and RGH respectively, 5 and 1 had PPROM >12hr on subsequent admission. As the number of women who were originally admitted for PTL but later developed PPROM was relatively small at each site, hereafter, for the purposes of further analysis, they were included in the PTL group.

Table 4.3 Comparison of Obstetric Characteristic of Women at the Three Sites in 1996

a) Continuous Variables:*

VARIABLES	FMC n=90 mean ±(95% CI)	PLC n=69 mean ±(95% CI)	RGH n=35 mean ±(95% CI)	*p* value
Gestational Age on Admission (weeks)	29.6 (29.0 to 30.1)	29.7 (29.0 to 30.4)	31.0 (30.0 to 31.9)	0.052
Total Length of Hospital Stay (days)	5.5 (4.5 to 6.7)	3.4 (2.9 to 3.4)	4.0 (3.3 to 4.7)	<0.001

*ANOVA was used for comparison

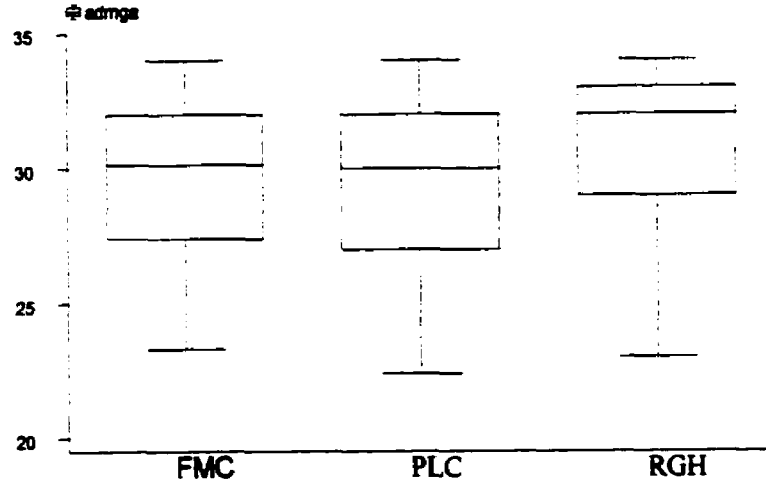
Table 4.3 Continued

b) Categorical Variables:**

VARIABLES	FMC n =90 n (%)	PLC n =69 n (%)	RGH n =35 n (%)	*p* value
Previous Preterm Birth				
Yes	26 (28.9)	8 (11.6)	4(11.5)	
No	50 (55.5)	44 (63.8)	20 (57.1)	0.024
No, First child	14 (15.6)	17 (24.6)	11(31.4)	
Admission Reason				
PTL				
-PTL with no PPROM	63 (70.0)	53 (76.8)	25 (71.4)	
-PTL with PPROM	1 (1.1)	5 (7.2)	1 (2.9)	0.16
PPROM	26 (28.9)	11 (15.9)	9 (25.7)	

** $\chi 2$ test was used for comparison

Figure 4.3 Box-plots for the Distribution of Gestation Age on Admission at Each Site in 1996



4.2.3 Comparison of the Three Hospitals in 1996: Antibiotic Use and History of Infection During Pregnancy

Table 4.4 shows the antibiotic use of women during their pregnancy both before admission to the hospital and during their hospital stay for PTL or PPROM in 1996. At RGH, 25.7% of these women were reported to have used antibiotics during their

pregnancy before admission to the hospital, which is not significantly different from 17.8% of women at FMC and 18.8% at RGH (p=0.59).

In 1996, 33.0% of women at FMC, 24.6% at PLC and 28.6% at RGH received antepartum antibiotics during their admissions to the hospital for PTL or PPROM (p=0.49). Antibiotics were used for a variety of reasons. In the majority of cases, no reason was stated or could be found in the chart for prescribing antibiotics during hospital stay (Table 4.4).

However, among those who did receive antibiotics, the most common reason was to treat urinary tract infection (13.3% at FMC, 41.2% at PLC and 20.0% at RGH). Only one patient at FMC and one patient at RGH had prolongation of pregnancy stated in the chart as the main reason for prescribing antibiotics.

History of infection prior to admission was also recorded from the patient charts. It was determined that 38.9% of women admitted to FMC, 43.5% admitted to PLC and 20.0% of those at RGH admitted for PTL or PPROM had a history of infection during pregnancy (Table 4.5).

The types of infection during pregnancy included bladder infection, bacterial vaginosis (BV), UTI, yeast infection, chlamydia and Group B Streptococcus GBS (Table 4.5).

Table 4.4 Comparison of Antibiotic Use During Pregnancy of Women Admitted to the Three Hospitals for PTL or PPROM in 1996.

Categorical variables:**

VARIABLES	FMC n=90 n (%)	PLC n=69 n (%)	RGH n =35 n (%)	*p* value
Antibiotic use Prior to admission				
Yes	16 (17.8)	13 (18.8)	9 (25.7)	
No	74 (82.2)	56 (81.2)	26 (74.3)	0.59
Antepartum antibiotics use in Hospital				
Yes	30 (33.3)	17 (24.6)	10 (28.6)	
No	60 (66.7)	52 (75.4)	25 (71.4)	0.49
Reason for Antibiotic use in hospital				
Prolongation	1 (3.3)	0 (0.0)	1 (10.0)	
UTI	4 (13.3)	7 (41.2)	2 (20.0)	
High Temperature	1 (3.3)	0 (0.0)	1 (10.0)	
Unknown	23 (76.7)	9 (52.9)	5 (50.0)	0.32
Others	1 (3.3)	1 (5.9)	1 (10.0)	

** $\chi 2$ test was used for comparison

Table 4.5 Comparison of History of Infection During Pregnancy of Women Admitted to the Three Hospitals for PTL or PPROM in 1996.

VARIABLES	FMC n=90 n (%)	PLC n=69 n (%)	RGH n=35 n (%)
Women with history of Infection prior to admission			
Yes*	35 (38.9)	30 (43.5)	7 (20.0)
No	31 (34.4)	21 (30.4)	6 (17.1)
Unknown	24 (26.7)	18 (26.1)	22 (34.3)
***Infections prior to hospital admission**			
Bladder	10	11	1
BV	2	1	0
Chlamydia	0	4	0
GBS	1	2	0
UTI	23	19	4
Yeast	4	3	0
Others**	11	7	2

(**sinusitis, sore throat, dental abscess, upper respiratory tract infection, tonsillitis)

A large number of the women at each hospital did not have any information regarding the "history of infection" in their charts and, therefore, the percentage of missing (unknown) data for this variable was very high (Table 4.5). To determine the influence of the "Unknown" category in testing for existence of significant difference among the three sites, ANOVA was used with the "Unknown" category included in the comparison ($p=0.001$). This statistically significant result is not meaningful as it is partly based on a category (i.e. "Unknown") that could also belong either to the "Yes" or to the "No" category of the variable "history of infection".

To resolve this problem, one solution was to assume that the reason for not mentioning history of infections in some of the charts, was because those women did not have any infection during their pregnancy. In this case, all "Unknown" history of infection could be included in the "No" history of infection category. With this assumption, a statistically significant difference between the two groups with a p-value of 0.052 was observed.

On the other hand, if it was assumed that all those with "Unknown" history of infection in fact did have infection but was not recorded, no statistically significant difference ($p=0.163$), was observed between the two groups. Hence, depending on which assumption was used, statistically significant differences was observed in one scenario and no significant difference in the other.

Therefore, due to inadequate information and a large number of unknown observations, the variable "history of infection" was not considered reliable. Thus, it was not possible to draw any meaningful conclusion about the history of infection during pregnancy for those women admitted during the year 1996.

4.2.4 Comparison of the Three Hospitals in 1996: Microbiologic Findings

The results of laboratory cultures and sensitivities taken from women admitted in 1996 for PTL or PPROM are shown in Table 4.6. Most women were not tested.

For *Chlamydia trachomatis*, 90% of women at FMC, 85.5% at PLC and 82.6% of women at RGH were not cultured. However, of those who were tested at PLC, 1 of 10 was positive for *Chlamydia trachomatis*. At both RGH and FMC, none of the tested women were positive for *Chlamydia trachomatis* .

At FMC, 16 women were cultured for bacterial vaginosis, only 1 (6.3%) was positive. Similarly, 3 (18.8%) of 16 women who were tested at PLC and 2 (40.0%) of 5 women tested at RGH were positive for bacterial vaginosis. There were no cases of *Neisseria gonorrhoeae* at any of the sites. At PLC, only one of 12 women tested for *Trichomonas vaginalis* was positive. At the other two hospitals, none of the women tested for *Trichomonas vaginalis* were positive (Table 4.6).

For Group B Streptococcus (GBS), 5 (20.0%) of 25 women tested were positive at FMC. At PLC three (50.0%) of the six women and 2 (15.4%) of the 13 women cultured at RGH tested positive.

Urine cultures were done on 50 women (55.5%) at FMC, 33 (47.8%) at PLC and 17 women (48.6%) at RGH. Of those tested, microorganisms were isolated from urine sample of 14 (28.0%), 26 (78.8%) and 9 (53.0%) women from FMC, PLC and RGH, respectively. The microorganisms isolated are shown in Table 4.6. These cultures were positive for gram-negative organisms such as E. Coli and *P. auroginosa* as well as gram-positive organisms such as coagulase-negative staphylococci (CNS), Enterococci and Lactobacillus sp. Some cultures grew multiple gram-positive cocci.

Table 4.6 Microbiologic Findings for Women Admitted to the Three Hospitals for PTL or PPROM during the year 1996.

VARIABLES	FMC n=90	PLC n=69	RGH n=35
Chlamydia trachomatis			
Tested, positive, *n*	0	1	0
Tested, negative, *n*	9	9	6
Not tested, *n (%)*	81 (90.0)	59 (85.5)	29 (82.9)
Bacterial Vaginosis			
Tested, positive, *n*	1	3	2
Tested, negative, *n*	15	13	3
Not tested, *n(%)*	74 (82.2)	53 (76.8)	30 (86.0)
Yeast sp.			
Tested, positive, *n*	0	1	1
Tested, negative, *n*	15	16	3
Not tested, *n(%)*	75 (83.3)	52 (75.4)	31 (88.6)
Trichomonas vaginalis			
Tested, positive, *n*	0	1	0
Tested, negative, *n*	14	11	2
Not tested, *n(%)*	76 (84.5)	57 (86.1)	33 (94.3)
Group B streptococcus			
Tested, positive, *n*	5	3	2
Tested, negative, *n*	20	3	11
Not tested, *n(%)*	65 (72.2)	62 (89.9)	22 (62.9)
Neisseria gonorrhoeae			
Tested, positive, *n*	0	0	0
Tested, negative, *n*	3	6	2
Not tested, *n(%)*	87 (96.7)	63 (91.3)	33 (94.3)
Urine cultures			
Tested, positive, *n*	14	26	9
Tested, negative, *n*	36	7	8
Not tested, *n(%)*	40 (44.5)	36 (52.2)	18 (51.4)
Organisms isolated from Urine cultures			
CNS, *n(%)*	2 (14.3)	3 (11.5)	3 (33.3)
E. Coli, *n(%)*	1 (7.1)	0 (0.0)	0 (0.0)
Lactobacillus sp., n(%)	9 (64.3)	1 (3.8)	1 (11.1)
P. auroginosa, n(%)	0 (0.0)	1 (3.8)	0 (0.0)
Candida albicans, n(%)	0 (0.0)	1 (3.8)	0 (0.0)
Multiple gram positives, *n(%)*	2 (14.3)	19 (73.1)	4 (44.4)
Enterococcus, *n(%)*	0 (0.0)	1 (3.8)	1 (11.1)

From a microbiological pint of view, when pathogenic microorganisms are present, urinary tract infection (UTI) exists (Fauci et al. 1998). However, some of the organisms found in this study, such as multiple gram-positives, are usually due to contamination of the urine culture. The other organisms, such as *Lactobacillus sp.*, do not commonly cause UTI.

4.2.5 Comparison of the Three Hospitals in 1996: Neonatal outcome

The neonatal outcome for women admitted at each hospital is summarized in Tables 4.7a and 4.7b. Only those neonates whose mothers had a delivery record available in their charts, at the same hospital that they were admitted for PPROM or PTL, were included. Those with delivery records elsewhere (outside the CRHA region, or at a different hospital than the one at which the mother had her PTL or PPROM admissions and care) are not included in Table 4.7a and 4.7b.

Even though the mean gestation age on first admission of mothers admitted to FMC (29.6 weeks) and PLC (29.7 weeks) were very similar (Table 4.3a), gestation age of the neonates, at birth, was significantly different at FMC compared to neonates at PLC and RGH (35.3 vs. 37.5 and 37.0 weeks respectively; $p<0.001$).

Birth weight, used as a health indicator for neonates, was significantly different among the three sites ($p=0.01$) with FMC neonates having the smallest mean birth weight (2596.5 g) and PLC neonates the largest mean birth weight (2987.6g). More than half (58.5%) of neonates born at FMC stayed in NICU during their hospital stay compared to 34.4% of those born at PLC and 38.2% of those born at RGH ($p=0.01$).

Birth weight was divided into three categories based on the clinical definitions for birth weight. According to the World Health Organization, infants born with less than 1500g are referred to as Very Low Birth Weight (VLBW) infants. Low birth weight infants (LBW) are defined as infants who are born weighing less than 2500g. (Health Services Delivery Highlights, CRHA 1998) and those with birth weight greater than 2500g are considered to have adequate birth weight. When divided into these categories, there was a clinically and statistically significant difference among the hospital sites. At FMC, 12.3% of all the babies in this study had VLBW compared to none at PLC and RGH. At FMC, only 55.4% of babies had birth weight greater than 2500g. compared to 76.6% at PLC and 73.5% at RVH.

There were no significant differences in gender, five-minute Apgar score, or delivery mode among the three hospitals (Table 4.7b).

Table 4.7. Comparison of Neonatal Outcome of Babies Born to Women Admitted to the Hospital for PTL or PPROM in 1996.

a) Continuous variables:*

VARIABLES	FMC n=65 mean ± (95% CI)	PLC n=64 mean ± (95% CI)	RGH n=34 mean ± (95% CI)	*p-value*
Gestation age at birth (weeks)	35.3 (34.3 to 36.3)	37.5 (36.9 to 38.1)	37.0 (36.0 to 38.0)	<0.001
Birth Weight (g)	2596.5 (2372.2 to 2820.9)	2987.6 (2825.1 to 3150.2)	2925.0 (2702.9 to 3147.3)	0.01

* ANOVA was used for comparison

b) Categorical variables: **

VARIABLES	FMC n=65 n (%)	PLC n=64 n (%)	RGH n=34 n (%)	*p-value*
Gender				
Male	43 (66.2)	30 (46.9)	20 (58.8)	0.08
Female	22 (33.9)	34 (53.1)	14 (41.2)	
Delivery mode				
Vaginal Delivery	54 (85.7)	57 (89.1)	31 (91.2)	0.72
Cesarean Delivery	9 (14.3)	7 (10.9)	3 (8.8)	
5 min Apgar score				
<7	3 (4.6)	1 (1.6)	1 (2.9)	0.64
≥7	62 (95.4)	62 (98.4)	33 (97.1)	
NICU stay				
Yes	38 (58.5)	22 (34.4)	13 (38.2)	
No	27 (38.5)	42 (65.6)	21 (61.8)	0.01
Birth Weight (g)				
≤1500	8 (12.3)	0 (0.0)	0 (0.0)	
1501-2500	21 (32.3)	15 (23.4)	9 (26.5)	0.004
≥2501	36 (55.4)	49 (76.6)	25 (73.5)	

** $\chi 2$ test used for comparison

4.3 Comparison of Site Specific Results in 1999: Socio-Demographic, Obstetric, and Neonatal Characteristics

In the following section the socio-demographic, obstetric, and neonatal characteristics of women admitted to FMC, PLC or RGH for preterm labour or preterm premature rupture of membrane during January 1st to December 31st 1999 are compared using chi-square test for categorical variables and ANOVA for continuous variables.

4.3.1 Comparison of the Three Hospitals in 1999: Socio-Demographic Characteristics

Tables 4.8a and 4.8b describe the characteristics of women who met the inclusion criteria for 1999. Maternal age of women admitted to the three sites had both normal distribution and equal variance. Therefore, ANOVA was used to compare these sites. The mean maternal age of women at FMC was 27.3 years compared to 26.6 years at PLC and 28.1 years at RGH and there was no statistically significant difference amongst the three sites (p=0.31).

Fourteen women (14%) at PLC consumed alcohol during their pregnancy compared to 4 (5.4%) at PLC and 3 (4.8%) at RGH (p=0.21). Though not significant, smoking during pregnancy for women admitted to FMC was 38.0% compared to 31.1% at PLC and 24.2% of women admitted to RGH.

In addition, 36 (36%) women admitted to FMC were living outside of Calgary but were transferred to Calgary for their care, compared to 5 (6.8%) women at PLC and 3 (4.8%) at RGH.

Table 4.8 Comparison of the Socio-Demographic Characteristics of Women at the Three Sites in 1999.

a) Continuous Variables:*

VARIABLES	FMC n=100 mean ±(95% CI)	PLC n=74 mean ±(95% CI)	RGH n=62 mean ±(95% CI)	*p* value
Age (years)	27.3 (26.1 to 28.5)	26.6 (25.3 to 27.9)	28.1 (26.7 to 29.5)	0.31

* ANOVA was used for comparison

b) Categorical Variables:**

VARIABLES	FMC n=100 n (%)	PLC n=74 n (%)	RGH n=62 n (%)	*p* value
City of residence				
Calgary	64 (64.0)	69 (93.2)	59 (95.2)	<0.001
Outside Calgary	36 (36.0)	5 (6.8)	3 (4.8)	
Smoking				
Yes	38 (38.0)	23 (31.1)	15 (24.2)	
No	61 (61.0)	47 (63.5)	46 (74.2)	0.20
Quit, before pregnancy	1 (1.0)	4 (5.4)	1 (1.6)	
Alcohol Consumption				
Yes	14 (14.0)	4 (5.4)	3 (4.8)	0.21
No	86 (86.0)	70 (94.6)	59 (95.2)	

** $\chi 2$ test used for comparison

4.3.2 Comparison of the Three Hospitals in 1999: Obstetric Characteristics

Tables 4.9a and 4.9b describe the obstetric characteristics of women who were admitted to any of the three sites for PTL or PPROM during the year 1999. The mean gestation age on first admission was significantly different amongst the three sites with FMC having the lowest gestation age of 28.7 weeks compared to 30.0 weeks at PLC and 30.2 weeks at RGH (p=0.001). This statistically significant difference revealed the existence of a relationship between admission gestation age and admission site. In other words, women admitted to FMC was more likely to have lower gestation age on admission compared to PLC and RGH.

At all sites more women were admitted for PTL than for PPROM; however, FMC had the largest number of admissions due to PPROM. Forty two percent (42.0%) of women admitted to FMC, compared to 20.3% at PLC and 17.7% at RGH, were admitted with diagnosis of PPROM on their first admission ($p=0.001$). Therefore, there appeared to be a relationship between site of admission and PPROM as the admission diagnosis. Fifty-two women (52.0%) were admitted for PTL at FMC, of these 52 women 5 were admitted for PTL on admission but on subsequent admissions had PPROM >12hr. Similarly, of the 58 (78.4%) and 51 (82.3) women admitted for PTL, at PLC and RGH respectively, 3 and 0 had PPROM >12hr on subsequent admission. As the number of women originally admitted for PTL but later having developed PPROM is relatively small at each site, hereafter, for the purposes of further analysis, they are included in the PTL group.

Eighteen women (18.0%) admitted to FMC had a history of previous preterm birth delivery compared with 11(4.9%) at PLC and 8 (13.1%) at RGH. However, this difference was not significant ($p=0.79$).

In addition, the mean total length of hospital stay (total inpatient days from first admission to delivery) of women admitted to FMC was significantly longer than for those admitted to PLC or RGH (6.1 days vs. 4.9 and 4.0 days respectively; $p<0.001$).

Table 4.9 Comparison of Obstetric Characteristics at the Three Sites in 1999

a) Continuous Variables:*

VARIABLES	FMC n=100 mean ±(95% CI)	PLC n=74 mean ±(95% CI)	RGH n=62 mean ±(95% CI)	*p* value
Gestational Age on Admission (weeks)	28.7 (28.2 to 29.5)	30.0 (29.3 to 30.7)	30.2 (29.4 to 31.0)	0.01
Total Length of Hospital Stay (days)	6.1 (5.2 to 7.2)	4.9 (4.2 to 5.6)	4.0 (349 to 4.6)	<0.001

*ANOVA was used for comparison

b) Categorical Variables:**

VARIABLES	FMC n=100 n (%)	PLC n=74 n (%)	RGH n=62 n (%)	*p* value
Previous Preterm Birth				
Yes	18 (18.0)	11 (14.9)	8(13.1)	
No	53 (53.0)	39 (52.7)	37 (60.7)	0.79
No, First child	29 (29.0)	24 (32.4)	16 (26.2)	
Admission Reason				
PTL				
-PTL with no PPROM	47 (47.0)	55 (74.3)	51 (82.3)	0.001
-PTL with PPROM	5 (5.0)	3 (4.1)	0 (0.0)	
PPROM	48 (48.0)	16 (21.6)	11 (17.7)	

** $\chi 2$ test was used for comparison

4.3.3 Comparison of the Three Hospitals in 1999: Antibiotic Use and History of Infection During Pregnancy

Table 4.10 describes antibiotic use by women during their pregnancy both before admission to the hospital and during their hospital stay for PTL or PPROM in 1999. Based on the information available in the patient's charts, 20.0% of women admitted to FMC used antibiotics during their pregnancy before admission to the hospital compared to 9.5% of women at PLC and 9.7% at RGH (p=0.07).

In 1999, 51.0% of women admitted to FMC for PTL or PPROM received antepartum antibiotics during their hospital stay. This was significantly (both clinically

and statistically) higher than the percentage of women who received antepartum antibiotics during their admission at PLC and RGH (33.8% and 35.5% respectively; p=0.03).

Antibiotics were used for a variety of reasons. The reasons for antibiotic use were collected using the information in progress notes or physician's notes. For the majority of cases, no reason was stated or could be found in the chart for prescribing antibiotics during the hospital stay. However, among those who did receive antibiotics, the most common reason was for prolongation of pregnancy for women admitted to FMC (76.5%) and RGH (31.8%) and for treating urinary tract infection for those admitted to PLC (36.0%).

History of infection prior to admission was also recorded from patient's charts. Twenty six percent (26%) of women admitted to FMC, 23.0% of those admitted to PLC and 30.0% of those admitted to RGH had a history of infection during pregnancy (Table 4.11). The infections during pregnancy included bladder infection, bacterial vaginosis (BV), urinary tract infection (UTI), yeast infection, chlamydia and GBS. The frequencies are shown in Table 4.11.

Table 4.10 Comparison of Antibiotic Use During Pregnancy of Women Admitted to the Hospital for PTL or PPROM in 1999.

Categorical variable:**

VARIABLES	FMC n=100 n (%)	PLC n=74 n (%)	RGH n=62 n (%)	*p* value
Antibiotic use Prior to admission				
Yes	20 (20.0)	7 (9.5)	6 (9.7)	0.07
No	80 (80.0)	67 (90.5)	56 (90.3)	
Antepartum antibiotics use in Hospital				
Yes	51 (51.0)	25 (33.8)	22 (35.5)	0.03
No	49 (49.0)	49 (66.2)	40 (64.5)	
Reason for Antibiotic use in hospital				
Prolongation	39 (76.5)	7 (28.0)	7 (31.8)	
UTI	4 (7.8)	9 (36.0)	3 (13.6)	
Unknown	7 (13.7)	9 (36.0)	12 (54.6)	
Others	1 (2.0)	0 (0.0)	0 (0.0)	

**$\chi 2$ test was used for comparison

Table 4.11 Comparison of History of Infection During Pregnancy of Women Admitted to the Hospital for PTL or PPROM in 1999.

VARIABLES	FMC n=100	PLC n=74	RGH n=62
Women with history of Infection prior to admission			
Yes*	26 (26.0)	17 (23.0)	13 (30.0)
No	9 (9.0)	4 (5.4)	2 (3.2)
Unknown	65 (65.0)	53 (71.6)	47 (75.8)
***Infections prior to hospital admission**			
Bladder	3	3	0
BV	1	0	0
Chlamydia	5	0	0
GBS	1	0	0
UTI	11	15	8
Yeast	4	0	0
Others	6	2	5

Some women had more than one infection

However, a large number of women at each site did not have any information on "history of infection" in their charts and, therefore, the percentage of missing (unknown) data for this variable was very high. To determine the influence of the "Unknown" category in testing for the existence of any significant difference among the three sites, ANOVA was used with the "Unknown" included in the comparison. The results did not show any statistically significant difference among the three sites ($p=0.52$).

Given the assumption that all of the women with "Unknown" history of infection did not have any infection, all observations in the "Unknown" category were assumed to be in the "No" history of infection category. In this case no significant difference was observed in history of infection among the three sites ($p=0.75$)

Similarly, if it was assumed that all those with "Unknown" history of infection in fact did have a history of infection, it was observed that there would be no statistically significant difference among the three sites in history of infection during pregnancy ($p=0.32$).

Therefore, we can conclude that even if the information on history of infection was available on all patients, whether all belonged to the "Yes" or "No" category, there would be no significant difference amongst the three sites. In other words, no evidence for a relationship between admission site and history of infection during pregnancy was found.

4.3.4. Comparison of the Three Hospitals in 1999: Microbiologic Findings

The results of laboratory cultures and sensitivities taken from women admitted for PTL or PPROM during 1999 are shown in Table 4.12. Most women were not tested for any of the following infections or microorganisms.

For *Chlamydia trachomatis*, 84.0% of women at FMC, 71.6% at PLC and 67.7% of women at RGH were not cultured. However, of those who were tested at FMC, only one of 16 women was positive for *Chlamydia trachomatis*. Both at RGH and PLC, none of the women tested positive.

There was only one woman at each site who tested positive for bacterial vaginosis of all those who were tested. There were no cases of positive *Neisseria gonorrhoeae* or *Trichomonas vaginalis* at any of the three sites, in women who were tested for these microorganisms.

For Group B Streptococcus, 3 (15.8%) of the 19 women tested were culture positive at FMC. At PLC, 4 (16.7%) of the 24 women and 3 (8.8%) of the 34 women cultured at RGH had positive results.

Furthermore, urine cultures were done for 48 women (48.0%) at FMC, 39 (52.7%) at PLC and 34 women (54.8%) at RGH. Of all those tested, microorganisms were isolated in 18 (37.5%), 21 (53.8%) and 14 (41.2%) of women from FMC, PLC and RGH respectively. The microorganisms isolated are shown in Table 4.12.

Table 4.12 Microbiologic Findings For Women Admitted to the Hospital for PTL or PPROM During the Year 1999.

VARIABLES	FMC n=100	PLC n=74	RGH n=62
Chlamydia trachomatis			
Tested, positive, *n*	1	0	0
Tested, negative, *n*	15	21	20
Not tested, *n(%)*	84 (84.0)	53 (71.6)	42 (67.7)
Bacterial Vaginosis			
Tested, positive, *n*	1	1	1
Tested, negative, *n*	13	17	14
Not tested, *n(%)*	86 (86.0)	56 (75.6)	47 (75.8)
Yeast sp.			
Tested, positive, *n*	2	0	2
Tested, negative, *n*	10	20	13
Not tested, *n(%)*	88 (88.0)	54 (73.0)	47 (75.8)
Trichomonas vaginalis			
Tested, positive, *n*	0	0	0
Tested, negative, *n*	3	3	2
Not tested, *n(%)*	97 (97.0)	71(96.0)	60 (96.8)
Group B streptococcus			
Tested, positive, *n*	3	4	3
Tested, negative, *n*	16	20	31
Not tested, *n(%)*	81 (81.0)	50 (67.6)	28 (45.2)
Neisseria gonorrhoeae			
Tested, positive, *n*	0	0	0
Tested, negative, *n*	10	18	10
Not tested, *n(%)*	90 (90.0)	56 (56.0)	52 (52.0)
Urine cultures			
Tested, positive, *n*	18	21	14
Tested, negative, *n*	30	18	20
Not tested, *n(%)*	52 (52.0)	35 (47.3)	28 (45.2)
Organisms isolated from Urine cultures			
CNS, *n*	0 (0.0)	1 (4.8)	1 (7.1)
E. Coli, *n*	0 (0.0)	0 (0.0)	1 (7.1)
Lactobacillus sp., n	3 (16.7)	3 (14.2)	1 (7.1)
P. auroginosa, n	0 (0.0)	0 (0.0)	0 (0.0)
Candida albicans, n	1 (5.6)	0 (0.0)	0 (0.0)
Multiple gram positives, *n*	15 (83.3)	16 (76.2)	11 (78.6)
Enterococcus, *n*	0 (0.0)	1 (4.8)	0 (0.0)

4.3.5 Comparison of the Three Hospitals in 1999: Neonatal Outcome

The neonatal outcome at each site is summarized in Tables 4.13a and 4.13b. Only those neonates whose mother had a delivery record available in their charts at the same hospital in which they were admitted for PPROM or PTL are included. Those with delivery records elsewhere (outside the CRHA region, or at a different hospital than the one at which the mother had her PTL or PPROM admissions and care) are not included in this table.

Gestation age at birth was significantly different among the three sites with the neonates born at FMC having the lowest gestational age at birth compared to PLC and RGH (32.2 vs. 36.2 and 37.5 respectively; $p<0.001$). As shown previously in Table 4.9a, the mothers of the babies born at FMC also had the lowest gestation age on admission (28.7 weeks) compared to PLC and RGH (30.0 and 30.2 weeks, respectively).

Birth weight was significantly different among the three sites ($p=0.01$) with FMC neonates having the smallest birth weight (1959.8 g) and RGH neonates the largest birth weight (3072.5 g). Birth weight was categorized into three different groups based on definitions of Low Birth Weight (LBW) and Very Low Birth Weight (VLBW) babies. According to the World Health Organization, infants born with less than 1500g are referred to as Very Low Birth Weight (VLBW) infants. Low birth weight infants (LBW) are defined as infants who are born weighing less than 2500g. (Health Services Delivery Highlights, CRHA 1998) and those with birth weight greater than 2500g are considered to have adequate birth weight. At FMC, 32.5% of the neonates were in the VLBW category compared to only 3.2% at PLC and 1.8% at FMC. In this study, the majority of the neonates at PLC and RGH were born with birth weight $\geq$ 2501grams. Additionally,

there were significantly more neonates at FMC with 5-minute Apgar score <7 compared to the other two hospitals (p=0.005). Furthermore, 76.5% of neonates at FMC stayed in NICU during their hospital stay compared to 44.4% at PLC and 39.7% at RGH (p=0.01).

However, there were no significant differences in gender or delivery mode amongst the three hospitals.

Table 4.13 Comparison of Neonatal Outcome of Babies Born to Women Admitted to the Hospital for PTL or PPROM in 1999

a) Continuous variables:*

VARIABLES	FMC n=81	PLC n=70	RGH n=58	*p-value*
Gestation age at birth (weeks)	32.2 (31.4 to 33.1)	36.2 (35.5 to 37.0)	37.5 (36.8 to 38.2)	<0.001
Birth Weight (g)	1959.8 (1771.7 to 2148.0)	2766.2 (2581.0 to 2951.4)	3072.5 (2891.8 to 3253.1)	<0.001

* ANOVA was used for comparison

b) Categorical Variables:**

VARIABLES	FMC n=81 n (%)	PLC n=70 n (%)	RGH n=58 n (%)	*p-value*
Gender				
Male	44 (54.3)	42 (60.0)	26 (44.8)	
Female	37 (45.7)	28 (40.0)	32 (55.2)	0.23
Delivery mode				
Vaginal Delivery	68 (83.9)	56 (80.0)	52 (89.7)	
Cesarean Delivery	13 (16.1)	14 (20.0)	6 (10.3)	0.33
5 min Apgar score				
<7	8 (9.9)	0 (0.0)	1 (1.7)	
≥7	71 (87.7)	70 (100.0)	56 (96.6)	0.006
NICU stay				
Yes	62 (76.5)	30 (44.4)	23 (39.7)	<0.001
No	19 (23.5)	40 (55.6)	35 (60.3)	
Birth Weight (g)				
≤1500	26 (32.5)	2 (3.2)	1 (1.8)	
1501-2500	34 (42.5)	20 (31.8)	10 (17.5)	<0.001
≥2501	20 (25.0)	41 (65.1)	46 (80.7)	

** $\chi 2$ test was used for comparison

CHAPTER FIVE: RESULTS - COMPARISON OF SOCIO-DEMOGRAPHIC AND OBSTETRIC CHARACTERISTICS BETWEEN YEARS 1996 AND 1999

5.1 Introduction

In this chapter the total sample size used for the analysis of this section is described and a comparison of the socio-demographic and obstetric characteristics of women admitted for preterm labour or preterm premature rupture of membrane in the CRHA between the years 1996 and 1999 is made. In addition, the frequencies of antepartum antibiotic use, and the types of antibiotics used between the years 1996 and 1999 are compared.

5.1.1 Total sample size

The total number of women from the three sites (FMC, PLC, RGH), who met the inclusion criteria, was **194** in 1996 and **236** in 1999.

5.2 Comparison of the Years 1996 and 1999: Socio-Demographic, Obstetric and Neonatal Characteristics

In the following section, the characteristics of women admitted to FMC, PLC or RGH for preterm labour (PTL) or preterm premature rupture of membrane (PPROM), from January 1st to December 31st 1996 and January 1st to December 31st 1999, are compared using chi-square test for categorical variables and two-sample t-test for continuous variables.

5.2.1 Comparison of the Years 1996 and 1999: Socio-Demographic Characteristics

Tables 5.1a and 5.1b compare the characteristics of women admitted to hospital for PTL or PPROM with admission gestation age between 22 and 34 weeks, in 1996 and 1999. The overall socio-demographic characteristics were similar in both 1996 and 1999.

Distribution of maternal age on admission was normal for both years. Comparison of the two years did not show any statistically significant difference in the mean maternal age on first admission (27.1 years vs. 27.3 years respectively; p=0.70).

Table 5.1 Comparison of the Socio-Demographic Characteristics of Women Between the Years 1996 and 1999.

a) Continuous Variables:*

VARIABLES	1996 n=194 mean ±(95% CI)	1999 n=236 mean ±(95% CI)	*p* value
Age (years)	27.1 (26.2 to 28.0)	27.3 (26.6 to 28.0)	0.70

*two-sample t-test used for comparison

b) Categorical Variables:**

VARIABLES	1996 n=194 n (%)	1999 n=236 n (%)	*p* value
City of Residence			
Calgary	162 (83.5)	192 (81.4)	0.56
Outside Calgary	32 (16.5)	44 (18.6)	
Smoking			
Yes	65 (33.5)	76 (32.2)	
No	120 (61.9)	154 (65.3)	0.45
Quit, before pregnancy	9 (4.6)	6 (2.5)	
Alcohol			
Yes	23 (11.9)	20 (8.5)	0.25
No	171 (88.1)	216 (91.5)	

** $\chi 2$ test was used for comparison

The overall prevalence of smoking among women admitted for PTL or PPROM was 33.5% in 1996 and 32.2% in 1999. The prevalence of alcohol consumption was 11.9% in 1996 and 8.5% in 1999. Even though the prevalence of alcohol use decreased from 1996 to 1999, this difference was not statistically significant (p=0.25).

5.2.2 Comparison of Years 1996 and 1999: Obstetric Characteristics

Table 5.2a and 5.2b compare the obstetric characteristics of women admitted for PTL or PPROM in the years 1996 and 1999.

The overall mean gestation age on first admission was 29.9 weeks in 1996 compared to 29.6 weeks in 1999 (p=0.28).

In both 1996 and 1999, there were more hospital admissions due to preterm labour than for premature rupture of membrane. Only 23.7% of women admitted in 1996 and 31.8% of women admitted in 1999, had diagnosis of premature rupture of membrane on first admission. However, the overall prpportion of PPROM increased from 23.7% in 1996 to 31.8% in 1999 (p=0.06). In fact, there seemed to be a trend towards increase admission due to PPROM at FMC and PLC from year 1996 to year 1999 (Table 4.3b and 4.9b) with FMC having the higher increase (28.9% in 1996 and 48.0% in 1999).

In addition, the distributions of the total length of hospital stay (total inpatient days from first admission to delivery) for women admitted for PTL or PPROM in 1996 and 1999 were compared. As shown in Figure 5.1 both distributions were asymmetrical (positively skewed). Therefore, the total length of stay (LOS) was transformed using natural log (ln) transformation to normalize the distribution (Figure 5.2). The assumption of normality seemed most valid in ln-transformed data. The mean and 95% confidence

intervals for ln(LOS) in both groups were transformed back to simplify interpretation. The mean length of stay was 4.4 days in 1996 and 5.1 days in 1999 (p=0.04). This difference was not clinically significant.

In 1996, 19.6% of women admitted for PTL or PPROM had a history of preterm birth compared to 15.7% in 1999 (p=0.17). This difference was not statistically significant.

Table 5.2 Comparison of the Obstetric Characteristics of Women Between the Years 1996 and 1999.

a) Continuous Variables:*

VARIABLES	1996 n=194 mean ±(95% CI)	1999 n=236 mean ±(95% CI)	*p* value
Gestational Age on Admission (weeks)	29.9 (29.4 to 30.3)	29.6 (29.2 to 30.0)	0.28
Total Length of Hospital Stay (days)	4.4 (3.9 to 4.9)	5.1 (4.6 to 5.7)	0.04

*two- sample t-test was used for comparison

b) Categorical Variables:**

VARIABLES	1996 n=194 n (%)	1999 n=236 n (%)	*p* value
Previous Preterm Birth			
Yes	38 (19.6)	37 (15.7)	
No	114 (58.8)	130 (55.1)	
No, First child	42 (21.7)	69 (29.2)	0.17
Admission Reason			
PTL	148 (76.3)	161 (68.2)	
PPROM	46 (23.7)	75 (31.8)	0.06

** $\chi 2$ test was used for comparison

Figure 5.1 Histograms for Total Length of Stay

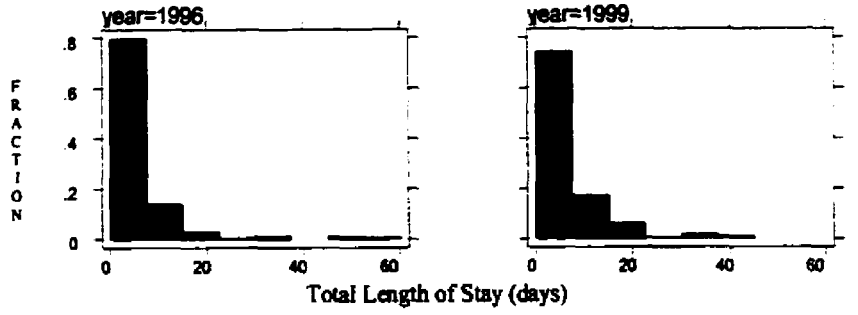
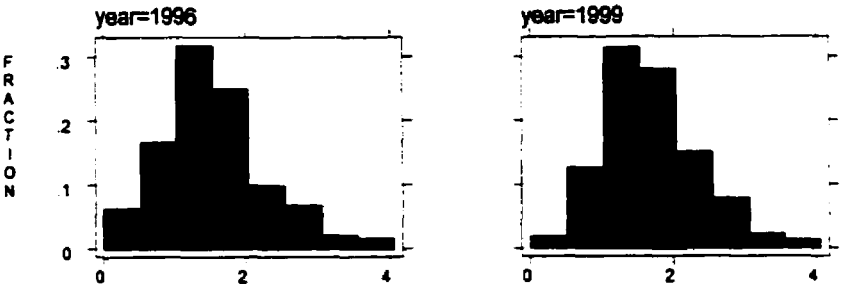


Figure 5.2 Histograms for ln(Total Length of Stay)



5.2.3 Comparison of the Years 1996 and 1999: Antibiotic Use and History of Infection During Pregnancy

The prevalence of antibiotic use prior to admission to hospital for PTL or PPROM was similar between the two groups. In 1996, 19.6% of the women admitted with PTL or PPROM had a history of infection during pregnancy compared to 14.0% of those admitted in 1999 (p=0.12)

To answer the first two objectives of this study, initially, the prevalence of overall antepartum antibiotic use in women admitted to any of the three hospitals in CRHA for PTL or PPROM was compared between the years 1996 and 1999. In 1996, 29.4% of women admitted for either PTL or PPROM received antepartum antibiotics for a variety of reasons. However, in 1999, 41.5% of women received antepartum antibiotics during

their hospital stay (p=0.009). Therefore, there appeared to be evidence of a relationship between the overall use of antepartum antibiotics and the year of admission to hospital.

Although the characteristics of the women admitted to CRHA hospitals in 1996 and 1999 were similar, in 1999, significantly more women were given antepartum antibiotics during their hospital stay for PTL or PPROM than those admitted in 1996 (Table 5.3).

Table 5.3 Comparison of Antibiotic use During Pregnancy for Women Admitted to the Hospital for PTL or PPROM Between the Years 1996 and 1999.

Categorical variables:**

VARIABLES	1996 n=194 n (%)	1999 n=236 n (%)	*P* value
Antibiotic use Prior to admission			
Yes	38 (19.6)	33 (14.0)	0.12
No	156 (80.4)	203 (86.0)	
Antepartum Antibiotic use in Hospital			
Yes*	57 (29.4)	98 (41.5)	0.009
No	137 (70.6)	138 (58.5)	
***Reason for Antibiotic use in hospital**			
Prolongation	2 (3.4)	53 (54.1)	
UTI	14 (23.7)	16 (16.3)	
High Temperature	2 (3.4)	0 (0.0)	<0.001
Unknown	38 (64.4)	28 (28.6)	
Others	3 (5.1)	1 (1.2)	

**$\chi 2$ test was used for comparison

The site-specific results in section 4.2 were assessed to determine whether antepartum antibiotic use was associated with site of admission. In 1996, even though FMC had the highest frequency of antepartum antibiotic use, the difference was not significantly different among the three sites (Table 4.4). On the other hand, in 1999,

frequency of antepartum antibiotic use was significantly higher at FMC compare to other two sites. Therefore, there seemed to be an association between the site at which the patient was admitted and antepartum antibiotic use. In other words, women admitted to FMC were more likely to receive antepartum antibiotics than those admitted to PLC or RGH (Table 4.10).

To further investigate the potential effect of admission site on the association between year of admission and antibiotic use, stratified analysis was performed. Antepartum antibiotic use was stratified by site for comparison. As the socio-demographic and obstetric characteristics of women admitted to PLC and RGH were similar (sections 4.2 and 4.3), these two sites were grouped together as one for the stratified analysis.

Table 5.4 Antepartum Antibiotic Use and Admission Year by Admission Site

a) FMC:
Prevalence Ratio: (30/90) / (51/100)=1.5 (95% CI: 1.1 to 2.2)

VARIABLE	1996 n=90 n (%)	1999 n=100 n (%)	*P* value
Antepartum antibiotic use in hospital			
Yes	**30 (33.3)**	**51 (51.0)**	**0.014**
No	**60 (66.7)**	**49 (49.0)**	

$\chi 2$ test was used for comparison

b) PLC+RGH:
Prevalence Ratio: (47/136) / (27/104)= 1.3 (95% CI: 0.89 to 1.98)

VARIABLE	1996 n=104 n (%)	1999 n=136 n (%)	*P* value
Antepartum antibiotic use in hospital			
Yes	**27 (26.0)**	**47 (34.6)**	**0.153**
No	**77 (74.0)**	**89 (65.4)**	

$\chi 2$ test was used for comparison

The stratified analysis showed that the prevalence of antibiotic use significantly increased at FMC (33.3% to 51.0%) but not at PLC+RGH between the years 1996 and 1999 (26.0% to 34.6%). Therefore, it would seem that the observed significant difference in the crude frequency of antepartum antibiotic use (Table 5.3) between 1996 and 1999 was mostly due to the difference observed at FMC.

In addition, comparing the frequencies between the three sites (Table 5.4) in 1999, 51.0% of women at FMC received antepartum antibiotics compared to 34.6% at PLC+RGH. Therefore, not only FMC had the highest increase in the frequency of antepartum antibiotic use from 1996 to 1999 but also, in 1999, FMC had the highest frequency of antibiotic use among the three sites.

Furthermore, as there was evidence for an increase in the frequency of admission due to PPROM from 1996 to 1999, antibiotic use was stratified by reason for admission (PTL vs. PPROM) in each year, in order to determine the effect of admission reason on the association between antibiotic use and the year of admission to hospital (Tables 5.5a and 5.5b).

In 1996, of all those admitted for PTL, 27.2% received antepartum antibiotics compared to 24.8% of those admitted with diagnosis of PTL in 1999. Therefore, there was no statistically significant difference in antibiotics use between the two groups (P=0.57). However, for those who were admitted with PPROM, 34.8% received antepartum antibiotics in 1996, compared to 77.3% of those who were admitted in 1999 (P<0.001).

In summary, this stratified analysis (Table 5.5) indicated that, for women admitted for PPROM in 1999 a significantly larger number received antepartum antibiotics (75.3%)

compared to the women admitted with PPROM in 1996 (34.8%). The crude prevalence ratio was 1.4 (95% CI: 1.1 to 1.8). The stratum specific ratios were 0.9 (95% CI: 0.5 to 1.5) for PTL group and 2.2 (95% CI: 1.5 to 3.3) for PPROM group. The estimate of the crude association lies between the stratum specific estimates. These differing point estimates suggest possible effect modification. Effect modification is to be described and reported, not controlled (Hennekens & Mayrent, 1987).

Table 5.5 Antepartum Antibiotic Use and Year of Admission by Reason of Admission

a) PTL

Prevalence Ratio: (40/161) / (41/148) = 0.9 (95% CI: 0.5 to 1.5)

VARIABLE	1996 n=148 n (%)	1999 n=161 n (%)	*p*-value
Antepartum antibiotic use in hospital			
Yes	41 (27.2)	40 (24.8)	0.57
No	107 (72.3)	121 (75.2)	

$\chi 2$ test was used for comparison

b) PPROM

Prevalence Ratio: (58/75) / (16/46) = 2.2 (1.5 to 3.3)

VARIABLE	1996 n=46 n (%)	1999 n=75 n (%)	*p*-value
Antepartum antibiotic use in hospital			
Yes	16 (34.8)	58 (75.3)	<0.001
No	30 (65.2)	17 (24.7)	

$\chi 2$ test was used for comparison

Since FMC had the highest increase in both frequencies of admission due to PPROM and antepartum antibiotic use from 1996 to 1999, a separate stratified analysis was performed for women admitted to FMC to determine the effect of admission reason on the association between antibiotic use and year of admission to the hospital.

The crude prevalence ratio was 1.5 (95% CI: 1.1 to 2.2) (Table 5.4a). The stratum specific ratios were 0.8 (95% CI: 0.3 to 1.8) for PTL group and 2.3 (95% CI: 1.3 to 4.0) for PPROM group. The estimate of the crude association lies between the stratum specific estimates. These differing point estimates suggest possible effect modification of the association between antibiotic used and year of admission to the hospital. Effect modification is to be described and reported, not controlled (Hennekens & Mayrent, 1987).

The results revealed that even at FMC, significantly larger number of women with PPROM received antepartum antibiotics in 1999 compared to 1996 (80.0% vs. 34.6%).

Table 5.6 Antepartum Antibiotic Use and Year of Admission by Reason of Admission at FMC

a) PTL

Prevalence Ratio: (15/55) / (21/64) = 0.8 (95% CI: 0.3 to 1.8)

VARIABLE	1996 n=64 n (%)	1999 n=55 n (%)	*p*-value
Antepartum antibiotic use in hospital			
Yes	21 (32.8)	15 (27.3)	0.51
No	43 (67.2)	40 (72.7)	

$\chi 2$ test was used for comparison

b) PPROM

Prevalence Ratio: (36/45) / (9/26) = 2.3 (95% CI: 1.3 to 4.0)

VARIABLE	1996 n=26 n (%)	1999 n=45 n (%)	*p*-value
Antepartum antibiotic use in hospital			
Yes	9 (34.6)	36 (80.0)	<0.001
No	17 (65.4)	9 (20.0)	

$\chi 2$ test was used for comparison

5.2.4 Comparison of Years the 1996 and 1999: Antibiotic Use for Prolongation of Pregnancy

The overall antepartum antibiotics used for women admitted with PTL or PPROM was categorized based on the reason for use to compare the frequency of antibiotic use for prolongation of pregnancy in 1996 and 1999.

In 1996, the most common reason for use of antepartum antibiotics was for treatment of urinary tract infection. Prolongation of pregnancy was stated as the reason for antibiotic treatment in only 3.4% of patients' charts. On the other hand, 54.1% of the women admitted in 1999 that received antepartum antibiotics received them for prolonging pregnancy. Of the 53 women in 1999 who received antepartum antibiotics for the purpose of prolongation of pregnancy, nine (16.7%) were admitted for PTL and 44 (83.0%) were admitted for PPROM.

Table 5.7 Reasons for Antepartum Antibiotic Use in 1996 and 1999.

VARIABLE	1996 n=57 n (%)	1999 n=98 n (%)
Reason for Antepartum antibiotics use in hospital		
Prolongation	2 (3.4)	53 (54.1)
UTI	13 (23.7)	16 (16.3)
High Temperature	2 (3.4)	0 (0.0)
Unknown	37 (64.4)	28 (28.6)
Others	3 (5.1)	1 (1.2)

However, 64.4% of women admitted in 1996 and 28.6% of those admitted in 1999 that received antepartum antibiotics did not have a reason for receiving antibiotics stated in their charts. This high percentage of missing (unknown) data for the variable

"Reason of antibiotics use in hospital" and the small number of observations in each stratum lead to imprecise estimates of the effect and also unreliable frequencies within each strata.

5.2.5 Comparison of the Years 1996 and 1999: Types of Antibiotics Used

The types of antepartum antibiotics used for women with PTL and PPROM in 1996 and 1999 are listed in Table 5.8. In both years, half of all the women who received antepartum antibiotics received ampicillin (IV). In 1996, the other two most commonly used antibiotics were cefazolin (IV) and nitrofurantoin (PO). However, in 1999, the second most common antibiotics used were erythromycin (PO) and amoxicillin (PO). The combination of antibiotics used for the purpose of prolongation usually initiated by intravenous broad-spectrum antibiotics such as ampicillin and erythromycin, followed by oral amoxicillin and erythromycin.

Figure 5.3 Comparison of Types of Antibiotic Used between 1996 and 1999

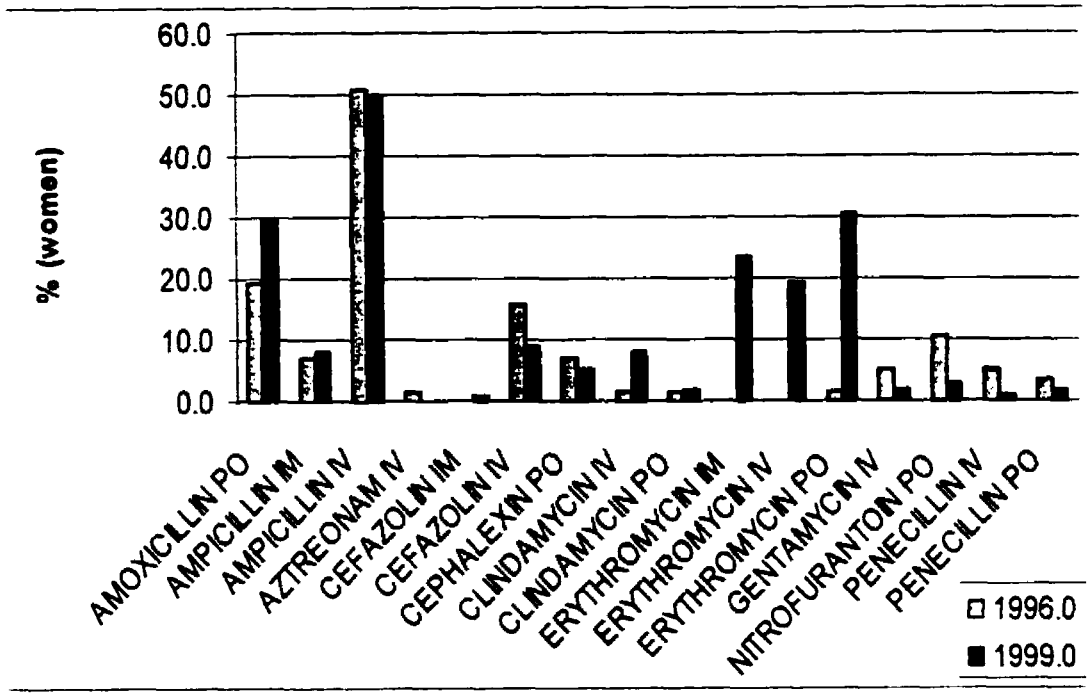


Table 5.8 Comparison of Types of Antibiotic Used between 1996 and 1999

Types of Antepartum Antibiotics Used	1996 (%) of women	1999 (%) of women
AMOXICILLIN PO	19.3	29.6
AMPICILLIN IM	7.0	8.2
AMPICILLIN IV	50.9	50.0
AZTREONAM IV	1.8	0.0
CEFAZOLIN IM	0.0	1.0
CEFAZOLIN IV	15.8	9.2
CEPHALEXIN PO	7.0	5.1
CLINDAMYCIN IV	1.8	8.2
CLINDAMYCIN PO	1.8	2.0
ERYTHROMYCIN IM	0.0	23.5
ERYTHROMYCIN IV	0.0	19.4
ERYTHROMYCIN PO	1.8	30.6
GENTAMYCIN IV	5.3	2.0
NITROFURANTOIN PO	10.5	3.1
PENECILLIN IV	5.3	1.0
PENECILLIN PO	3.5	2.0

5.2.6 Comparison of Years 1996 and 1999: Neonatal Outcome

The neonatal outcome for each year is summarized in Tables 5.9a and 5.9b. Only those neonates whose mothers had a delivery record available in their charts at the same hospital in which they were admitted for PPROM or PTL are included. Those with delivery records elsewhere (outside the CRHA region, or at a different hospital than the one at which the mother had her PTL or PPROM admissions and care) are not included in these tables.

The overall gestation age at birth was significantly different between the two years with the neonates born in 1999 having the lower gestational age at birth compared to 1996. Categorizing gestation age at birth into three groups (22-32 weeks, 32.1 to 37.0 weeks and 37.1-42.0 weeks), revealed that in 1996, 46.6% of the babies born to women admitted to hospital for PTL or PPROM had preterm birth (<37.0 weeks) compared to 65.5% in 1999.

Similar to previous chapters, birth weight was categorized based on definitions of VLBW and LBW. When divided into these categories, there was clinically and statistically significant difference in birth weight from 1996 to 1999. In 1996, 32.5% of babies born to women admitted for PTL or PPROM in CRHA had birth weight of less than 2500g compared to 44.5% in 1999. Consequently, more babies were admitted to NICU in 1999 (55.0%) compared to 1996 (44.8%).

There was no significant difference between gender, delivery mode or 5-minute Apgar score between the two years.

Table 5.9 Comparison of Neonatal Outcome of Babies Born to Women Admitted to the Hospital for PTL or PPROM between the Years 1996 and 1999.

a) Continuous variables:*

VARIABLES	1996 n=163 mean ±(95% CI)	1999 n=209 mean ±(95% CI)	*p-value*
Gestation age at birth (weeks)	36.5 (36.0 to 37.0)	35.1 (34.5 to 35.6)	<0.001
Birth Weight (g)	2818.6 (2698.3 to 2938.9)	2530.9 (2405.0 to 2656.9)	0.001

* ANOVA was used for comparison

b) Categorical Variables:**

VARIABLES	1996 n=163 n (%)	1999 n=209 n (%)	*p-value*
Gender			
Male	93 (57.1)	112 (53.6)	0.50
Female	70 (42.9)	97 (46.4)	
Delivery mode			
Vaginal Delivery	142 (88.2)	176 (84.2)	0.27
Cesarean Delivery	19 (11.8)	33 (15.8)	
5 min Apgar score			
<7	5 (3.1)	9 (4.4)	0.52
≥7	157 (96.9	197 (95.6)	
NICU stay			
Yes	73 (44.8)	115 (55.0)	0.05
No	90 (55.2)	94 (45.0)	
Birth Weight (g)			
≤1500	8 (4.9)	29 (13.9)	
1501-2500	45 (27.6)	64 (30.6)	0.003
≥2501	110 (67.5)	107 (51.2)	
Gestation age at birth (week)			
23-32	18 (11.0)	46 (22.0)	
32.1-37	58 (35.6)	91 (43.5)	<0.001
37.1-42	87 (53.4)	72 (34.5)	

** $\chi 2$ test was used for comparison

CHAPTER SIX: RESULTS- ANTIBIOTIC USE AND PROLONGATION OF PREGNANCY

6.1 Introduction

The third objective of this study, was to examine the association between antibiotic use and prolongation of pregnancy in women admitted to any of the three hospitals in CRHA, with preterm labour and intact membranes (PTL) or with preterm premature rupture of membranes (PPROM). To meet this objective, the following chapter first compares the socio-demographic and obstetric characteristics of women who received antepartum antibiotics and those who did not receive any antibiotic during their admissions for PTL or PPROM and secondly, examines the association between antibiotic use and prolongation of pregnancy.

6.1.1 Total Sample Size

Contrary to the previous two chapters, which looked at the site-specific and the year-specific practices of antibiotic use and the characteristics of women admitted for PTL or PPROM, this chapter looks at the overall association of antibiotic use and prolongation of pregnancy regardless of the year or the site of admission. Therefore, all 430 women who were eligible for the analysis in the first two chapters could be included in the analysis of this chapter.

The outcome of the third objective was prolongation of pregnancy (from admission to delivery). Therefore, only those women whose delivery records were available at one of the three sites (FMC, RGH and PLC) and those who had a normal course of delivery without the need for induction or cesarean section, due to maternal or

fetal complications, would have been suitable for inclusion in the analysis of this chapter. In other words, the conservative approach examining the true prolongation of pregnancy was to exclude *all* women who were induced or had a cesarean section, in addition to those who did not have a delivery record available. A less stringent approach would be to also include women who were induced beyond 40 weeks gestation or those who had a cesarean section for reasons other than maternal or fetal complications. However, to limit variables that might confound the outcome of pregnancy prolongation, the conservative approach was used.

Following the conservative approach, 36 women were excluded because delivery records were not available at any of the three acute care hospitals. Fifty women were excluded due to induction of pregnancy and another fifty were excluded due to having cesarean section delivery. In cases which one woman was admitted to multiple sites during her pregnancy, the data from all the sites was aggregated and counted as one unit for analysis (n=22).

The final sample size consisted of 272 women with either PTL or PPROM who were admitted to hospital during the year 1996 (January 1st -December 31st) or 1999 (January 1st -December 31st). One hundred and one women received antepartum antibiotics during their hospital admission for PTL or PROM and 171 women did not receive any antibiotics.

6.1.2 Missing Data

The following variables had missing observations.

1. Highest temperature 24hr before deliver
   - 8 missing from antibiotic group
   -18 missing from no-antibiotic group

2. White blood cell count
   - 24 missing from antibiotic group
   - 49 missing from no-antibiotic group

3. Neonatal Birth Weight
   - 0 missing from antibiotic group
   - 4 missing from no-antibiotic group

4. History of Infection During Pregnancy
   - 50 missing from antibiotic group
   - 92 missing from no-antibiotic group

5. Reason for antibiotic use in hospital
   - 44 missing from antibiotic group

6.2 Comparison of Antibiotic Group and No-Antibiotic Group: Socio-Demographic, Obstetric and Neonatal Characteristics

In the following sections the characteristics of women who received antepartum antibiotics and those who did not receive antibiotics are compared using chi-square test for categorical variables and two sample t-test for continuous variables.

6.2.1 Comparison of Antibiotic Group and No-Antibiotic Group: Socio-Demographic Characteristics

Tables 6.1a and 6.1b compare the socio-demographic characteristics of 101 women who received antepartum antibiotics with the 171 who did not receive any antepartum antibiotics during their hospital admissions. Maternal age on admission in

both groups had a normal distribution and similar variance (Figure 6.1). Therefore, a two sample t-test was used to compare the two groups (Table 6.1a).

Table 6.1 Comparison of Socio-Demographic Characteristics of All Women Who Received Antepartum antibiotics With Those Who Did Not Receive Any Antibiotic.

a) Continuous Variables:*

VARIABLE	Received Antepartum Antibiotics n=101 mean ± (95% CI)	Did Not Receive Antepartum Antibiotics n =171 mean ± (95% CI)	*P*-Value
Age (years)	26.9 (25.7 to 28.1)	27.1 (26.2 to 28.0)	0.80

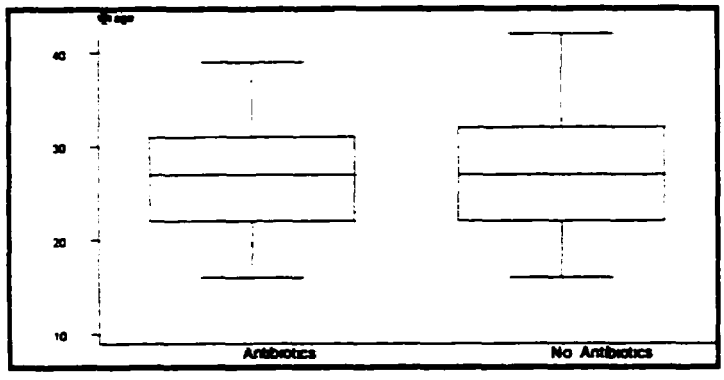
* two sample t-test was used for comparison

b) Categorical Variables:**

VARIABLES	Received Antepartum Antibiotics n=101 n (%)	Did Not Receive Antepartum Antibiotics n =171 n (%)	*P*-Value
City of Residence			
Calgary	84 (83.2)	156 (91.2)	
Outside Calgary	17 (16.8)	15 (8.8)	0.05
Smoking During Pregnancy			
Yes	34 (33.7)	58 (33.9)	
No	65 (64.4)	104 (60.8)	
Quit, before pregnancy	2 (2.0)	9 (5.3)	0.40
Alcohol Consumption During Pregnancy			
Yes	10 (9.9)	21 (12.3)	
No	91 (90.1)	150 (87.7)	0.55

** $\chi 2$ test was used for comparison

Figure 6.1 Box-plot of Age Distribution in the Antibiotic Group and No-antibiotic Group



The mean maternal age at time of first admission was very similar between the two groups. Women who received antibiotic had a mean age of 26.9 years compared to 27.1 years for those who did not receive any antibiotic (p= 0.80) (Table 6.1a).

Smoking and alcohol consumption during pregnancy was not significantly different between the two groups. In both groups, as many as 34% of women smoked during their pregnancy (Table 6.1b).

In addition, 16.8% of women in antibiotic group were living outside Calgary but were transferred to Calgary for their care, compared to 8.8% of women in no-antibiotic group (p=0.05) (Table 6.1b).

6.2.2 Comparison of Antibiotic Group and No-Antibiotic Group: Obstetric Characteristics

Tables 6.2a and 6.2b describe the obstetric characteristics of those women who received antibiotic and those who did not receive any antepartum antibiotics during admission for PTL or PPROM.

Admission gestation age had an approximately normal distribution and similar variance between the two groups. Therefore, a two sample t-test was used for comparison. Among those who received antepartum antibiotics, the mean gestation age on first admission was 29.8 weeks compared to 29.9 weeks in the no-antibiotic group ($p=0.78$). The 95% confidence interval almost completely overlapped between the two groups (Table 6.2a).

Among the 101 women who received antibiotics, 56 (55.4%) were admitted for preterm labour with intact membrane. Of these 56 women, 6 (5.9%) were admitted for PTL on first admission but on subsequent admissions had preterm premature rupture of membrane greater than 12 hours. Forty-five women (44.6%) were admitted for preterm premature rupture of membrane (Table 6.2b).

In the group of women who did not receive antibiotic, 143 (83.6%) were admitted for preterm labour with intact membrane. Of these 143 women, 5 (2.9%) were admitted for PTL on first admission but on subsequent admissions had preterm premature rupture of membrane>12 hours. Twenty eight (16.4%) women who did not receive any antepartum antibiotics, were admitted for premature rupture of membrane (Table 6.2b).

Therefore, there was some evidence that those who received antepartum antibiotics were more likely to have come to the hospital due to premature ruptured membrane than those who did not receive any antepartum antibiotics ($p<0.001$).

Table 6.2. Comparison of Obstetric Characteristics of All Women Who Received Antepartum Antibiotics With Those Who Did Not Receive Any Antibiotics.

a) Continuous Variables:*

VARIABLES	Received Antepartum Antibiotics n=101 mean ± (95% CI)	Did Not Receive Antepartum Antibiotics n =171 mean ± (95% CI)	*p*-value
Gestational Age on Admission (weeks)	29.8 (29.2 to 30.5)	29.9 (29.5 to 30.3)	0.78
Highest temperature 24hr before delivery (°C)	36.9 (36.8 to 37.0)	36.9 (36.7 to 37.0)	0.41
WBC count $x10^9/L$	14.0 (13.0 to 15.0)	14.3 (12.8 to 15.8)	0.76
Total Length Of Hospital Stay (days)	5.5 (4.7 to 6.3)	4.3 (3.9 to 4.8)	0.007

*two sample t-test was used for comparison

b) Categorical Variables:**

VARIABLES	Received Antepartum Antibiotics n=101 n (%)	Did Not Receive Antepartum Antibiotics n =171 n (%)	*p*-value
Admission Reason			
PTL			
-PTL with no PROM	50 (49.5)	138 (80.7)	<0.001
-PTL with PROM	6 (5.9)	5 (2.9)	
PPROM	45 (44.6)	28 (16.4)	
Previous Preterm Birth			
Yes	19 (18.8)	25 (14.6)	
No	53 (52.4)	94 (55.0)	
No, First child	29 (28.7)	52 (30.4)	0.66
Tocolytics received during admission			
Yes	59 (58.4)	134 (78.4)	
No	42 (41.6)	37 (21.6)	<0.001
Corticosteroids received during admission			
Yes	89 (88.1)	143 (83.7)	0.31
No	12 (11.8)	28 (16.4)	

** $\chi 2$ test used for comparison

Tocolytics, used to inhibit uterine contractions and to prolong pregnancy after initiation of preterm labour, were administered more commonly to those who did not receive antibiotics during their admission. Fifty-nine (58.4%) women in the antibiotic group compared to 134 (78.4%) women in the no-antibiotic group received tocolytics as part of their treatment for cessation of labour ($p<0.001$). The influence of the reason of admission on the relationship between tocolytics and antibiotic use was assessed by comparing the crude and stratum specific prevalence ratios. The crude prevalence ratio was 0.75 (95% CI: 0.62 to 0.89). The tocolytics use was stratified by reason of admission (PTL vs. PPROM). The stratum specific prevalence ratios were 1.0 (95% CI: 0.89 to 1.1) for PTL group and 0.69 (95%CI: 0.32 to 1.4) for PPROM group. The confidence interval for both stratum included one. Therefore, the difference in tocolytics use among the antibiotic group and no-antibiotic group was not significant when admission reason was taken into account (Table 6.3a and 6.3b).

Table 6.3 Tocolytics Use in Antibiotic group and No-Antibiotic group By Reason Of Admission

a) Preterm Labour:

Prevalence Ratio: (49/56) / (125/143)= 1.0 (95% CI: 0.89 to 1.1)

Variable*	Received Antepartum Antibiotics n=56 n (%)	Did Not Receive Antepartum Antibiotics n =143 n (%)	*P*-Value
Tocolytics during admission			
Yes	49 (87.5)	125 (87.4)	
No	7 (12.5)	18 (12.6)	0.99

*$\chi 2$ test was used for comparison

Table 6.3 Continued-

b) Premature Rupture of Membrane:

Prevalence Ratio: (10/45) / (9/28)= 0.69 (95%CI: 0.32 to 1.4)

Variable*	Received Antepartum Antibiotics n=45 n (%)	Did Not Receive Antepartum Antibiotics n =171 n (%)	*P*-Value
Tocolytics during admission			
Yes	10 (22.2)	9 (32.1)	0.35
No	35 (77.8)	19 (67.9)	

*$\chi 2$ test was used for comparison

Most of the women in both groups, 89 (88.1%) in the antibiotics group and 143 (83.7%) in the non-antibiotic group, received corticosteroids as part of the management of labour for stimulating fetal lung maturity. Data on the highest temperature (as a possible marker for infection) recorded in patients charts during the last 24hr before delivery was also collected. The mean highest temperature was 36.9°C in both groups. The White Blood Cell (WBC) count was also collected from the patient's charts. If more than one WBC count was available, the highest was recorded as a marker for presence of infection. The mean WBC count was about 14.0×10^9/L in women who received antibiotics as well as in those who did not receive antibiotic during their admissions for PTL or PROM.

Total length of hospital stay (LOS) was calculated as the total number of inpatient days for each admission, including the delivery admission. The distribution of length of stay was compared between the antibiotic group and no-antibiotic group (Figure 6.2). Both distributions were asymmetrical (positively skewed). The variable LOS was

transformed using natural logarithm (ln) transformation to normalize the distribution. The assumption of normality appeared most valid in ln-transformed data. Figure 6.3 shows that after transformation, the positive skewness, in both groups, was reduced.

The mean and the 95% confidence intervals for ln(LOS) in both groups were transformed back to make it easier for interpretation. The mean total length of hospital stay was 5.5 days for those women who received antepartum antibiotics during their hospital stay compared to 4.3 days for women who did not receive any antepartum antibiotics.

Figure 6.2 Histogram of Total Length of Stay for Women in Antibiotic group and No-Antibiotic Group

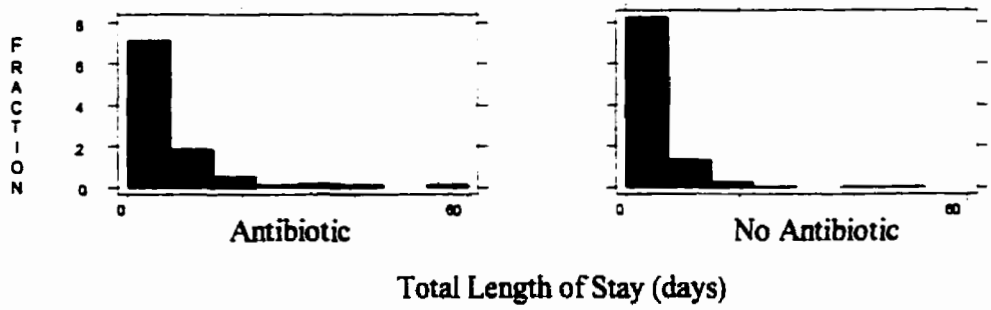
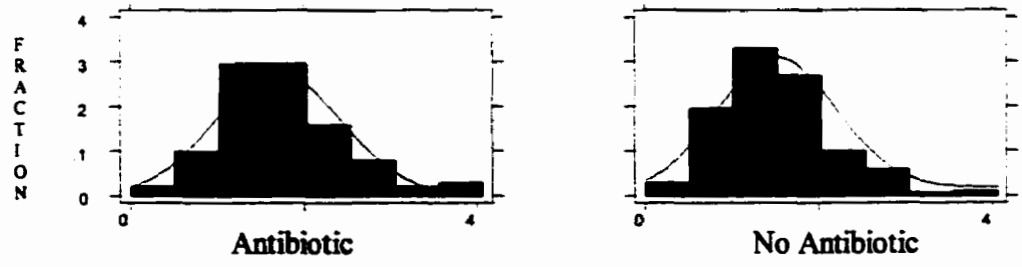


Figure 6.3 Histogram of ln (Total Length of Stay) for Women in Antibiotic Group and No Antibiotic Group



6.2.3 Comparison of the Antibiotic Group and No-Antibiotic Group: Antibiotic Use Prior to Admission and History of Infection During Pregnancy.

Table 6.4 describes the antibiotic use prior to admission to hospital as well as any history of infection during pregnancy. Antibiotic use during pregnancy was not significantly different between the two groups (P=0.42).

As mentioned in previous chapters, the variable "history of infection" during pregnancy had a high percentage of missing data. About 50 (50%) women in the antibiotic group and 92 (53.8%) women in the no-antibiotic group had no information in regards to history of infection in their charts. Therefore, due to inadequate information, this variable was not considered reliable to draw any meaningful conclusions on the existence of significant difference in past history of infection for women with PTL or PPROM between the antibiotic and no-antibiotic group (Table 6.4).

However, to determine the influence of the missing data, for the variable "history of infection", in testing for existence of significant difference among the two groups, two assumptions could be made. The first assumption would be that the reason for not mentioning history of infections in some of the charts was because those women did not have any infection during their pregnancy. In this case, all "Unknown" history of infection could be included in the "No" history of infection category. With this assumption, there was no evidence for a statistically significant difference among the women who received antepartum antibiotics and those who did not receive any antibiotic during their hospital admissions for PTL or PROM ($p= 0.13$). The second assumption would be that all those with "Unknown" history of infection in fact did have infection but it was not recorded in their charts. With this assumption, again there was no evidence for

statistically significant difference among the women who received antepartum antibiotics and those who did not receive any antibiotic during their hospital admissions for PTL or PPROM (p= 0.31).

Table 6.4 Comparison of Antibiotic Use Prior to Admission and History of Infection During Pregnancy of Women who Received Antepartum Antibiotics With Those Who Did Not Receive Any Antibiotics.

Categorical variables:**

VARIABLES	Received Antepartum Antibiotics n =101 n(%)	Did Not Receive Antepartum Antibiotics n =171 n(%)	*p*-value
Antibiotic use Prior to admission			
Yes	19 (18.8)	26 (15.2)	
No	82 (81.2)	145 (84.8)	0.42
Women with history of Infection prior to admission			
Yes*	38 (37.6)	49 (28.7)	
No	13 (12.8)	30 (17.5)	
Unknown	50 (49.50)	92 (53.8)	NA
***Infections prior to hospital admission**			
Bladder	9	11	
BV	2	1	
Chlamydia	2	4	
GBS	2	1	
UTI	23	24	
Yeast	4	4	
URTI	5	5	
Others	3	5	

** $\chi 2$ test was used for comparison

Therefore, it is possible to conclude that even if the information on history of infection was available on all patients, whether all belonged to the "Yes" or "No" category, there would be no significant difference among the two groups. In other words,

there is no evidence for a relationship between history of infection during pregnancy and receiving antepartum antibiotics during admission for PTL or PPROM.

Among those women in either group who did have information on history of infection during pregnancy, the most common infection was urinary tract infection. History of chlamydia infection during pregnancy was recorded for two women in the antibiotic group and for four women in the no-antibiotic group (Table 6.4). The age of these six women at the time of first admission ranged from 17 to 23 years.
The other infections are listed in Table 6.4 The total number of infection for the variable "Infections prior to hospital admission" listed in Table 6.4 were greater than the number of women with history of infection since one women could have more than one infection during her pregnancy.

6.2.4 Comparison of Antibiotic Group and No-Antibiotic Group: Microbiologic Findings.

Table 6.5 shows the microbiological findings during the hospital stays of women who received antepartum antibiotics and those who did not receive any antibiotics. Most of the women in both groups were not tested.

For *Chlamydia trachomatis*, 83.2% of women in the antibiotic group and 78.9% of women in the no-antibiotic group were not cultured. However, of those who were tested, 1 of 17 women in the antibiotic group and 1 of the 36 in the no-antibiotic group had positive culture for *Chlamydia trachomatis*. It is interesting to note that in the previous table of history of infection during pregnancy (Table 6.4), 2 women in antibiotic group and 4 women in the no-antibiotic group had *Chlamydia trachomatis* recorded in their history of complications during current pregnancy. Of these six women, three were

tested for Chlamydia during their hospital stay with two of them having positive results, one in the antibiotic group and one in the no-antibiotic group. The other three women with a history of Chlamydia were not tested during any of their admissions for PTL or PPROM.

Among the women who received antepartum antibiotics during their hospital stay, 3 (14.3%) of the 21 women tested had positive results for bacterial vaginosis compared to 4 of the 35 women tested in the no-antibiotic group. There were no women positive for *Neisseria gonorrhoeae* or *Trichomonas vaginalis* cultures in either of the two groups.

For Group B Streptococcus, 4 (17.4%) of the 23 women tested were positive in the group who received antepartum antibiotics compared to 9 (15.0%) of the 60 women tested in the group who did not receive any antepartum antibiotics (Table 6.5).

Table 6.5 Comparison of the Microbiologic Findings of Women Who Received Antepartum Antibiotics With Those Who Did not Receive any Antibiotics During Their Hospital Admission.

VARIABLES	Received Antepartum Antibiotics n=101 n (%)	Did Not Receive Antepartum Antibiotics n =171 n (%)
Chlamydia trachomatis		
Tested, positive, *n*	1	1
Tested, negative, *n*	16	35
Not tested, *n(%)*	84 (83.2)	135
Bacterial Vaginosis		
Tested, positive, *n*	3	4
Tested, negative, *n*	18	31
Not tested, *n(%)*	80 (79.2)	136
Yeast sp.		
Tested, positive, *n*	1	3
Tested, negative, *n*	17	31
Not tested, *n(%)*	83 (82.2)	137
Trichomonas vaginalis		
Tested, positive, *n*	0	0
Tested, negative, *n*	9	10
Not tested, *n(%)*	92 (91.1)	161 (94.2)
Group B streptococcus		
Tested, positive, *n*	4	9
Tested, negative, *n*	19	51
Not tested, *n(%)*	78 (77.2)	111 (64.9)
Neisseria gonorrhoeae		
Tested, positive, *n*	0	0
Tested, negative, *n*	12	23
Not tested, *n(%)*	89 (88.1)	148 (86.6)
Urine cultures		
Tested, positive, *n*	24	42
Tested, negative, *n*	25	46
Not tested, *n(%)*	50 (49.5)	82 (48.0)
Organisms isolated from Urine cultures		
CNS, *n*	4 (16.6)	4 (9.5)
E. Coli, *n*	0 (0.0)	1 (2.4)
Lactobacillus sp., n	1 (4.2)	11 (26.2)
P. auroginosa, n	1 (4.2)	0 (0.0)
Multiple gram positives, *n*	18 (75.0)	26 (61.9)

Urine cultures were also done on 50 (49.5%) women in the antibiotic group and on 82 (48.0%) women in the no-antibiotic group. In both groups, approximately half of the women who were tested had a positive urine culture. These cultures were positive for gram-negative organisms such as *E. Coli* and *P. auroginosa* as well as gram-positive organisms such as coagulase-negative staphylococci (CNS), and Lactobacillus sp. Some cultures grew multiple gram positive cocci. From a microbiological point of view, when pathogenic microorganisms are present, urinary tract infection (UTI) exists. However, some of the organisms found in this study, such as multiple gram positives, are usually due to contamination of the urine culture and others such as *Lactobacillus sp.* do not commonly cause UTI.

In fact, among the women who received antepartum antibiotics, 20 (19.8%) were treated for UTI. Of these 20 women, the microbiological findings revealed that 8 (40.0%) had multiple gram-positive organisms in their urine cultures, 2 (10.0%) had CNS, 1 (5.0%) had *P. auroginosa*, 1 (5.0%) had *lactobacillus sp.* 4 (20.0%) of them had no urine test done and 4 (20.0%) others were tested but their cultures did not grow any microorganisms. Thirteen (65.0%) of these 20 women also had UTI recorded in their history of infections during their current pregnancy.

6.2.5 Comparison of Antibiotic Group and No-Antibiotic Group: Neonatal Outcome

Table 6.6 summarizes the neonatal characteristics of babies born to women who received antepartum antibiotics compared to those who did not receive any antibiotic.

Five minute Apgar score, the numerical index (0 to10) of well being applied to newborns infants, was categorized into three categories based on clinical importance. An Apgar score of 7-10 is considered to be normal. An Apgar of 4-6 is considered to

Table 6.6 Comparison of the Neonatal Outcome of Babies Born to Women Who Received Antepartum Antibiotics With Those Who Did Not Receive Any Antibiotics During Their Hospital Admission.

Categorical Variables:**

VARIABLES	Received Antepartum Antibiotics n=101 mean ± (95% CI)	Did Not Receive Antepartum Antibiotics n =171 mean ± (95% CI)	*p-value*
Gender			
Male	55 (54.5)	96 (56.1)	
Female	46(45.5)	75 (43.9)	0.74
5 min Apgar score			
0-3	4 (3.9)	0 (0.0)	
4-6	4 (3.9)	3 (1.8)	0.03
7-10	93 (92.2)	168 (98.3)	
NICU stay			
Yes	66 (65.3)	72 (42.1)	
No	35 (34.7)	99 (57.9)	<0.001
Birth Weight (gm)			
≤1500	19 (18.8)	6 (3.6)	
1501-2500	37 (36.6)	45 (27.0)	<0.001
≥2501	45 (44.6)	116 (69.4)	
Gestation age at birth (weeks)			
23-32	25 (24.8)	18 (10.5)	
32.1-37	48 (47.5)	60 (35.1)	<0.001
37.1-42	28 (27.7)	93 (54.4)	

** $\chi 2$ test used for comparison

represent mild to moderate physiological depression whereas Apgar score of 0-3 is indicative of severe depression in the neonate (Dunniho 1992).

There seemed to be some evidence that the babies born to women who received antepartum antibiotics were more likely to have a 5-min Apgar score of less than seven. Three of the babies in the antepartum antibiotics group died shortly after birth. However, the likelihood of survival was low for the babies of these women on admission since the they were admitted with PPROM and gestational ages of 22, 24, 26.5 weeks.

When the reason of admission was taken into account in the relationship between maternal antepartum antibiotic use and neonatal Apgar score (stratified by admission reason), there was no significant difference between 5-min Apgar score of the babies in the antibiotic group and the no-antibiotic group.

Similarly, data suggested that the babies born to mothers who received antepartum antibiotics were more likely to have been admitted to the Neonatal Intensive Care Unit (NICU) after birth compared to babies of those women who did not receive any antepartum antibiotics during their hospital stay (65.3% vs. 42.1% respectively). Birth weight of the babies was divided into three categories based on the clinical definitions of Very Low Birth Weight (<1500g) and Low birth Weight (1500-2500g) an adequate birth weight (>2500g). The crude prevalence ratio of VLBW and LBW in the antibiotic group compared to the no-antibiotic group was 1.82 (95% CI: 1.4 to 2.4). That is, babies of mothers who received antepartum antibiotics were 1.8 times more likely to have very low or low birth weight compared to mothers who did not receive any antepartum antibiotics. Nineteen babies in the antibiotic group (18.8%) had a birth weight of less than or equal to 1500g compared to only 6 (3.6%) in the group who did not receive any antibiotic.

Since women with PPROM are considered to be at higher risk for preterm birth and consequently low birth weight babies, a stratified analysis was performed to assess the effect of admission reason on the relationship between birth weight and maternal antepartum antibiotics (Table 6.7a and 6.7b). The stratum specific prevalence ratios were similar and did not approximate the crude prevalence ratio which indicated that admission reason may have acted as potential confounder in the association between maternal antibiotic use and birth weight.

The stratified analysis, revealed that after controlling for the effect of admission reason, there seemed to be no association between antibiotic use and birth weight of neonates. However, the proportion of very low birth weight and low birth weight babies were much higher in both antibiotic and no-antibiotic groups of women with PPROM compared to those with PTL.

Table 6.7 Birth Weight and Antibiotic Use by Admission Reason

a) Preterm Labour:

Prevalence Ratio = (18/56) / (31/140)= 1.45; 95%CI (0.89 to 2.4)

VARIABLE	Received Antepartum Antibiotics n=56 n (%)	Did Not Receive Antepartum Antibiotics n =140 n (%)	*p-value*
Birth Weight (g)			
≤1500	**4 (7.1)**	**3 (2.1)**	
1501-2500	**14 (25.0)**	**28 (20.0)**	**0.15**
≥2501	**38 (67.9)**	**109 (77.9)**	

b) Preterm Premature Rupture of Membrane:

Prevalence Ratio = (38/45) / (20/27)= 1.14; 95%CI=(0.89 to 1.5)

VARIABLES	Received Antepartum Antibiotics n=45 n (%)	Did Not Receive Antepartum Antibiotics n =27 n (%)	*p-value*
Birth Weight (g)			
≤1500	15 (33.3)	3 (11.1)	
1501-2500	23 (51.1)	17 (70.0)	0.1
≥2501	7 (15.6)	7 (25.9)	

The distribution of neonatal gestation age at birth was compared between women who received antepartum antibiotics and those who did not. Figure 6.4 shows that the distribution of gestation age in both groups was asymmetrical and negatively skewed.

Figure 6.4 Histogram of Distribution of Gestation Age by Antibiotic Use

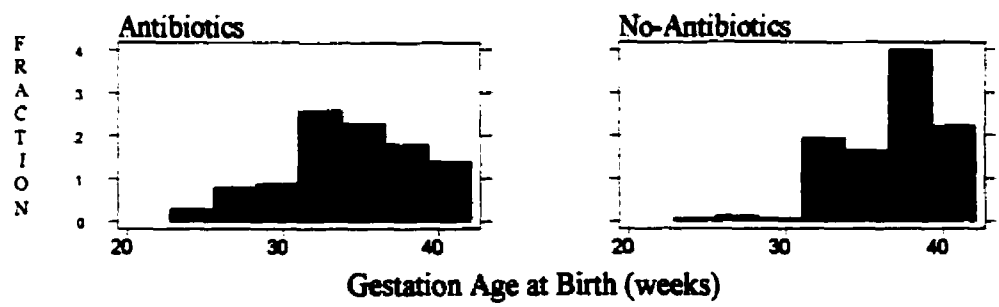
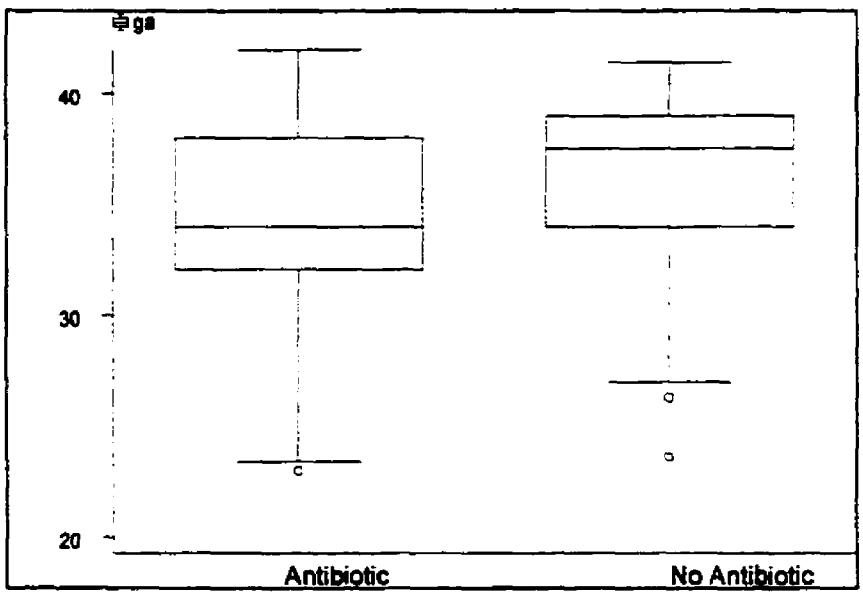


Figure 6.5 shows the interquartile and median gestation age at birth for women who received antibiotic and those who did not receive any antepartum antibiotics. The range of gestation age at birth among the antibiotic group was from 23.0 weeks to 42.0 weeks compared to the range in the no-antibiotic group of 23.6 to 41.4 weeks. The mean gestation age at birth was 34.2 weeks for babies whose mothers received antepartum

antibiotics compared to a mean of 37.5 weeks for those babies whose mothers did not receive any antepartum antibiotics. Gestation age at birth was categorized to three groups: (1) 23-32 weeks, (2) 32.1 to 37 weeks and (3) 37.1 to 42 weeks. As this variable was categorized for analysis, transformation of data was not necessary (Table 6.8).

Figure 6.5 Box-plots of Gestation Age by Antibiotic Use



Based on the definition of preterm birth (less than 37 weeks), 73 (72.3%) babies born to mothers in the antepartum antibiotics group were born preterm compared to 78 (45.6%) babies born to mothers in the no-antibiotic group ($p<0.001$).

Once again the influence of admission reason on the relationship between antibiotic use and gestation age at delivery was assessed by comparing the crude and stratum specific prevalence ratios.

The crude prevalence ratio for preterm birth in antibiotic group to no-antibiotic group was 1.58 (95%CI: 1.3 to 1.9). The stratum specific prevalence ratios were 1.47 (95% CI: 1.1 to 2.1) for PTL group and 1.02 (95% CI: 0.91 to 1.2) for PPROM group. These estimates revealed that admission reason may have acted as a potential confounder in the relationship between maternal antepartum antibiotic use and gestation age of neonate at birth. Stratification results suggested that for those with PTL, there seem to be an association between maternal antibiotic use and gestational age at birth but not for those with PPROM (95%CI of the prevalence ration included one).

Table 6.8 Gestation Age at Birth and Antibiotic use by Admission Reason

a) Preterm Labour

Prevalence Ratio: (30/56) /(52/143)= 1.5 (95%CI: 1.1 to 2.1)

VARIABLE	Received Antepartum Antibiotics n=56 n (%)	Did Not Receive Antepartum Antibiotics n =143 n (%)	*p-value*
Gestation age at birth (weeks)			
23-32	**7 (12.5)**	**7 (4.9)**	
32.1-37	**23 (41.1)**	**45 (31.5)**	**0.04**
37.1-42	**26 (46.4)**	**91 (63.6)**	

b) Premature Rupture of Membrane

Prevalence Ratio: (43/45) /(26/28)= 1.02 (95% CI: 0.91 to 1.2)

VARIABLE	Received Antepartum Antibiotics n=45 n (%)	Did Not Receive Antepartum Antibiotics n =28 n (%)	*p-value*
Gestation age at birth (weeks)			
23-32	**18 (40.0)**	**11 (39.3)**	
32.1-37	**25 (55.6)**	**15 (53.6)**	**0.89**
37.1-42	**2 (4.4)**	**2 (7.1)**	

6.3 Antibiotic Use and Prolongation of Pregnancy

This section examines the relationship between overall antepartum antibiotic use and prolongation of pregnancy. The analysis of this section includes a total of 272 women, 101 in the antepartum antibiotics group and 171 in the no-antepartum antibiotics group.

6.3.1 Antepartum antibiotic Use and Prolongation of Pregnancy

Prolongation of pregnancy was measured as the number of days from the date of first admission or date of premature rupture of membrane (whichever happened first) to delivery. Figure 6.6 demonstrates the distribution of number of the days that pregnancy was prolonged in women with PTL or PPROM who received antepartum antibiotics compared to those who did not. The histogram of pregnancy prolongation revealed that the distribution is positively skewed in both groups.

Figure 6.6 Histogram of Pregnancy Prolongation by Antibiotic Use

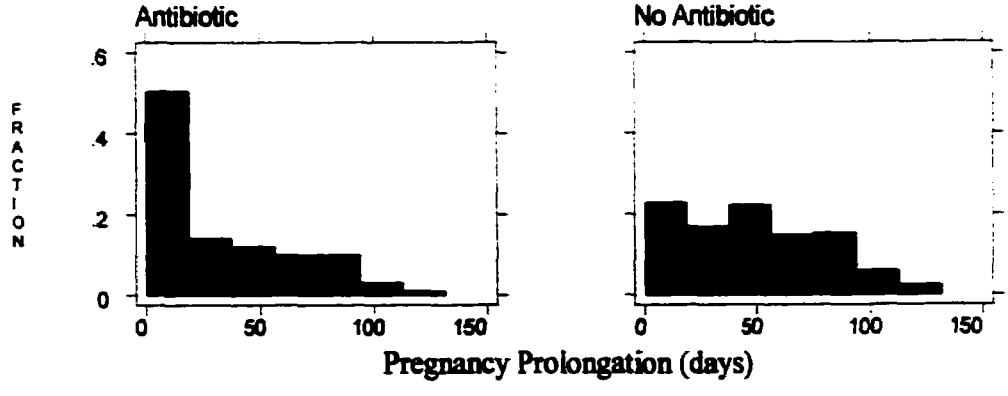


Table 6.9 shows the inter-quartile range, mean and median days of prolongation for the two groups. The mean (30.2 days) and median (16.0 days) prolongation for the antepartum group were very different which once again hilighted the asymmetric distribution of prolongation in this group.

Table 6.9 Data Summary of Prolongation (days) for Antepartum Antibiotics Group and No-Antepartum Antibiotic Group.

GROUP:	MEAN	MIN.	25%	MEDIAN	75%	MAX.
Antepartum Antibiotics	30.2	1	3	16	52	113
No-Antepartum Antibiotics	47.0	1	20	49	72	127

The mean prolongation was compared between the two groups using two-sample t-test. For the purpose of comparison and because of the relatively large sample size in each group, normal distribution was assumed for the two groups. The assumption of equal variance between the two groups was also met.

The overall results showed that there is a statistically and also clinically significant difference (17 days prolongation) between the antibiotic group and no-antibiotic group. In other words, the women who received antepartum antibiotics were more likely to have shorter prolongation of pregnancy.

Table 6.10 Antepartum Antibiotic Use and Prolongation of Pregnancy

Continuous variables:*

VARIABLE	Received Antepartum Antibiotics n=101 mean ± (95% CI)	Did Not Receive Antepartum Antibiotics n =171 mean ± (95% CI)	*p-value*
Latency from admission to delivery (days)	30.1	47.0	<0.001

*two-sample t-test used for comparison

Previous comparisons of obstetric characteristics made between antibiotic group and no antibiotic group revealed that admission reason seemed to be an important factor in regards to antepartum antibiotics use in hospitals.

In addition, a two-sample t-test of the relationship between admission reason and prolongation of pregnancy showed evidence for longer prolongation of pregnancy in women with preterm labour on admission compared to those with premature rupture of membrane (51.4 vs. 11.2 days respectively; $p<0.001$).

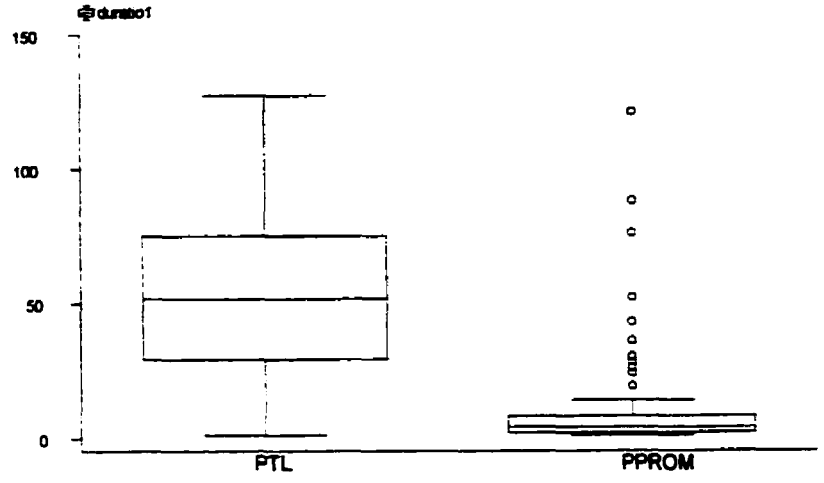
Table 6.11 Data Summary of Prolongation (days) for PTL Group and PPROM Group

GROUP:		MEAN (SD)*	MIN.	25%	MEDIAN	75%	MAX.
PTL	n=200	51.4 (29.5)	1	29	51.5	75	116
PPROM	n=72	11.2 (20.7)	1	2	4	8	121

*$p<0.001$; SD= Standard Deviation

The inter-quartile ranges and box-plots of the distribution of prolongation of pregnancy for the PTL and PPROM group showed that, PPROM group was highly asymmetrical (positively skewed). A number of outliners were also observed and their effect on the result was assessed later.

Figure 6.7 Box-plots of the Distribution of Prolongation of Pregnancy (days) in PTL and PPROM Group



Therefore, admission reason seemed to have acted as a potential confounder in the relationship between antepartum antibiotic use and prolongation of pregnancy. To assess and control for the effect of admission reason, the relationship between antibiotic use and prolongation of pregnancy was stratified by admission reasons (PTL or PPROM) (Table 6.11a and 6.11b).

Table 6.12 Stratified Analysis of Antepartum Antibiotic Use and Prolongation by Admission Reason

a) Preterm Labour:

VARIABLE*	Received Antepartum Antibiotics n=56 mean ± (95% CI)	Did Not Receive Antepartum Antibiotics n =143 mean ± (95% CI)	*p-value*
Latency from admission to delivery (days)	43.8 (35.6 to 52.0)	54.0 (49.3 to 58.7)	0.03

*two-sample t-test was used for comparison

Table 6.12 Continued

b) Premature Rupture of Membrane:

VARIABLE*	Received Antepartum Antibiotics n=45 mean ± (95% CI)	Did Not Receive Antepartum Antibiotics n =28 mean ± (95% CI)	*p-value*
Latency from admission to delivery (days)	13.3 (6.4 to 20.2)	11.4 (1.7 to 21.0)	0.74

* two sample t-test was used for comparison

The results showed that women with preterm labour, as their admission reason, who received antepartum antibiotics seemed to have shorter mean prolongation of 43.8 days compared to 54.0 days in women who did not receive any antepartum antibiotics and. Therefore, there was no evidence that in women with preterm labour antepartum antibiotics would prolong pregnancy (Table 6.12a and 6.12b).

The women who were admitted for PTL but later had PPROM, were also included in the PTL group for purpose of this analysis. Even though, this subgroup of the PTL admissions crossed over to PPROM, analysis was done according to the original subject classification. In other words, if a woman was admitted with preterm labour for her first admission, she would be classified in the PTL group regardless of whether or not she developed premature rupture of membrane (<34weeks) for greater than 12 hours. The same analysis was performed without the 11 women who crossed over from PTL group to PPROM group. The exclusion of these eleven women did not influence the results and therefore, they were kept in the analysis.

On the other hand, those women who were admitted for premature rupture of membrane and received antepartum antibiotics appeared to have longer mean

prolongation of pregnancy compared to the women with PPROM who did not receive antepartum antibiotics. Even though this result was not statistically significant (p=0.74) it could have clinical importance since pregnancy was prolonged as much as 48hr in the women who received antepartum antibiotics (6.12b).

A sub-analysis of women with PPROM was performed to look at the influence of gestation age on prolongation of pregnancy in women admitted with PPROM. Gestation age on first admission was divided into two categories: (1) 22-30 weeks and (2) 30.1-34 weeks. As shown in Table 6.13, the result of this analysis revealed that women with PPROM under 30 weeks gestation on first admission had mean prolongation of pregnancy of 22.3 days. On the other hand, women with gestation age greater than 30 weeks, who were admitted for PPROM and received antepartum antibiotics, had a mean prolongation of pregnancy of 5.4 days. Therefore, it seemed that antepartum antibiotics were most beneficial before 30 weeks gestation.

Table 6.13 Prolongation of Pregnancy in Women with PPROM Who Received Antepartum Antibiotics Before 30 Weeks Gestation Age Compared to those Who Received Antibiotic after 30 Weeks Gestation Age

VARIABLE*	PPROM<30 Weeks n=21 mean ± (95% CI)	PPROM>30 weeks n =24 mean ± (95% CI)
Latency from admission to delivery (days)	22.3 (8.2 to 36.4)	5.4 (2.8 to 7.9)

6.3.1.1 Influence of Outliers

Outliers are defined as points which lie outside the obvious cluster of scores (Portney et al. 1993) or as defined by Last, outliers are observations that differ from the rest of the data which lead one to suspect that a gross error may have been committed or suggesting that these values come from a different population (Last 1995).

In this study, the box plot of the distribution of pregnancy prolongation in the PPROM group revealed that a number of women had much longer prolongation of pregnancy than expected. A closer look at the data showed that there were four women in the study who were admitted for PPROM and did not deliver until 40 weeks gestation. In most cases if a woman had PPROM and did not deliver by 34 to 36 weeks gestation, she would be induced. However, the cases of these four women were different.

The data collected on these four women were assessed again for possible errors. The recording of data was correct. The other possibility was to think that maybe these women were misdiagnosed and did not have PPROM on admission but based on the criteria used in this study for PPROM, all women did have PPROM. In fact, they were all diagnosed and treated as PPROM on their subsequent admissions. Therefore, these women did belong to PPROM group. Another possibility was that maybe these women had different characteristics and belonged to a different population.

The four women were as follows:

1) A 20 year old woman admitted to FMC with PPROM at 28 weeks gestation on first admission. She had UTI (caused by *E. Coli*) during pregnancy, which she was treated for with Ampicillin. On her first admission she did not receive any tocolytics but was given steroids and antibiotics (Ampicillin IV). She stayed in the hospital for three

days and then was discharged. Her next admission was to PLC where she delivered at 40 weeks gestation. The date of PPROM on the delivery record was the same as the date on her first admission (prolongation pregnancy=88 days)

2) A 19 year old woman admitted to FMC with PPROM at 32.6 weeks on first admission. She had no history of infection during her pregnancy. She did not have tocolytics, steroids or antibiotics on this admission. She stayed in the hospital for 12 days. Her next admission was also to FMC where she delivered at 40 weeks gestation (prolongation duration=52 days).
3) A 23 year old woman admitted to PLC at 22.4 weeks gestation with PPROM. She had history of UTI during pregnancy and was treated with nitrofurantoin. She received steroids and tocolytics but no antibiotics on her first admission. She stayed in the hospital for 3 days. Her next admission was to PLC again at 40.2 weeks gestation (prolongation of pregnancy=121 days).
4) A 26 year woman admitted to FMC at 25.5 weeks gestation. She had history of upper respiratory tract infection during pregnancy. On first admission, she received antibiotics (ampicillin and amoxicillin) but no steroids or tocolytics. She had four subsequent admissions with PPROM to FMC and PLC at 28.5 weeks, 30.4, 34.1 and 40 weeks when she delivered at PLC (prolongation of pregnancy=109 days).

To determine the effect of these outliers on the results, the previous analysis for relationship between antibiotic use and prolongation of pregnancy in women with PPROM was performed with these four women excluded from the analysis.

Table 6.14 Stratified Analysis of Antepartum Antibiotic Use and Prolongation by Admission Reason in Women with PPROM with Exclusion of the Outliers

Premature Rupture of Membrane:

VARIABLE*	Received Antepartum Antibiotics n=43 mean ± (95% CI)	Did Not Receive Antepartum Antibiotics n =26 mean ± (95% CI)	*p-value*
Latency from admission to delivery (days)	9.3 (5.1 to 13.5)	5.6 (1.9 to 9.23)	0.22

* two sample t-test was used for comparison

Results (Table 6.14) revealed that, exclusion of these four women influence the mean prolongation of pregnancy in women with PPROM who received antibiotics to those who did not receive any antibiotics. In fact, women who received antibiotics were prolonged by about four days compared to those who did not receive antibiotics. These changes in the results also highlighted the limitations of dealing with small sample size. If the sample size was larger, it was possible that less discrepancy would be observed between the outliers and the rest of observations. The effect of outliers on the analysis can be reduced by different strategies such as transforming the data, categorizing or using non-parametric tests of significance. Here the exclusion of the outliers was done for the purpose of sensitivity analysis.

6.3.2 Reasons for Antepartum Antibiotic Use

The reasons for receiving antepartum antibiotics were examined in preterm labour and premature rupture of membrane groups. Those women admitted for preterm labour

were more likely to receive antibiotics due to a complication of pregnancy such as urinary tract infection which may have resulted in faster delivery and shorter prolongation compared to women in PTL group who did not receive any antibiotics (Table 6.14). Majority of women (62.2%) in PPROM group received antibiotics for purpose of prolongation of pregnancy regardless of symptoms for infection.

Furthermore, the reason for antibiotic use was unknown in 50% of the PTL group compared to only 30% of the PPROM group. This seems like a substantial difference. Because the "unknowns" are half of the PTL sample size, there could easily be many reasons for shorter prolongation of pregnancy hidden in this category.

Table 6.15 Reasons for Antibiotic Use in Hospital by Admission Reason

Variables	PTL N=56	PPROM N=45
Reason for Antibiotic use in hospital		
Prolongation	4 (7.4)	28 (62.2)
UTI	18 (32.1)	2 (4.5)
High Temperature	1 (1.8)	1 (2.2)
Unknown	30 (53.6)	14 (31.1)
Others	3 (5.1)	0 (0.0)

Only four women with PTL received antepartum antibiotics for purpose of prolongation of pregnancy (Table 6.15). Thus, as the sample size for number of women who received antepartum antibiotics for prolongation of pregnancy was very small, it was not possible to assess the relationship between antibiotics that are used specifically for the purpose of prolongation on prolongation of pregnancy.

CHAPTER SEVEN: DISCUSSION

7.1 Introduction

The objectives of this study were to determine the frequencies of antepartum antibiotic use in women admitted to hospitals with preterm labour and intact membrane (PTL) or with preterm premature rupture of membrane (PPROM) within the CRHA during the years 1996 and 1999, to compare the frequencies between the two years and to examine the association of antibiotic use and prolongation of pregnancy. The objectives of this final chapter are to: (a) summarize the findings, (b) assess the impact of various biases, (c) address the strength and limitations of the study, and (d) suggest areas for further study.

7.1.1 Summary of Findings

The year 1996 was chosen for comparison with 1999, for a number of reasons. In 1997, Mercer et al., recommended the use of antibiotics for the prolongation of pregnancy in cases with PPROM. Subsequent evidence on the effective use of antibiotics in the prolongation for pregnancy in PPROM promoted the use of antepartum antibiotics in the Calgary region (Personal communication; Dr. Wood et al. November 1999). Prior to 1997, this practice was not common and therefore, 1996 was appropriate for comparing the frequencies of antibiotic use before and after recommendations were made and its impacts on prolongation of pregnancy. Secondly, 1996 data from Health Records was readily and easily accessible.

In chapter four, the comparison of the socio-demographic and obstetric characteristics of women admitted for PTL or PPROM to either FMC, PLC or RGH

during years 1996 and 1999 showed that in both 1996 and 1999, FMC had significantly more women transferred from cities around Calgary region for their care. Also the gestation age of mothers on first admission was the lowest at FMC. These findings are expected since FMC is the hospital designated for high-risk pregnancy cases.

Some of the known risk factors for PTL and PPROM such as previous preterm birth and smoking during pregnancy were similar among the three sites in 1999. In contrast, in 1996, FMC had the highest proportion of women with previous history of preterm birth compared to PLC and RGH.

In chapter five, comparing the overall characteristics of women admitted to any of the three acute care hospitals in CRHA in 1996 with 1999, showed that there were no significant differences in the socio-demographic characteristics of women admitted to hospitals between the two years.

Women in both years had their first admission for PPROM or PTL at about 30 weeks gestation. In both years, the majority of women were admitted to hospitals for PTL as the admission reason than for PPROM. However, the overall proportion of PPROM in CRHA increased from 23.7% in1996 to 31.8% in1999. In fact, there seemed to be a trend towards increased admissions due to PPROM at FMC and PLC from year 1996 to year 1999 with FMC having the higher increase (28.9% in 1996 and 48.0% in 1999). The increased proportion of PPROM at FMC could be the result of regionalization of health services in Calgary. Women with high risk pregnancies were probably referred to an obstetrician who specialized in high risk pregnancies. Therefore, in the event of PTL or PPROM, these women were more likely to go to FMC for their care as their obstetrician would have been based at that hospital.

Even though the other obstetric characteristics of the women admitted to CRHA hospitals in 1996 and 1999 were similar, in 1999, more women were given antepartum antibiotics during their hospital admissions for PTL or PPROM (from 29.4% to 41.5%). The trend for increased antibiotic use was observed at all the three sites with FMC having the most significant increase. At FMC, antepartum antibiotic use increased from 33.3% in 1996 to 51.0% in 1999, from 24.6% to 33.8% at PLC and from 28.6% to 35.5% at RGH. In both years, the prevalence of antibiotic use at FMC was the highest among the three sites.

It is important to note that there were numerous changes taking place in health care that were not measured by this study. For example, health regions were formally created in Alberta in April, 1994, in an effort to improve governance of health services in Alberta (regionalization). Each authority also manages the assessment of the health needs of region, and the allocation of resources once priorities have been established. Regionalization along with other changes in the health system such as changes in clinical practice and availability or lack of new services and programs at different acute care hospitals could have influenced the results of this study between years1996 and 1999. The influence of these changes on the study variables or outcomes are difficult to control for in cross sectional studies.

For instance, the increase in antepartum antibiotic use from 1996 to 1999 was mostly due to changes in the clinical practice for management of women with PPROM. The changes in the management of women with PPROM were based on published data of clinical trials performed in United States in the past two decades and recommendations which were made by the authors in 1997.Considering that women with PPROM were

more likely to receive antibiotics, and also that the proportion of PPROM increased from 1996 to 1999, it was important to take into account this increase in prevalence of PPROM when looking at increased antepartum antibiotic use between the two years. The stratified analysis of antepartum antibiotic use and year of admission to hospital revealed that there was no significant difference in antepartum antibiotic use, between 1996 and 1999 in those women admitted with PTL. On the other hand, for those women admitted to any of the three acute care hospitals in CRHA with PPROM, 75.3% received antepartum antibiotics in 1999 compared to 34.8% in 1996.

Since FMC had the largest increase, from 1996 to 1999, in the proportion of both admissions for PPROM and antepartum antibiotic use, the same stratified analysis was performed specifically for women at FMC. Results revealed that in 1996, 34.6% of women admitted to FMC with PPROM received antepartum antibiotics compared to 80.0% of those admitted with PPROM in 1999. Therefore, this study showed that even after controlling for PPROM, at FMC more women received antibiotics in 1999 compared to 1996.

In both years, half of all the women who received antepartum antibiotics received ampicillin (IV). In 1996, the other two most commonly used antibiotics were cefazolin (IV) and nitrofurantoin (PO). However, in 1999, the second most common antibiotics used were erythromycin (PO) and amoxicillin (PO). The combination of antibiotics used for the purpose of prolongation usually initiated by intravenous broad-spectrum antibiotics such as ampicillin and erythromycin, followed by oral amoxicillin and erythromycin.

In 1999, approximately half of the antepartum antibiotics used were for prolongation of pregnancy compared to only 3.4% in 1996. In fact, in 1996 the most common reason for use of antepartum antibiotics was for treatment of urinary tract infection. The studies which have shown benefit from antibiotic use in PTL or PPROM for prolongation of pregnancy were based on obstetric populations in US with a much higher prevalence of intrauterine infections. Therefore, the generalizability of such results to the obstetric population in Canada has been questionable. Thus, in chapter six, the association between antepartum antibiotic use and prolongation of pregnancy was examined in CRHA.

Comparison of the prolongation of pregnancy (from first admission for PTL or PPROM to delivery) showed that those women who received antepartum antibiotics had a mean prolongation of 30.1 days compared to 47.0 days in those who did not receive antibiotic. Further analysis showed that shorter prolongation of pregnancy in women who received antibiotics was partly due to a greater proportion of PPROM in this group (antibiotic group). Since PPROM was also associated with shorter duration of pregnancy, looking at duration of pregnancy in PTL and PPROM women combined made the effect of antibiotic use to be detrimental for prolongation of pregnancy. When the results were stratified for the effect of admission reason (PTL vs. PPROM) on prolongation, women who were admitted for PPROM and received antibiotic had prolongation pregnancy of 13.3 days compared to 11.4 days in those who did not receive any antibiotics. Therefore, in the group of women admitted for PPROM there was evidence for clinically (but not statistically) significant prolongation of pregnancy. Fourty eight hours prolongation can

be clinically significant in women with low gestational age since it provides enough time for administration of steroids to enhance lung maturation.

Furthermore, those women admitted with PPROM and with a pregnancy gestation age of less than 30 weeks seemed to benefit the most from antibiotic use for prolongation. The prolongation of pregnancy in the group of women with PPROM and gestation age less than 30 weeks was 22.3 days compared to 5.3 days in those with PPROM and gestation age greater than 30 weeks. These results are in accordance with some of the theories that PTL or PPROM less than 30 weeks gestation are more likely to be due to an infective etiology and hence, would benefit more from antibiotic treatment for prolongation of pregnancy. (Lamnot et al. 1998, Mercer et al. 1997, McGregor et al. 1991). Currently, the literature does not provide adequate information regarding the impact of antibiotic use on women presenting with PPROM before 32 weeks gestation.

In the group of women admitted with PTL, those who received antibiotics had a shorter duration of pregnancy compared to those who did not receive any antepartum antibiotics (43.8 days vs. 54.0 days respectively). Therefore, women admitted for preterm labour did not seem to benefit from antibiotic use for prolongation of pregnancy. This shorter duration of pregnancy in the antibiotic group could be related to the reason for antibiotic use. As mentioned previously, women with PTL were more likely to receive antepartum antibiotics if there were signs and symptoms for infection (i.e. UTI). Thus, as there is evidence that infection is associated with preterm birth, women who had sign of infection and received antibiotic for it, were more likely to have early delivery than those with PTL who did not have sign of infection and did not receive antibiotic.

Comparing the neonatal outcome in babies of mothers who received antibiotic to those who did not receive any antepartum antibiotics during their admission for PTL or PPROM was as follow: In the antibiotic group, 7.8% of the babies had a 5-minute Apgar score less than seven compared to only 1.8% of babies in no-antibiotics group. More than half of the babies (65.3%) whose mother received antepartum antibiotics were admitted to NICU after birth compared to 30.6% of the babies in no-antibiotic. Of all babies born to mothers in the group who received antibiotics, 72.0% were born preterm (<37weeks) compared to 45.6% in the no-antibiotic group.

In addition, comparing the neonatal outcome between the years 1996 and 1999, showed that in 1996, 46.6% of the babies born to women admitted to any of the three hospitals in CRHA, for PTL or PPROM, had preterm birth (<37.0 weeks) compared to 65.5% in 1999. In 1996, 32.5% of babies born to women admitted for PTL or PPROM in CRHA had birth weight of less than 2500g compared to 44.5% in 1999. Consequently, more babies were admitted to NICU in 1999 (55.0%) compared to 1996 (44.8%). FMC had the lowest mean gestation age at birth of 32.2 weeks compared to other two hospitals in both years 1996 and 1999. In summary, babies born in 1999 were more likely to be preterm (<37 weeks) and also more likely to have low birth weight (<2500g).

It is important to note that the above associations for antibiotic use and neonatal outcomes or the neonatal outcome between the two years are based on a cross-sectional study and causal relationships can not be concluded.

7.1.2 The Impact of Major Biases on the Findings

Prior to any interpretation of findings, the impact of bias was assessed. Bias is defined as "any trend in the collection, analysis, interpretation, publication, overview of data that can lead to conclusions that are systematically different from truth" (Last 1995).

In this study confounding was one of the biases identified. Confounding is defined as " a mixing effect that occurs when a factor (confounder) associated with the exposure of interest is also associated with the outcome of interest independent of exposure" (Choi & Noseworthy 1992). Stratification was used to control for the effect of confounding where it was thought to be influencing the results. However, there are other potential confounders that were not known or not measured in this study but could have influenced the results. For instance, we observed that women who were admitted for preterm labour and who had received antibiotic had a shorter duration of pregnancy compared to those who did not receive any antibiotic. Without considering the effects of potential biases, this would mean that there is an association between antepartum antibiotic use and shorter duration of pregnancy. However it is likely that intrauterine infection can act as confounder in this relationship. Research has shown that infection is associated with increased risk for preterm birth (shorter duration of pregnancy) (Yost et al. 2000, Andrews et al. 1995, Dodson et al.1988). Infection is also associated with antibiotic use. The more signs and symptoms there are for infection, the more likely women with preterm labour are to receive antibiotic. Therefore, infection is associated with both the outcome of interest (prolongation of pregnancy) and the exposure of interest (antibiotic use) and may act as a confounder in the relationship between antibiotic use and prolongation of pregnancy.

While an attempt was made to collect information on the microbiological findings of women admitted to hospital and also to collect information on history of infection during the current pregnancy, many subjects had missing or unknown information on these variables. Therefore, the impact of infection prior or during the patient's admission on prolongation of pregnancy could not be assessed or controlled for.

Infection as a confounder was a lesser issue for women with PPROM since, in this study, many women who received antepartum antibiotics, received it for PPROM and not necessarily for existence of symptoms of any infection. Therefore, the estimates of mean prolongation of pregnancy are likely to be more accurate for the group of women with PPROM compared to those in the PTL group.

Furthermore, controlling for confounding is based on accurate measurement of the confounder. If subjects are misclassified based on the confounding variable, then an accurate control for confounding would not be possible. For instance, in this study, the reason for admission acted as a confounder in the relationship between antibiotic use and prolongation of pregnancy. PPROM as an admission reason is associated with shorter duration of pregnancy compared to PTL. In addition, PPROM was more prevalent among the women who received antibiotic. Therefore, the confounder (admission reason) was associated both with the outcome (prolongation of pregnancy) and with the exposure (antibiotic use). However, some of the women in the PTL group ended up having PPROM for greater than 12 hours and before 34 weeks of gestation (the definition used to include women in the PPROM group). Therefore, some of the women who were initially classified as PTL and remained in this group, should have been in the PPROM group. In this study the number of women with PTL who later had PPROM was very

small and did not influence the conclusions even when excluded. Otherwise, this could result in imprecise estimates even after controlling for the confounder (admission reason).

Another bias that could influence the results of this study was selection bias. Selection bias is defined as bias that results from procedures used to select subjects that lead to an effect estimate among subjects included in the study different from the estimates from the entire population theoretically targeted (Rothman 1986). In this study, all of the women who were admitted to any of the acute care hospitals in CRHA for preterm labour or preterm premature rupture of membrane and met the inclusion criteria of the study were included. Therefore, selection bias was not an issue. However, if only patients who were admitted to FMC were included in the study, the estimates for some of the variables of interest (ie antibiotic use) obtained from that sample would differ from estimates obtained at other sites and therefore, would not be representative of the estimates in the target population (ie. all women with PTL or PPROM).

7.1.3 Strengths and Limitations

7.1.3.1 Strengths

Prior to this study, there was a lack of information about the current practices of antibiotic use for prolongation of pregnancy in women admitted with PTL or PPROM in CRHA. In addition, the generalizability of the published data from US on the effect of antibiotic use on prolongation of pregnancy has never been assessed in a Canadian population. Despite the fact that, this study was descriptive in design and therefore did not provide information about existence of causal relationships, it provides baseline

information about antibiotic use and its association with prolongation of pregnancy in the CRHA.

Another strength of this study was the collection of the study sample. As all the three acute care hospitals in the CRHA region were included, the results are based on a good representative sample of all women with preterm labour or premature rupture of membrane and therefore, could be generalizable to other cities in Alberta or even Canada if the characteristics of women admitted to hospitals are similar to the characteristics observed in Calgary.

Furthermore, the advantage of using secondary data such as hospital charts was that much information was available for a large number of women in the study and collection of data was relatively inexpensive.

7.1.3.2 Limitations

Review of medical charts is an example of the use of secondary data. Such information is collected for the administrative purposes and therefore, may not contain all the information needed. Medical records are often incomplete and while the information is somewhat standardized, there are some differences from hospital to hospital and even from physician to physician (treatment/diagnostic variability). Therefore, information on some of the variables of interest was not available from the charts, which results in great number of unknowns and imprecise estimates in the analysis.

Hennekens and Buring (1987) noted that "whenever an inference about the characteristics of a population is made using information obtained from a sample, there is always the possibility that the inference will be either inaccurate or imprecise, simply

because of the play of chance or sampling variability". Estimates that are based on a large sample size are less vulnerable to random error because there is less variability in the estimates. As the sample size increases, it is more likely that the sample will correctly reflect the characteristics of the population to which the inference is intended. There was considerable sampling variability when estimates were based on stratum specific rates.

Random error may have impacted the study findings because there were multiple comparisons in the analysis. Some of the observed associations may have arisen due to chance (Type I error). Type I error can be defined as "the error of rejecting a true null hypothesis" (Last, 1995). A Type I error would have resulted in the conclusion that an association between a specific variable and prolongation of pregnancy existed when in fact it did not.

A further limitation of this study was the sample size. The small number of subjects within strata made evaluation of these variables difficult. The study may have had inadequate power to detect meaningful associations between antibiotic use and prolongation of pregnancy (Type II error). Therefore, the results should not be interpreted as evidence that associations did not exist. The relatively small numbers of women in strata may have resulted in a lack of ability to detect an association if one existed (Type II error). As the power in the study decreases, the probability of making a Type II error increases.

One other limitation of the study was related to measuring the outcome (prolongation of pregnancy). Since the antibiotic group and no-antibiotic group were compared for prolongation of pregnancy, a point in time had to be used that is measurable

in both groups. Therefore, prolongation was defined as the time from first admission to hospital or from time of PPROM to delivery. This could be measured in both groups.

However, a more accurate definition would be prolongation from time of antibiotic administration to delivery in the antibiotic group and from time of administration of a placebo to delivery in the control group which was not possible with a cross-sectional study design. Therefore, a more precise effect of antibiotic on prolongation could not be assessed.

In addition, cross sectional studies have the disadvantages in the design in that the researcher is unable to determine any casual association between the exposure and the disease. However, cross sectional study can generate hypothesis related to causal relationships.

7.2. Recommendations for Further Study

This study has provided baseline information on antepartum antibiotics used for women with preterm labour and preterm premature rupture of membrane. To be able to make conclusions on causal effect of antibiotic use on prolongation, clinical trials similar to those performed in Unites States would be necessary. Another recommendation for future study comes from the limitation identified in previous section. The effect of antibiotic use on prolongation would be most accurate and meaningful when considered from time of administration of antibiotic to delivery and not from time of admission to hospital. Therefore, it would be much more meaningful to look at prolongation of pregnancy from time of administration of antibiotic to delivery in one group compared to time of administration of placebo to delivery in control group.

Another follow up from this study would be to assess the neonatal outcome related to antibiotics by looking at the effect of antibiotic use of mothers and development of antibiotic resistance in their babies.

Hopefully, the results of this study and future studies related to antibiotic use for PTL and PPROM would initiate the process for development of standard guidelines for treatment of those women whose preterm labour or premature rupture of membranes is most likely caused by an underlying infection.

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APPENDICES

A. Review of Clinical Trials

Table I. Clinical Trials of Antibiotic Therapy in Preterm Labour With Intact Membranes.

Author	Publication Year	Antibiotic used	Gestation age (weeks) on Admission	# of patients enrolled	Significant delay from admission to delivery, antibiotic vs. placebo group ($p<0.05$)
McGregor et al.	1986	Erythromycin (333mg, 3 times/day for 7days, orally)	<34	Antibiotic=8 Placebo=9	Yes (p=0.027) (32.5 vs. 22.4 days)
Morales et al.	1988	Erythromycin or Ampicillin (500mg every 6 hr. for 10 days, orally)	21-34	Ampicillin=53 Erythromycin= 50 Placebo=47	Yes (31.7 and 28.5 vs. 16.6 days)
Newton et al.	1989	Ampicillin (2g IV every 6 hr for 12 doses and Erythromycin (333 mg every 8 hr for 7 days, orally)	24-34	Antibiotic=48 Placebo=47	No (34.2 vs. 34.1 days)
McGeregor et al	1991	Clindamycin (900 mg IV every hr for 9 doses followed by 300 mg oral 4 times a day for 4 days)	≤ 34	Antibiotic=53 Placebo=50	Yes (p=0.02) (35.3 vs. 25.4 days) For women with bacterial vaginosis: (36 vs. 19 days)
Newton et al.	1991	Ampicillin (2 g of IV) and Sulbactam (1 g of IV) every 6h for 12 doses	24-34	Antibiotic=43 Placebo=43	No
Romero et al.	1993	Ampicillin (1g IV every 4hr) and Erythromycin (250 mg IV every 6hr for 48 hr, followed by Amoxicillin (250 mg, oral) plus Erythromycin (333 mg oral) every 8 hr for 5d	24-34	Antibiotic=129 Placebo=144	No

Table I. continued

Author	Publication Year	Antibiotic used	Gestation age (weeks)	# of patients enrolled	Significant delay from admission to delivery, antibiotic vs. placebo group ($p<0.05$)
Norman et al.	1994	Ampicillin (1g IV, /6 hr for 24 hr) followed by Amoxicillin (500 mg oral, 8 hr for 5 days) concurrent Metronidazole (400 mg oral, 8 hr for 5d	26-34	Antibiotic=43 Placebo=38	Yes (15 vs.2.5 days)
Gorden et al.	1995	Ceftizoxime (2g IV every 8 hr for 9 doses)	24-35	Antibiotic=58 Placebo=59	No
Cox et al.	1996	Ampicillin (2 gm) and Sulbactam (1 gm) every six hours for 8 dose; followed by Ampicillin-clavulanate (250 mg orally every 8 hours for 5 days)	24-34	Antibiotic=39 Placebo=39	No
Svare et al.	1997	Ampicillin (2g IV every six hours for 24 hours followed by pivampicillin 500 mg orally every 8 hours for 24 hr followed by Metronidazole (400 mg orally every 8 hr for 7 days)	26-34	Antibiotic=59 Placebo=51	Yes ($p<0.05$) (47.5 vs. 27 days)
Oyarzun et al.	1998	Amoxicillin (250 mg orally every 8 hr) and erythromycin (500 mg orally every 6 hr) for 7 days	22-36	Antibiotic=80 Placebo=90	No

Table II. Methodological Review of the Clinical Trials of Antibiotic Therapy in Preterm Labour With Intact Membranes.

Author	Study design	Criteria for diagnosis of preterm labour	study limitations
McGregor et al. 1986	Prospective randomized. double blinded. placebo controlled	Clinical diagnosis of preterm labour, not clearly defined	-analysis performed without "intent to treat" -37 of 58 patients are eliminated after randomization resulting in 8 patients in erythromycin group and 9 in control group; sample size too small for significant result - insufficient clinical diagnostic criteria for preterm labour
Morales et al. 1988	Prospective randomized trial	Cervical dilatation greater than 1cm and less than 5cm and regular uterine contractions	- analysis performed without "intent to treat" -27% post randomization exclusion resulting in 53 patients in Ampicillin group, 50 in erythromycin group and 47 in placebo; could reduce internal validity of the study
Newton et al. 1989	Prospective randomized. blinded. placebo controlled trial	3 contractions/20 min, cervical dilation ≥ 1 cm	- 25% of eligible patients were not enrolled due to refused enrollment or not being able to identify them -significant gestational age difference among the antibiotic and placebo group upon enrollment
McGregor et al. 1991	Prospective. randomized. double blind. placebo-controlled trial	≥2 uterine contractions in 20min. persisted after bed rest and required administration of parenteral tocolytic therapy due to changes in cervical dilatation or effacement	- high rate of side effects observed due to Clindamycin treatment (28%) of treatment group and 32% of placebo
Newton et al. 1991	Prospective. randomized. double blind. placebo-controlled trial	3 contractions /20 min. cervical dilatation ≥2 cm. 50% effacement or progressive effacement	The bacterial vaginosis was significantly higher in placebo group compared with antibiotic group; this result might dilute the benefit of antibiotics in the antibiotic group
Romero et al. 1993	Prospective. multi-center. randomized. double blind. placebo-controlled trial	1) History of regular uterine contractions associated with cervical dilatation ≥ 2 and effacement of ≥ 80% or 2) regular uterine contractions occurring at a frequency of 4 in 20 min with duration of 1 hour	- more than half of the patients enrolled have gestational age > 32 weeks; therefore potential benefit of antibiotic may have been diluted. - Significant difference in baseline characteristics between treatment and placebo group which could influence results against antibiotics treatment.

Table II. Continued

Author	Study design	Criteria for diagnosis of preterm labour	study limitations
Norman et al. 1994	Prospective, multi-center, randomized, placebo-controlled trial	Three contractions /20 min, progressive cervical dilatation 1-5 cm	-not a double blinded placebo-control trial - the calculated sample size is not met due to time limitations: therefore small sample size - the infection status of patient's not identified - methods of randomization from different center not identified
Gordon et al. 1995	Prospective, randomized, double blind, placebo-controlled trial	1)History of regular uterine contractions with cervical change or 2) a history of regular uterine contractions (six or more per hour) with an initial cervical dilatation of 2 cm or effacement of > 50% unresponsive to lateral bed rest and intravenous fluids	- the study population is less likely to have an infectious stimulus for preterm labour since they excluded all subjects with any evidence of infection even those with white blood cells counts of > 15,000/mm^3 - therefore this population might be less likely to show benefit of antibacterial use (selection bias)
Cox et al. 1996	Prospective, randomized, double blind, placebo-controlled trial	Regular uterine contractions associated with cervical dilatation ≥ 1cm but <5 cm or cervical change documented by the same examiner	- only 39 patients in each group. sample size is too small - infectious status of women enrolled is unknown
Svare et al. 1997	Prospective, multi-center, randomized, placebo-controlled trial	Regular uterine contraction with < 10min interval for > 60 min.	- 267 women were eligible but were not enrolled due to time limitations: - women not included had lower gestational age than those included: therefore reduces the external validity of the trial
Oyarzun et al., 1998	Prospective, randomized, double blind, placebo-controlled trial	1) History of regular uterine contractions associated with cervical dilatation ≥ 2 and effacement of ≥ 80% or 2) regular uterine contractions occurring at a frequency of 4 in 20 min with duration of 1 hour	- the intrauterine infection status of patient's not identified

Table III. Randomized Double Blind Placebo-Controlled Clinical Trials of Antibiotic Therapy in Preterm Premature Rupture of Membranes

Author	Antibiotic used	Gestational age (weeks)	# of patients enrolled	Prolonged pregnancy in antibiotic group vs. Placebo (day)	Limitations
Johnston et al. (1990)	mezlocillin for 48 hr followed by oral Ampicillin until delivery	20-34	85	Yes ($p<0.05$)	-80% study population is African American with only 45% having perinatal care: therefore external validity is of concern
McGregor et al.(1991)	Erythromycin 333mg 3 times/day until active labour started	23-34	65	significant increase only for those between 22-32 weeks gest (292 vs. 54) hr	small sample size no other specific limitation
Kurki et al. (1992)	2 doses of IV penecillin (5mu) every 6 hours	23-36	101	no significant difference	- not controlled for the effect of tocolytic on prolongation
Mercer et al.(1992)	Oral 333 mg erythromycin every 8 hours till delivery	20-34	220	Yes ($p=0.02$)	-75% study population is African American with high rate of *Niesseria Gonorrhoeae* therefore external validity is of concern -not controlled for the effect of tocolytic and steroid on prolongation
Lockwood et al. (1993)	Pipericillin 3 g IV every 6 hours for 72 hours	24-34	75	Yes (11.4 vs. 6.1) days	-small sample size -infection status of the study population is not reported - not controlled for the effect of tocolytic and steroids
Ernest et al. (1994)	Benzylpenecillin, IV, 1 million unit every 4 hr for 12-24hr and oral 250mg penecillin twice /day till delivery	21-36	148	No significant increase in prolongation of pregnancy	-high post randomization exclusion -PROM patients in labour included: can dilute the effectiveness of antibiotic therapy

Table III. Continued

Author	Antibiotic used	Gestational age (weeks)	# of patients enrolled	Prolonged pregnancy in antibiotic group vs. Placebo (day)	Limitations
Mercer et al. (1997)	Ampicillin 2g every 6 hr and erythromycin 250mg every 6 hr IV for 48 hr followed by oral amoxicyllin 250 mg every 8 hour and erythromycin 333 mg every 8 hour for 5 days.	24-32	611	For the overall population significant improvement in latency ($p<0.001$). For GBS negative group (6.1 vs. 2.9 days)	External validity is of concern: large number of African Americans in the study group and higher rates of STD infections

B. Applicable ICD.9.CM Codes:

644.xx **644.00** **644.03**	**Early or threatened labour** Threatened premature labour without delivery (22 wks to <37 wks) Threatened premature labour without delivery with antepartum condition or complications
658.1x **658.2x**	**Premature rupture of membranes** <24hr prior to onset of labour **Delayed delivery after spontaneous or unspecified rupture of membranes** Prolonged rupture of membranes not otherwise specified or rupture of membranes >24 hr prior to onset of labour
644.2x	**Early onset of delivery** Premature labour with onset of delivery
641.xx **641.0x** **641.1x** **641.2x** **641.3x** **641.8x**	**Antepartum hemorrhage, abruptio placentae, and placenta previa** Placenta previa without hemorrhage Hemorrhage from placenta previa Premature separation of placenta: Abruptio placentae Antepartum or intrapartum hemorrhage associated with coagulation defect Other Antepartum or intrapartum associated with: trauma, uterine leiomyoma
642.xx **642.0x** **642.1x** **642.2x** **642.3x** **642.4x** **642.5x** **642.6x** **642.7x**	**Hypertension complicating pregnancy, childbirth and the puerperium** Benign essential hypertension Hypertension secondary to renal disease Hypertensive heart and renal diseases Transient hypertension of pregnancy mild or unspecified pre-eclampsia severe pre-eclampsia Eclampsia Pre-eclampsia or eclampsia superimposed on pre-existing hypertension
651.xx **651.0x to** **651.9x**	**Multiple gestation**
656.3x	**Fetal distress**
656.4x	**Intrauterine death (fetal death)**
648.5x	**Congenital cardiovascular disorders complicating pregnancy, childbirth and the puerperium**
648.6	**Other Cardiovascular diseases complicating pregnancy, childbirth and the puerperium** conditions classifiable to 390-398 (acute and chronic rheumatic fever), 410-429 (ischemic heart diseases and, other forms of heart disease) and 440- 459 (diseases of arteries, arterioles, and capillaries and other diseases related to circulation)

C. Data Collection Forms

Data collection form (1)

Exclusion criteria (Medical reasons for continuing labour to delivery):

- ☐ Abruption of placenta
- or ☐ Cervical dilation ≥ 5
- or ☐ Fetal anomaly or death
- or ☐ Fetal distress necessitating delivery
- or ☐ Placenta previa
- or ☐ Preterm premature rupture of membranes duration ≤12hrs
- or ☐ Preterm labour with admission to delivery duration ≤12hrs
- or ☐ Multiple gestation
- or ☐ Significant hemorrhage

Maternal medical complications:

- or ☐ Cardiac disease
- or ☐ Hypertensive disorders of pregnancy
- or ☐ Pulmonary hypertension
- or ☐ Renal disorder

Inclusion criteria:

- ☐ Identified to have preterm labour with intact membranes at time of admission
- or ☐ Preterm premature rupture of membranes duration >12hrs
- or ☐ Preterm labour with admission to delivery duration >12hrs
- and ☐ Between gestation age 22 to 34 weeks

Data Collection Form 2 (Front Sheet)

YY/ MM/ DD/ # in filing cabinet

Study ID: [redacted]

Patient's name: _____
Last/ first/middle

Mother's date of birth: (Y/M/D) | | | | | | |

Chart number: | | | | | | | | | | |

PHN: | | | | | | | | | |

SINGLE ADMISSION

YY/ MM/ DD/ # in filing cabinet

Study ID: [redacted]

1. Mother's residence postal code: | | | | | | |

2. Chart Number | | | | | | | |

3. PHN | | | | | | | | | |

4.Site: | | 1= FMC 2= PLC 3= RVH

5. Mother transported? | | 1= Yes 2= No

6. If Yes, Site of origin: | | 1= FMC 2= PLC 3= RVH

7. Date of admission (Y/M/D) | | | | | | |

8. Gestational age at admission | | |

9. Date of discharge (Y/M/D/) | | | | | | |

10. Mother admitted for: | |
1= Preterm labour with intact membranes
2= PPROM

11. If admitted with intact membrane, premature rupture of membranes (PPROM) after admission to hospital | | 1=Yes 2=No

12. Time of PPROM : | | | |

13. Date of PPROM Y/M/D | | | |

Maternal Data

14. Age: ☐☐ Years

15. Smoking Status: ☐ 1=Yes 2= No
2=Yes, but quit in pregnancy -9= Unknown

16. Alcohol use during pregnancy: ☐ 1=Yes 2=No -9=Unknown

17. Previous preterm birth: ☐ 1=Yes 2=No

18. History of infection during pregnancy: ☐ 1=Yes (tested) 2= No
3=Unknown

19. If yes, specify: _____
_____

20. Patient on any antibiotic prior to admission to the hospital: ☐
1= Yes 2=No 9=Unknown

Labour /PPROM and Infection Status

21. Any lab test performed for identifying infection:

	Tested	Positive	Organisms
GBS			
Urine Analysis			
Genital/Vaginal Colonization			
STD			
Other Infection			
Viral Analysis			
WBC (*10^9)			
Histologic Chorioamnionitis			

22. Highest recorded temperature in the 24 hrs prior to delivery: ☐☐ °C

Treatment for prolongation of delivery:

23.Tocolytics: ☐ 1=Yes 2=No 3=Otherwise

24.Steroids: ☐ 1=Yes 2=No 3=Otherwise

25.Antibiotics: ☐ 1=Yes 2=No 3=Otherwise

26. If yes, type(s) and dosage: (This question will be coded after the data is collected)

	Type	Dosage
1)	_____	_____
2)	_____	_____
3)	_____	_____

Delivery:

27.Mode of delivery: ☐ 1= vaginal
2=C-Section

28. Time of delivery: ☐☐☐☐

29.Date of delivery (M/D): ☐☐☐☐

Neonatal data:

30. Live birth: ☐ 1=Yes 2=No

31. Gender: ☐ 1=Male 2=Female

32. Gestation age at delivery: ☐☐ weeks

33.Birth weight: ☐☐ kg

34. Apgar score: 1min: ☐☐ 5 min ☐

Multiple admission-Admission #1

YY/ MM/ DD/ # in filing cabinet

Study ID: [redacted]

1. Mother's residence postal code: | | | | | | |

2. Chart Number | | | | | | | |

3. PHN | | | | | | | | | |

4.Site: | | 1= FMC 2= PLC 3= RVH

5. Mother transported? | | 1= Yes 2= No

6. If Yes, Site of origin: | | 1= FMC 2= PLC 3= RVH

7. Date of admission (Y/M/D) | | | | | | |

8. Gestational age at admission | | |

9. Date of discharge (Y/M/D/) | | | | | | |

10. Mother admitted for: | | 1= Preterm labour with intact membranes
2= PPROM

11. If admitted with intact membrane, premature rupture of membranes (PPROM) after admission to hospital | | 1=Yes 2=No

12. Time of PPROM : | | | | |

13. Date of PPROM Y/M/D | | | | | | |

Maternal Data | |

14. Age: Years

15. Smoking Status: ☐ 1=Yes 2= No
2=Yes, but quit in pregnancy -9= Unknown

16. Alcohol use during pregnancy: ☐ 1=Yes 2=No -9=Unknown

17. Previous preterm birth: ☐ 1=Yes 2=No

18. History of infection during pregnancy: ☐ 1=Yes (tested) 2= No
3=Unknown

19. If yes, specify: _____
_____

20. Patient on any antibiotic prior to admission to the hospital: ☐
1= Yes 2=No 9=Unknown

Labour /PPROM and Infection Status

21. Any lab test performed for identifying infection:

	Tested	Positive	Organisms
GBS			
Urine Analysis			
Genital/Vaginal Colonization			
STD			
Other Infection			
Viral Analysis			
WBC (*10^9)			
Histologic Chorioamnionitis			

22. Highest recorded temperature in the 24 hrs prior to delivery: ☐☐ °C

Treatment for prolongation of delivery:

23. Tocolytics: ☐	1=Yes	2=No	3=Otherwise
24. Steroids: ☐	1=Yes	2=No	3=Otherwise
25. Antibiotics: ☐	1=Yes	2=No	3=Otherwise

26. If yes, type(s) and dosage: (This question will be coded after the data is collected)

	Type	Dosage
1)	_____	_____
2)	_____	_____
3)	_____	_____

Readmission #

2. Chart Number

3. PHN

4.Site: 1= FMC 2= PLC 3= RVH

5. Mother transported? 1= Yes 2= No

6. If Yes, Site of origin: 1= FMC 2= PLC 3= RVH

7. Date of admission (Y/M/D)

8. Gestational age at admission

9. Date of discharge (Y/M/D/)

10. Mother admitted for: 1= Preterm labour with intact membranes
2= PPROM

11. If admitted with intact membrane, premature rupture of membranes (PPROM) after admission to hospital 1=Yes 2=No

12. Time of PPROM :

13. Date of PPROM Y/M/D

Labour /PPROM and Infection Status

21. Any lab test performed for identifying infection:

	Tested	Positive	Organisms
GBS			
Urine Analysis			
Genital/Vaginal Colonization			
STD			
Other Infection			
Viral Analysis			
WBC (*10^9)			
Histologic Chorioamnionitis			

Treatment for prolongation of delivery:

23. Tocolytics: ☐ 1=Yes 2=No 3=Otherwise

24. Steroids: ☐ 1=Yes 2=No 3=Otherwise

25. Antibiotics: ☐ 1=Yes 2=No 3=Otherwise

26. If yes, type(s) and dosage: (This question will be coded after the data is collected)

Type Dosage

1) _____, _____

2) _____, _____

3) _____, _____

Admission with delivery

1. Chart Number

2. PHN

3.Site: 1= FMC 2= PLC 3= RVH

4. Mother transported? 1= Yes 2= No

5. If Yes, Site of origin: 1= FMC 2= PLC 3= RVH

6. Date of admission (Y/M/D)

7. Gestational age at admission

8. Date of discharge (Y/M/D/)

9. Mother admitted for:
1= Preterm labour with intact membranes
2= PPROM

10. If admitted with intact membrane, premature rupture of membranes (PPROM) after admission to hospital 1=Yes 2=No

11. Time of PPROM :

12. Date of PPROM Y/M/D

Labour /PPROM and Infection Status

13. Any lab test performed for identifying infection:

	Tested	Positive	Organisms
GBS			
Urine Analysis			
Genital/Vaginal Colonization			
STD			
Other Infection			
Viral Analysis			
WBC (*10^9)			
Histologic Chorioamnionitis			

14. Highest recorded temperature in the 24 hrs prior to delivery: ☐☐ °C

Treatment for prolongation of delivery:

15. Tocolytics: ☐ 1=Yes 2=No 3=Otherwise

16. Steroids: ☐ 1=Yes 2=No 3=Otherwise

17. Antibiotics: ☐ 1=Yes 2=No 3=Otherwise

18. If yes, type(s) and dosage: (This question will be coded after the data is collected)

Type Dosage

1) _____, _____

2) _____, _____

3) _____, _____

Delivery:

19. Mode of delivery: ☐ 1= vaginal 2=C-Section

20. Time of delivery: ☐☐☐☐

21. Date of delivery (M/D): ☐☐☐☐

Neonatal data:

22. Live birth: ☐ 1=Yes 2=No

23. Gender: ☐ 1=Male 2=Female

24. Gestation age at delivery: ☐☐ weeks

25. Birth weight: ☐☐ kg

26. Apgar score: 1min: ☐☐ 5 min ☐

D. Sample Size Calculation

Sample size needed to detect a15% significant increase in proportion of women in preterm labour or PPROM who were given antibiotics to prolong pregnancy in 1996 (p_1) compared to 1999 (p_2):

p_1 (1996)

p_1 (1999)	30%	35%	40%	45%
45%	268			
50%		280		
55%			286	
60%				286