MATERNAL
GROUP B STREPTOCOCCAL
COLONIZATION

AND

PRETERM PREMATURE RUPTURE
OF THE FETAL MEMBRANES.

by

RANDA M. S. NOOH

Thesis submitted to
the School of Graduate Studies and Research
in partial fulfillment of the requirements for
the M.Sc. degree in Epidemiology.

UNIVERSITY OF OTTAWA

MARCH 1994

ISBN 0-315-95964-9

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

ACKNOWLEDGEMENT

My sincere thanks to my husband and partner Adel Babesail, whom I credit for his patience, continuous encouragement and loving support, without which this wouldn't have been possible. My special thanks to my beautiful sons Abdul Mohsen and Mohammed, for their tolerance and trust, whose smiles and love are all the support I ever need. I express my deep gratitude to my beloved parents; Professor Mohammed Nooh and Mrs. Fattan Hasseeb, who always stand by me and encourage me to reach my highest potential. I would also like to thank my supervisors; Dr. Nicholas Birkett and Dr. Paula Stewart, who gave me their time, suggestions, and expertise. My special thanks to Silvia Declich, for her friendship throughout the cold and lonely years of studying in Ottawa, and to Fay Draper for all her kindness and sincere efforts. And, last but not least, my genuine gratitude to Dr. Rama Nair, who gave me this chance.

TABLE OF CONTENTS

CONTENTS OF FIGURES

CHAPTER 1: LITERATURE REVIEW:

CONTENTS OF TABLES

CHAPTER 1: LITERATURE REVIEW:

3.1 THE TOTAL STUDY POPULATION:

3.2 THE PREVALENCE STUDY:

3.2.1 : Group B Streptococcal colonization status.

3.2.2 : Degree of colonization of GBS positive women.

3.2.3 : Other micro-organisms cultured at 28 weeks of gestation.

3.2.4 : Age distribution of cultured women.

3.2.5 : Marital status of cultured women.

3.2.6 : Height distribution of cultured women.

3.2.7 : Weight distribution of cultured women.

3.2.8 : Parity of cultured women.

3.2.9 : Gravidity of cultured women.

3.2.10: Employment status of cultured women.

3.2.11: Occupations of cultured women.

3.2.12: Smoking status of cultured women.

3.2.13: Number of cigarettes smoked per day.

3.2.14: Alcohol intake during the pregnancy.

3.2.15: Past medical history of cultured women.

3.2.16: Past obstetrical and gynecological history of cultured women.

3.2.17: History of the current pregnancy of cultured women.

3.3 THE COHORT STUDY:

3.3.1 : The association between vaginal GBS colonization and preterm PROM.

ABSTRACT

THE PROBLEM:

Group B Streptococci (GBS) are one of the most frequent causes of life-threatening infections in newly born infants, who acquire the micro-organism while passing through the genital tracts of their asymptomatic colonized mothers. Some previous studies have suggested that maternal genital colonization by GBS is associated with preterm rupture of the fetal membranes and preterm delivery. In this thesis both a prevalence study and a historical cohort study were conducted, to investigate the prevalence of maternal GBS colonization at 28 weeks of gestation, and whether there is an association between colonization and preterm rupture of the fetal membranes.

BACKGROUND INFORMATION:

Different rates for maternal GBS colonization during pregnancy have been reported, ranging from 4.6% up to 40%. The association between maternal GBS colonization and preterm rupture of the membranes has been reported in some studies, but other studies have not supported this view, which led to differences in opinions and the lack of a specific conclusion. The variations in the findings of these studies may have been due to several factors, which include differences in cultured sites and phase of

pregnancy at which culture was obtained, in addition to the wide variations in the definition of premature rupture of the membranes used by various authors.

AIMS AND OBJECTIVES:

1) To determine the prevalence of maternal Group B Streptococcal colonization at 28 weeks of gestation for women delivering at the Ottawa General Hospital during a study period of one year.
2) To determine whether vaginal colonization with Group B Streptococci at 28 weeks of gestation is independently associated with preterm premature rupture of the fetal membranes.

TYPE OF STUDY AND METHODS:

This study is composed of two main parts. The first part is a prevalence study to determine the prevalence of maternal GBS colonization at 28 weeks of gestation, and the second part is a historical cohort study to investigate whether there is an association between vaginal colonization by GBS and preterm rupture of the fetal membranes. Data for this study were collected for women delivering at the Ottawa General Hospital during a study period of one year, and who had been registered for antenatal care with any of the obstetrical specialists who had antenatal clinics at the hospital.

STATISTICAL ANALYSIS:

Analysis of the prevalence study consisted of basic descriptive statistics, and calculation of the rate of GBS colonization. Analysis of the cohort study consisted of calculating the incidence rates of preterm rupture of the membranes among the cohorts under study, and comparing them for those exposed and those non-exposed. Chi-square was calculated to compare between the study groups, and the relative risk of preterm rupture of membranes for GBS positive women was calculated to estimate the magnitude of the association along with confidence intervals. Stratified analysis was performed to control for potential confounders, in addition to logistic regression analysis to obtain an adjusted relative risk and confidence interval.

RESULTS:

Vaginal cultures at 28 weeks of gestation revealed GBS colonization in 12.6% of the study population. The differences between GBS positive and negative mothers was statistically significant in terms of mean maternal height, the rate being higher in women under 150 centimeters in height. The prevalence was also significantly higher among women with medical history and current pregnancy history of diabetes mellitus, and in those who had early bleeding during the current pregnancy. The difference in alcohol intake between GBS positive and negative mothers showed borderline statistical significance.

Results of the cohort study showed a significant difference in gestational age at delivery between GBS positive and negative women, the rate of colonization being higher among women delivering before 37 weeks of gestation. There was a higher percentage of GBS positive women whose labour was induced or had elective caesarian sections, and the mean birthweight of infants born to positive mothers was lower than that of infants born to negative mothers. There were 29 cases (3.0%) who had preterm PROM. The number of colonized mothers who had preterm PROM was 17 (14.2%), and the number non-colonized was 12 (1.4%).

The association between vaginal GBS colonization and preterm rupture of the membranes showed a Relative Risk of 9.94 (95% Confidence Interval = $4.9 < RR < 20.3$). When GBS positive and negative women were compared, there were significant differences in maternal height, marital status, gravidity, current pregnancy history of early bleeding, and urinary tract infection. Comparison of women whose pregnancy ended by preterm rupture of the membranes and women who did not, revealed significant differences in gravidity, past history of preterm labour, and current pregnancy history of early and late bleeding. Stratified analysis showed effect modification by maternal age, gravidity, height, weight, employment status, alcohol intake during the pregnancy, in addition to current pregnancy history of early and late bleeding. Stepwise logistic regression analysis showed an adjusted relative risk of preterm PROM for GBS positive women of 13.4 (95% Confidence Interval = $5.93 < RR < 30.1$).

CONCLUSION:

The prevalence of maternal GBS colonization at 28 weeks of gestation was 12.6%. The relative risk of preterm rupture of the membranes for positive mothers was 9.94, and the adjusted relative risk was 13.4. The results of this study support the hypothesis that maternal genital colonization by Group B Streptococci during pregnancy increases the risk of preterm premature rupture of the fetal membranes. Therefore, this is a significant health problem that is worthy of future research to explore what can be done to bring down this high prevalence rate and decrease its impact, in addition to methods of prevention of preterm premature rupture of the fetal membranes for GBS positive mothers.

INTRODUCTION:

The Group B Streptococci (GBS) are one of the most common causes of life-threatening infections in newly born infants. The reservoir of GBS is mainly the mother's vaginal or anorectal flora or both. Infants acquire the infection while passing through the genital tracts of their asymptomatic colonized mothers during labour and delivery.[1]

Although most previous work on Group B Streptococcal colonization during pregnancy has centered on neonatal sepsis, there has been an increasing interest in the effect of maternal genital colonization and infection on the outcome of the pregnancy. Maternal colonization by GBS during pregnancy, in addition to being the most likely cause of early onset group B streptococcal disease in infants, has been associated with many complications of pregnancy and the puerperium. Group B Streptococci have been implicated as a cause of maternal urinary tract infections, amnionitis caused by ascending infection from the cervix and vagina, in addition to intrapartum and postpartum bacteraemia.[2] Some previous studies have also found that maternal vaginal or cervical colonization by GBS is associated with preterm labour and delivery by means of initiating preterm premature rupture of the fetal membranes and subsequently, preterm delivery, while other studies have failed to find any association.[3]

To determine the magnitude of the problem of Group B Streptococcal colonization during pregnancy, and its role as an important cause of both maternal and neonatal mortality and morbidity, and in order to plan appropriate preventive measures against GBS disease in infants, the natural history and the prevalence of maternal GBS colonization during pregnancy have to be investigated. In addition, the epidemiology of preterm premature rupture of the fetal membranes and preterm birth have to be clarified and understood. The prevalence of maternal GBS colonization during pregnancy, and whether it has a role in initiating the early rupture of the fetal membranes have to be explored.

In this study I have investigated the prevalence of GBS colonization in a select group of pregnant women, and examined whether there is an association between maternal genital colonization by GBS during pregnancy and the consequent onset of preterm premature rupture of the fetal membranes (PPROM), which has been a controversial area for many years.

CHAPTER 1: LITERATURE REVIEW:

1.1 EPIDEMIOLOGY OF PRETERM BIRTH:

Term gestation is usually defined as 37 completed weeks of gestation. Preterm labour is commonly understood as labour occurring prior to 37 completed weeks of gestation. The definition of preterm birth and preterm labour as given in Danforth's Obstetrics and Gynecology textbook[4] is:

> "... preterm birth is a birth prior to 37 completed weeks, and preterm labour is the onset of labour prior to 37 completed weeks of gestation ..."

The definition of the preterm infant given by the World Health Organization[5] is:

> "... that neonate who is delivered at a gestational age of less than but not including 37 completed weeks or 259 days, regardless of its weight ..."

Preterm birth is the actual delivery occurring prior to 37 weeks of gestation. In Canada, the rate of preterm birth was 6.5% in 1991[6], and in the Ottawa-Carleton region the rate of livebirths born before 37 weeks of pregnancy was 7.1% in the same year[7]. In the United States almost 9% of all neonates are born before 37 completed weeks of gestation, and 6% are born before 36 weeks.[8] Preterm birth occurs as a result of either or both maternal and fetal complications that arise during the pregnancy; these include obstetrical conditions like preterm labour and preterm premature rupture of the fetal membranes (PPROM), maternal medical or obstetrical complications, in addition to fetal conditions that complicate the pregnancy, and which may cause preterm birth as a result of elective preterm delivery. Some authors have reported that preterm births result equally from either of these set of conditions.[9] Preterm labour, in itself, also occurs as a result of preterm premature rupture of the fetal membranes, which is known to be the cause in more than one-third of cases.[4]

Some studies have reported that the main obstetrical condition predisposing to preterm birth differs according to the population studied. This was demonstrated by Meis and his co-workers[10] who studied two groups of about 1,500 women each. The first group was receiving public medical assistance, while the second group had private insurance. In the group receiving public assistance, 34% of preterm births occurred due to preterm labour, 46% due to PPROM, and 20% due to other medical complications. On the other hand, in the private insurance group, 55% of preterm births occurred due to preterm labour, 27% due to PPROM, and 18% due to medical complications.

Several risk factors have been associated with preterm birth, which include; demographic factors, behavioral factors, factors pertaining to maternal health care during pregnancy, maternal medical and obstetrical risk factors, in addition to maternal and fetal complications arising during the current pregnancy.[11]

Demographic risk factors for preterm birth include maternal age of less than 19 or over 40 years, unmarried status, low socio-economic conditions, limited maternal education, and ethnic and racial factors. In the United States it has been reported that a black mother is twice as likely to deliver a preterm infant as a white, Mexican, Cuban, Chinese, Japanese, or American Indian mother.[12] The preterm delivery rate before 37 completed weeks of gestation for black women is reported to be almost twice that for white women (16.3% compared to 7.7% in 1982).[12]

Behavioral risk factors that contribute to preterm birth include smoking during the pregnancy, which is also known to lower infant birth weight by relative intra-uterine fetal growth retardation. In the United States 13-20% of all preterm births can be attributed to maternal smoking.[9,13] Maternal smoking also increases the occurrence of preterm premature rupture of the fetal membranes, in addition to abruptio-placenta, placenta previa, intra-uterine fetal growth retardation, and intra-uterine fetal deaths.[9] Other behavioral risk factors include alcohol intake during pregnancy, which increases the risk of delivering low birth weight infants, in addition to drug and substance abuse, which affects the gestational age at delivery unfavorably by causing preterm labour.[14]

Poor maternal nutrition, low maternal pre-pregnancy weight and poor weight gain during the pregnancy are important maternal factors associated with preterm birth. Poor or inadequate prenatal care is another important factor in the etiology of preterm birth,[13] and women who do not receive antenatal care are at a higher risk of delivering low birth weight infants, especially in mothers of lower socio-economic status.

Miller and associates[13] studied maternal behavioral risk factors, smoking, and poor weight gain during pregnancy in 1,077 black women and 2,333 white women. They concluded that there were several important behavioral risk factors that contribute to the etiology of preterm birth and low infant birth weight. These factors were: usage of alcohol or drugs, inadequate or no prenatal care, maternal age over 35 or under 17 years, mothers underweight for height at conception, low weight gain during the pregnancy, and cigarette smoking.

Poor medical and obstetrical history also contribute to the etiology of preterm birth. Previous preterm delivery is known to have a recurrence rate of 17-40%, which increases with the number of previous preterm deliveries and decreases with the number of term deliveries.[15] Past obstetrical and gynaecological conditions which predispose to preterm birth include genito-urinary anomalies and uterine malformations like unicornuate and bicornuate uteri. Women with uterine fibromyomas are also known to be more susceptible to ante-partum hemorrhage and preterm rupture of the fetal membranes.

Obstetrical conditions that complicate the pregnancy and may predispose to preterm birth include cervical incompetence, which is the premature dilatation of the cervix in the second trimester of pregnancy, and may cause preterm labour or premature rupture of the membranes. Cervical incompetence may occur due to trauma, and may also occur as a result of the intra-uterine exposure of the mother to diethylstilbestrol (DES).[16] Women exposed to DES in utero have a 15-28% higher risk for preterm delivery and a 20-24% higher risk of spontaneous abortions.[16] Abruptio-placenta, which is a type of antepartum hemorrhage that occurs following the premature separation of a normally implanted placenta from the uterine wall, leads to the subsequent onset of labour by initiating strong uterine contractions that precipitate delivery, whether preterm or at term.[17] Furthermore, any condition that causes excessive uterine enlargement, like multiple pregnancy or poly-hydramnios, where the presence of excessive amniotic fluid stretches and weakens the fetal membranes, may precipitate preterm labour. Another predisposing condition is intra-amniotic infection which produces specific types of prostaglandins that result in preterm uterine contractions and subsequent labour. Past maternal history of multiple spontaneous abortions, short inter-pregnancy intervals, maternal genetic factors, history of pre-eclampsia, and maternal medical conditions, like hypertension and diabetes, in addition to maternal infections like pyelonephritis have all been implicated as causes of preterm birth.[8]

Recently, maternal colonization of the genital tract during pregnancy has been implicated as a cause of preterm birth. Bacterial colonization is thought to contribute to the occurrence of preterm rupture of the membranes, and even to initiate preterm labour, the mechanisms of which are not clearly understood.

1.2 MATERNAL GENITAL COLONIZATION AND PRETERM BIRTH:

There is accumulating evidence that in many cases of preterm birth maternal genital bacterial colonization during the pregnancy plays a major role in weakening the fetal membranes, which leads to their rupture and the subsequent onset of preterm labour.[18]

The traditional concern with genital colonization of the pregnant mother and premature rupture of the fetal membranes was that once the membranes ruptured, the protective barrier surrounding the fetus is removed, which facilitates the introduction of infection from the vagina, and the subsequent development of intra-amniotic infection and chorio-amnionitis. This is likely to occur in cases of PROM in which infection develops after the membranes have ruptured at term (Figure 1).

TRADITIONAL VIEW ON THE ASSOCIATION OF MATERNAL GENITAL COLONIZATION AND PRETERM RUPTURE OF THE MEMBRANES

Fetal membranes rupture

↓

Protective barrier surrounding the fetus is eroded

↓

Introduction of infection from the vagina

↓

Intra-amniotic infection and chorio-amnionitis

Figure 1

On the other hand, recent interest has focused on maternal genital colonization during pregnancy as a cause of premature rupture of the fetal membranes rather than a result, especially when the rupture occurs before term (i.e. before 37 weeks of gestation). It has been postulated that bacteria colonizing the maternal genital tract ascend from the vagina before the membranes rupture, and gain access to the fetal membranes. This subsequently provokes the inflammatory process thus causing a sub-clinical or clinical infection which, in turn, weakens the membranes and precipitates the rupture regardless of gestational age (Figure 2).

CURRENT VIEW ON THE ASSOCIATION OF MATERNAL GENITAL COLONIZATION AND PRETERM RUPTURE OF THE MEMBRANES

Bacteria ascend from the vagina

↓

They gain access to the fetal membranes

↓

Inflammatory process is provoked

↓

Membranes are weakened
and rupture occurs.

Figure 2

1.3 MATERNAL GENITAL COLONIZATION BY GROUP B STREPTOCOCCI:

The Group B Streptococci or *Streptococcus agalactiae* are usually found as commensal microorganisms in the genital flora of both males and females. Genital colonization with Group B Streptococci (GBS) is asymptomatic in most cases, but the micro-organism may be sexually transmitted.[19]

Reported rates of asymptomatic vaginal colonization by GBS has ranged between 4.6% to 36% of pregnant women.[20,21,22,23] This rate has been found to vary according to maternal age, gravidity, duration of the pregnancy, number and location of sites cultured, and the choice of culture medium. The reported rates are highest for women under 20 years of age, and when the cultured site is the lower genital tract, rather than the cervix. It has been suggested that the primary reservoir of GBS is the colon and rectum[23], and that colonization of the maternal genital tract occurs by ascending transmission[23] from the vagina, which accounts for the highest yield in culture when the swab is taken from the lower genital tract. Some studies have reported that maternal GBS genital colonization during pregnancy may be persistent, transient or intermittent.[3]

Lewin and Amstey[21] studied the natural history of GBS colonization in a cohort of pregnant women in 1981. They obtained specimens from the cervix and vagina of 722 pregnant women during their first, second, and third trimesters of pregnancy, and at the time of delivery. The authors reported that the colonization rate was 7% to 8% in any trimester of pregnancy, and 19% of the women were colonized at some time during the pregnancy. 50% of infants born to colonized mothers were colonized themselves. The authors also reported variations in the pattern of maternal colonization over time; 32% of colonized women were positive in only one of the trimesters, 27% were positive in two trimesters, while 41% were positive in all three trimesters. This suggests that mothers positive for GBS may lose the organism spontaneously at some time during the pregnancy.

Baker, Barrett, and Yow[24] obtained cultures from the throat and vagina of 388 pregnant women at their second trimester of pregnancy, between 20-28 weeks of gestation, and during the third trimester on admission for labour and delivery. They determined that maternal colonization rates increased from 14.8% to 25.4% between the second and the third trimesters of pregnancy ($p<0.025$), and 72% of the infants born to colonized mothers were colonized themselves.

Ancona, Ferrieri and Williams[25] studied the maternal factors that influence the acquisition of GBS by newly-born infants. During a 27 month study period, cultures were obtained from 1,416 women during labour, 113 or 8.0% of whom were found to be colonized. In addition, cultures were obtained from 1,675 infants born during that period, 57 or 3.4% of whom yielded at least one positive culture at birth, and 98 or 5.9% of whom yielded positive cultures at more than one occasion after birth. 67% of the neonates born to colonized mothers were colonized themselves, and only 1% of the infants born to non-colonized mothers were colonized with GBS. The authors also reported that the heavier the vaginal colonization by GBS in the mother, the more likely the infant is to acquire the micro-organism.

Regan, Chao, and James[26] investigated whether there is an association between maternal colonization with GBS and prematurity. They cultured the cervix of 6,706 pregnant women admitted for labour and delivery. They reported GBS colonization in 877 women, which indicated a maternal colonization rate of 13.4%.

Minkoff and associates[18] undertook a microbiologic screen of women in their second trimester of pregnancy, to study the vaginal flora and the effect of each microorganism on the outcome of pregnancy. They cultured 233 patients at the time of their first prenatal visit (average of 14 weeks of gestation). The culture site was the posterior vaginal fornix, and GBS was isolated in 23 women or 9.9% of the study population.

Hastings and associates[27] studied maternal Group B Streptococcal colonization and obtained cultures from the lower vagina and rectum of pregnant women. Cultures were obtained at the first prenatal visit, then at 28 and 36 weeks of gestation and during labour. The overall colonization rate was found to be 28.4%.

Bobitt, Damato and Sakakini[28] in 1985 studied GBS maternal colonization rates, whether perinatal complications occurred more frequently in GBS carriers, the predictive value of prenatal GBS cultures, and whether inoculum size or the long-term presence of GBS carrier status affected maternal and neonatal morbidity. In a study population of 718 pregnant women, vaginal cultures were taken at the first prenatal visit, at 24 weeks of gestation, then every four weeks, and finally on admission for labour and delivery. The culture sites were the lateral and posterior vaginal fornices. Their results showed that 11.3% of the mothers had at least one positive GBS culture during their pregnancy or at delivery, and GBS isolation antenatally was twice as frequent as at delivery (4.6% antenatally, and 2.5% at delivery). In addition, morbidity and low birth weight was more frequent in GBS carriers. The authors found that the risk of morbidity in chronic carriers of GBS or those with at least three positive cultures was not greater than that of the transient carriers or those with GBS isolated only once. With regards to inoculum size, they found that the risk was about the same in heavily or lightly colonized patients, and therefore heavy colonization was not associated with an increased risk of perinatal complications when compared to lighter colonization.

Canadian studies of maternal Group B Streptococcal colonization are very few. The first Canadian study to investigate maternal and fetal colonization by GBS was conducted by Macdonald and Mackenzie[29] in 1977. They studied the rates of GBS colonization in both parturient mothers and their newly born infants in the Ottawa region. Both vaginal and rectal swabs were obtained from mothers delivering at the Ottawa Civic Hospital at the time of admission for labour and delivery. In addition, umbilical, groin, and ear swabs were taken from the infants within five minutes of birth. The authors reported a colonization rate at delivery of 20% for the mothers, and 8% for the infants. In addition, 35% of mothers colonized with GBS delivered colonized infants. Compared to other studies, these rates are relatively high, which may be attributed to the collection of swabs from both vaginal and rectal sites in the mothers and from multiple sites in the infants.

Allardice and co-workers[30] conducted a study in 1982 in Winnipeg, Manitoba, Canada, to investigate maternal vaginal colonization by GBS. The aim of their study was to determine the rates of GBS colonization in a group of mothers antenatally and during labour, and to find the rate of transmission of GBS to newly born infants. Cultures were obtained from the lateral vaginal walls of pregnant women between 28 and 34 weeks of gestation, and again on admission for labour and delivery. The antenatal colonization rate was reported to be 10.3%, and the rate of colonization during labour was 7.6%.

Joshi, Chen, and Turnell[22] in 1987 conducted another study, in which they obtained vaginal swabs from all the women admitted to Regina General Hospital for labour and delivery during a period of one year. For a total of 3,078 women delivering during that time, 2.3% were positive for GBS.

Yow and Leeds[31] studied the natural history of GBS colonization in pregnant women. They reported a vaginal colonization rate of 20.4%, and 42% of infants born to positive mothers were positive for GBS. The authors also demonstrated that colonization was influenced by maternal gravidity and ethnic group.

In the studies previously mentioned, different rates have been reported for maternal GBS colonization, during pregnancy or at delivery, which varied widely from as low as 2.3%[22] to as high as 28.4%[27]. Table 1 summarizes the previously obtained maternal GBS colonization rates.

Table 1: Maternal Group B Streptococcal colonization rates obtained in previous studies.

Author(s)	Cultured site(s)	* Gestation	Rate
Joshi, Chen, & Turnell	Vagina	During labour	2.3%
Lewin & Amstey	Cervix & vagina	1st, 2nd, & 3rd trim.& delivery	7.0% to 8.0%
Ancona, Ferrieri & Williams.	Vagina	During labour	8.0%
Minkoff et.al.	Posterior vag.fornix	2nd trimester	9.9%
Allardice et.al.	Lateral vag.wall	2nd trimester & during labour	10.3% & 7.6%
Bobitt, Damato, & Sakakini	Vagina	2nd trimester	11.3%
Regan, Chao, & James	Cervix	Labour	13.4%
Baker, Barrett & Yow	Throat & vagina	2nd trimester	14% to 25.4%
Macdonald & Mackenzie	Vagina & rectum	Delivery	20.0%
Yow & Leeds	Vagina	Labour	20.4%
Hastings et.al.	Lower vag. & rectum	1st visit, 2nd, & 3rd trimester	28.4%

* Gestation indicates the stage of pregnancy at which culture was obtained from the mother.

The prevalence rates of maternal GBS colonization are influenced by many factors, which include; maternal age, parity, gravidity, ethnic background, geographical location, maternal socio-economic status, in addition to the number of sites cultured, the distance of culture site from the cervix, and the selectivity and phase of the culture medium. Colonization by GBS is also thought to be higher in pregnant teenagers.

The most important problem related to maternal GBS colonization during pregnancy is the consequent colonization and infection of the newly born infant. Transmission of GBS from mother to infant occurs either before delivery by ascending infection from the vagina, which may precipitate rupture of the membranes, or during delivery while the infant passes through the birth canal, which may lead to early neonatal infection and sepsis. In addition, the heavier the mother is colonized, the more likely the infant is to acquire the infection.[32]

1.4 GROUP B STREPTOCOCCI AND PERINATAL INFECTION:

The association between Group B Streptococci and perinatal infection was first reported as early as 1938. Meningitis caused by GBS was first described between 1958 and 1968, and this was followed by an increasing awareness and interest in GBS morbidity. Since 1964, however, there was a significant increase in the number of reports that documented serious neonatal infection or sepsis caused by GBS, which has been implicated as the major etiologic agent of meningitis occurring in the first month of life.[24]

In the 1970's medical interest was mainly focused on the relation of GBS to neonatal sepsis. In 1977, Baker[32] estimated that in the United States there were between 12,000 to 15,000 newborns with GBS infection annually, with a mortality rate higher than 50%. Since then, it has been established that infants became infected by GBS mainly through vertical transmission from the mother by passage through the birth canal.[1]

There are two clinical forms of GBS disease that are seen in infants; early-onset GBS disease, and late-onset disease. The early-onset form of the disease is diagnosed within a few hours to a few days after birth, but usually within the first 24 hours of life. It is more common than late-onset disease, and its mortality and morbidity are higher, in spite of appropriate antibiotic therapy. It is characterized by fever, generalized septicaemia, signs of respiratory distress, decreased peripheral circulation, tachypnea, apnoeic attacks, cyanosis and pulmonary infiltration. Clinically and radiologically it presents with a picture similar to Respiratory Distress Syndrome. Hematological changes include thrombocytopenia, leucocytosis or leukopenia, and positive blood and/or cerebrospinal fluid cultures for GBS. Histologically, GBS are found embedded within hyaline membranes. This form of the disease is associated with low birth weight, preterm labour, preterm and/or prolonged PROM, and maternal fever. The reported rates of early-onset GBS disease range from 1.1 to 3.7 per 1000 live births, with case-fatality rates of 22% up to 80%.[26,34,35]

The late onset form of GBS disease, on the other hand, appears later in the neonatal period, usually after the first week of life and up to three months after birth, and has a case fatality rate of about 23%. It occurs in infants who are usually born healthy, and its most common clinical manifestations are poor infant feeding, meningitis, and seizures. This form of the disease carries a high morbidity, with neurologic sequelae to the meningitis occurring in 30 to 50% of cases, in the form of blindness, deafness and spasticity. Other manifestations of late-onset GBS disease include asymptomatic bacteremia, cellulitis, septic arthritis, and osteomyelitis.[35]

Early-onset GBS disease has been attributed to maternal genital colonization with GBS, and it has been postulated that the infant acquires the infection through vertical transmission from the mother while passing through the birth canal, which explains the early onset of the disease within the first few hours of life. On the other hand, late-onset GBS disease is thought to occur after delivery, mainly as a result of horizontal rather than vertical transmission, by means of nosocomial or hospital-acquired infection.[36]

Boyer and his co-workers[37] studied infants with the early-onset form of GBS disease during a period of nine years. Of a total of 32,384 live births at their hospital, 61 cases developed GBS bacteremia, which indicated an attack rate of 1.9 per 1000 live births. The annual rate of GBS disease ranged from 0.6 to 3.7 per 1000 live births. The authors concluded that most cases of the disease had an intra-uterine pathogenesis, as cultures were obtained from the infants soon after delivery and the diagnosis of GBS disease was made during the first 24 hours of life. Their findings correspond with those of Pass and his associates[38] who studied 2,407 infants born over a seven month period, and reported that the incidence of early-onset GBS disease within their study population was 3.7 per 1000 livebirths, and 67% of colonized infants were ill within one hour of birth.

Pyatti and his co-workers[39] obtained blood cultures within one hour of birth from 1,187 premature infants. They found the rate of GBS disease to be 20.2 per 1000 livebirths, and 88% of the infants with GBS disease were bacteraemic at birth.

Allardice and his co-workers[30] studied GBS neonatal infection at their centre in Winnipeg, Manitoba, Canada, between 1973 and 1977, and reported a sevenfold increase in neonatal infections during that period. They also reported that it was associated with 10% of all neonatal deaths. The authors obtained antenatal cultures for GBS to study the rate of GBS colonization and, in addition, one of their objectives was to determine the effect of antibiotic intervention during labour on the positive group. Women admitted for labour and delivery with known positive antenatal cultures were given intravenous antibiotic treatment, while in another sample of women admitted in labour without prior antenatal screening, cultures were obtained from them during labour, but they were left without the antibiotic intervention. Of the known antenatally positive mothers who also had positive labour cultures, 10% of their infants were GBS positive. In cases of women treated with antibiotics, none of the infants developed GBS disease, while in the untreated group 45.6% of infants born to GBS positive mothers carried the organism, and 7.4% of the infants developed GBS disease. Associated conditions in the infants who developed GBS sepsis were prolonged rupture of the fetal membranes and low birth weight.

Gerards and his co-workers[40] studied the degree of infant streptococcal colonization as a determinant of early onset neonatal GBS disease. In a sample of 1,150 infants admitted to the neonatal intensive care unit at their center, GBS was cultured from 145 or 12.6% of them. Of this positive group 14.5% had early onset GBS disease, and 3.5% had late onset disease. The rest were asymptomatic. Vertical transmission of GBS was assumed when cultures taken immediately after birth were positive, and horizontal transmission was assumed when sites that had been culture negative for GBS during the first week after birth became positive after that. 87 infants or 60% of the positive group were assumed to have acquired GBS through vertical transmission, 21 infants or 24% of which developed early onset disease. Horizontal transmission was established in 28 infants or 19% of the positive group, in which no cases of early-onset disease were found. These findings support the view that vertical transmission is the main method of transmission in infants developing early-onset disease. The authors also noted that the number of positive sites in the infant, in addition to the degree of colonization of each site were important determinants of neonatal GBS disease. In a previous study by the same authors, they had also demonstrated that vaginal colonization of the mothers, in addition to the degree of colonization, were important determinants of vertical transmission of GBS.[41]

It is apparent that GBS colonization of the pregnant mother is the most important determinant of GBS sepsis in the infant, especially in case of early-onset GBS disease. It is also evident that in case of early-onset GBS disease, the infant acquires the infection by vertical transmission from the mother. GBS morbidity and low infant birth weight are more frequent in infants born to mothers colonized by GBS. The risk of GBS morbidity in infants born to mothers found to be chronic carriers of GBS was not greater than that of infants born to transient carriers[28]. In addition, the risk of infant GBS morbidity remains the same whether the mother was heavily or lightly colonized[28]. The importance of GBS disease stems from its high mortality and morbidity, which is likely to be higher in preterm infants. To prevent this excessive mortality and morbidity, it becomes important to research maternal GBS colonization and methods of controlling it.

1.5 MATERNAL GROUP B STREPTOCOCCAL COLONIZATION AND PRETERM PREMATURE RUPTURE OF THE FETAL MEMBRANES:

One of the most important consequences to maternal GBS colonization during pregnancy, in addition to neonatal infection, is its suggested association with preterm rupture of the fetal membranes. To study this association further, the nature of these membranes, in addition to their function, and the significance and consequences of their preterm rupture have to be understood.

The fetal membranes are usually fully formed by the twelveth week of pregnancy by the fusion of the amnion and chorion that surround the developing fetus. This creates one compartment which is known as the gestational sac, and which functions throughout the pregnancy to protect the developing fetus. This gestational sac contains the amniotic fluid which cushions and protects the developing fetus from injury caused by exterior trauma, in addition to enhancing normal fetal muscle development and promoting fetal growth. One of the most important functions of these membranes is to act as a barrier to protect the fetus and its environment from external infections caused by invading or ascending micro-organisms.[8]

Normal fetal membranes are very strong early in the pregnancy. As the pregnancy progresses, the membranes undergo certain biochemical and biophysical changes that involve modifications in their collagen content. These changes gradually weaken the fetal membranes, which ultimately facilitates their rupture at term.[17]

The term "Premature rupture of membranes" (PROM) may be thought to mean rupture of the fetal membranes prematurely or before term. However, in clinical practice this term is used for all the cases in which the membranes have ruptured prior to the onset of regular uterine contractions regardless of gestational age, i.e. whether at term or not. The definition of premature rupture of the fetal membranes as given by Danforth's Obstetrics[4] is:

> "... rupture of the fetal membranes before the onset of labour ..."

Most cases of PROM occur at or near term, and it is usually viewed as a normal event which may precede the onset of labour. About 8% to 10% of all deliveries are preceded by PROM, 80% of which occur in term patients. Worldwide reports on the frequency of PROM have ranged between 5% and 45% of all deliveries.[42,43] The most important problem attributed to PROM is that it is the most common cause of preterm birth.

In case of term gestation, premature rupture of the membranes does not produce much morbidity, especially if it is quickly followed by the onset of labour. On the other hand, a preterm rupture has many detrimental effects on both the mother and the infant, regardless of whether it was followed by subsequent labour or not. The earlier the rupture occurs in the pregnancy the worse the prognosis for both mother and infant, especially when rupture occurs before 32 weeks of gestation. In addition, the risk to both the mother and the infant increases greatly, especially if labour does not start within 24 to 48 hours after the rupture. Consequently, we need to consider preterm PROM which occurs before term, or prior to 37 completed weeks of gestation, as a separate entity to that which occurs at or near term. Therefore, preterm premature rupture of the membranes (PPROM) may be defined as: rupture of the fetal membranes before 37 completed weeks of gestation and prior to the onset of labour.

The most important problem attributed to preterm PROM is that it accounts for a larger number of preterm deliveries than any other cause, and over one-third of all preterm births are preceded by PPROM.[44,45,46] Kaltreider and Kohl[44] found that 34% of all preterm deliveries were preceded by preterm PROM. Furthermore, preterm PROM has also been reported to have a recurrence rate of 21%.[45]

In most cases, labour occurs spontaneously within a short period of time following rupture of the membranes. In other cases, preterm delivery has to be induced if maternal or fetal complications or infections arise following the rupture. Further complications that are associated with preterm PROM, other than preterm labour, include maternal and/or fetal or neonatal infections, early-onset and late-onset GBS disease, meningitis, in addition to other fetal complications associated with prolapse or compression of the umbilical cord.

The most important epidemiologic factor that has been associated with an increased risk of preterm PROM is maternal smoking during the pregnancy. No relation has been found between preterm PROM and maternal age or parity, maternal weight, external trauma, fetal weight or position, increased intra-amniotic pressure, tensile strength of the membranes, or the presence of meconium in the amniotic fluid.[47,48]

As previously mentioned, multiple pregnancy is known to precipitate preterm PROM and preterm labour by stretching and weakening the fetal membranes. In addition, certain obstetrical complications that arise during the pregnancy may cause preterm PROM and subsequent preterm delivery, like polyhydramnios, which also stretches the fetal membranes, thereby precipitating their rupture. Abruptio placenta is known to be associated with preterm PROM, the mechanism of which is not clearly understood. Uterine fibromyomas have also been associated with an increased risk of antepartum hemorrhage and rupture of the membranes. Preterm PROM may occur following certain invasive obstetrical procedures like amniocentesis, and cervical cerclage (a surgical procedure performed in women with cervical incompetence to strengthen the cervix in order to prevent the onset of preterm labour). In addition, in cases of cervical incompetence, the membranes may rupture after having bulged into the vagina for some time. Preterm uterine activity, and premature cervical dilatation have also been implicated as causes of preterm PROM.[8]

The mechanism by which rupture of membranes occurs is still not known. It has been suggested that as the pregnancy advances, there is a decrease in the collagen content of the membranes, which weakens them. Recent studies have postulated that a local reaction occurs in the membranes which bring about their rupture. This reaction is probably caused by genital microorganisms which ascend from the vagina, and invade the fetal membranes, which consequently causes a subclinical or clinical infection.[45]

Genital colonization of pregnant mothers by Group B Streptococci has been implicated to cause preterm PROM, and subsequent preterm delivery. This association has been investigated in several studies. Three of the main studies conducted have supported the presence of an association, while three have indicated that no association exists.

The association of maternal GBS colonization during pregnancy and the subsequent onset of preterm PROM and preterm labour was first reported by Regan and his associates in 1981.[26] They studied cervical colonization with GBS in pregnant women in labour to investigate whether it was associated with Premature rupture of the membranes and subsequent preterm delivery. During a study period of three years, cervical swabs were obtained from pregnant women on their admission for labour and delivery. The time of rupture of the membranes and the time of onset of labour were both documented, and PROM was designated if the time interval between the rupture of the membranes and the onset of uterine contractions was more than one hour. In a total number of 6,706 patients, 877 (13.4%) had GBS isolated from their cervix. PROM occurred in 545 (8.1%) of the total population studied, 134 (24.6%) of whom were colonized with GBS. 15.3% of GBS-positive mothers had PROM compared to 8.1% of the total population. The difference in the occurrence of PROM between the population of colonized mothers and the total population was statistically significant ($\underline{X}^2$ = 49.2, $p < 0.005$). 47 (5.4%) of the 877 mothers found to be colonized by GBS had a preterm delivery of < 32 weeks of gestation, compared to 123 (1.8%) of the total study population. This difference was also statistically significant ($\underline{X}^2$ = 52.1, $p < 0.005$). On the whole, 24.6% of mothers who developed PROM, and 38% of those who had preterm deliveries were colonized antenatally by GBS. The differences in the rate of colonization for the total population (13.4%) and the groups who had PROM (15.3%) and those who had preterm delivery (5.4%) were also highly significant ($\underline{X}^2$ = 69.7, $p < 0.005$, and $\underline{X}^2$ = 65.2, $p < 0.005$ respectively). The main draw back to this study was the inclusion of cases of ruptured membranes at or near term, in whom not much morbidity is expected, with the preterm PROM cases, which has totally different clinical implications on both the mother and infant. In addition, from the definition of PROM used by the authors, it is apparent that they have also included cases of prolonged rupture of the membranes, or those cases who had a prolonged time period or latency period between rupture of the membranes and the onset of labour contractions regardless of gestational age, and who might have developed a post rupture infection, thereby affecting maternal colonization status.

Baker, Barret and Yow[24] did not find any correlation between maternal GBS colonization and premature labour, PROM, or the birth of a preterm or low birth weight baby. They conducted a cohort study in which cultures were obtained from the throat and vagina of 388 pregnant women during either the second trimester of pregnancy between 20 to 28 weeks of gestation (n = 183), or the third trimester on admission for labour and delivery (n = 205). Among women cultured during the second trimester, preterm labour occurred more often in the colonized group (3/27 or 11%) than among non-colonized mothers (10/156 or 6.3%), but this difference was not statistically significant. The authors also reported that prolonged rupture of the fetal membranes (> 24 hours) occurred more often in the colonized group (3/27 or 11%), compared to the non-colonized group (6/156 or 3.8%). The main disadvantage of this study, in addition to its low power, is the authors' inclusion of cases with prolonged rupture of membranes with the PROM group, irrespective of whether the rupture occurred at term or preterm.

Minkoff and his associates[18] found an association between GBS colonization and preterm labour, but this difference was not statistically significant. They reported no association between colonization and PROM. The authors undertook a microbiologic screen of women in their second trimester of pregnancy, to study the prevalence of all micro-organisms of the vaginal flora and the effect of each microorganism on the outcome of pregnancy, and whether any were associated with PROM or preterm labour, using a cohort study design. Vaginal cultures were obtained from a total of 233 women at their first antenatal visit (average of 14 weeks gestation). Culture swabs were taken from the posterior vaginal fornix. GBS was isolated in 23/233 or 9.9%. They also reported that 17.1% (6/35) of positive mothers had subsequent preterm labour, compared to 8.7% (16/183) in non-colonized mothers, but this difference was not statistically significant ($p = 0.22$). There was no difference in the frequency of PROM among their GBS positive patients (4/40 or 10%), compared to their GBS negative group (13/148 or 8.8%), and there was no significant association between GBS colonization and preterm labour or PROM. The authors did not report a Relative Risk. In addition to the very low power of this study, the main draw-back is that the authors also included PROM cases that occurred at or near term with the preterm PROM cases.

Hastings and associates[27] also found no association between GBS colonization and preterm PROM or preterm labour. They conducted a cohort study in which they cultured the lower vagina and rectum of 1,457 pregnant women at their first prenatal visit, then at 28 and 36 weeks of gestation, and finally during labour. In this study the authors documented the age, parity, and race of the mothers, in addition to the duration of labour and rupture of the membranes, and intra- and post-partum pyrexia (> 37.5°c). The authors reported an overall colonization rate of 414/1457 or 28%. No associations were found between GBS colonization and maternal age or parity. Colonization varied widely among various racial groups, being highest in blacks and lowest among mothers of Asian origin. There were no significant differences in the rates of miscarriages, stillbirths, prematurity, and low birth weight among colonized and non-colonized mothers. The frequency of preterm labour in the two groups was 6.5% (19/294) and 6.4% (49/765) respectively (p-value = 0.9), which indicated that colonized mothers did not have a higher incidence of preterm labour than non-colonized mothers. The only difference between the two groups was intra-partum pyrexia which occurred more often in colonized mothers. The authors' findings showed that the only adverse outcome related to vaginal colonization with GBS was intrapartum pyrexia, and that it had no association with preterm labour or PROM. The draw-back of this study was that the PROM group included both preterm and term PROM cases. The authors definition of PROM included all cases which had "...membranes ruptured prior to admission..." regardless of the gestational age at which that rupture occurred.

A more recent study published in 1988 which supports the findings of Regan and his associates[26] is that conducted by Alger and co-workers.[49] The authors studied 52 pregnant women admitted to the hospital with preterm PROM between 20 to 37 weeks of gestation. The control group was a total of 84 women selected from public and private prenatal clinics, who delivered at term. The control group were matched to the case group, in a case to control ratio of 2:1 for 32 women and 1:1 for 20 women, for age (+ or - 1 year), parity (nulliparous or multiparous), and gestational age (+ or - 2 weeks). Specimens were obtained from the endocervical canal of the case group during labour, and from the control group at the same gestational age corresponding to the matched case. Statistical analysis was performed by logistic regression, controlling for maternal age, parity, race, marital status, gestational age at delivery, health care payment plan, and source of prenatal care. The authors reported that GBS were isolated significantly more often in women with preterm PROM (15.6%) compared to the controls (3.8%). The odds ratio of preterm PROM associated with GBS colonization was found to be 8.04 (p-value = 0.007). This was the only study in the literature to investigate preterm PROM per se, as that occurring prior to 37 weeks of gestation.

Matoras and his associates[50] published a study in 1989, investigating the association between GBS, PROM and preterm delivery which also supported the view that maternal GBS colonization during pregnancy is associated with PROM and subsequent preterm labour. The authors conducted a cohort study, in which samples were obtained from 1,050 pregnant women, from the lower vagina, rectum, and cervix of each pregnant mother at any time in the pregnancy between 17 to 42 weeks of gestation (average 32.98 weeks). PROM was found to be statistically higher in women with vaginal and/or rectal colonization with GBS (26.4%) than non-colonized women (17.8%). ($\underline{X}^2 = 5.32$ and $p < 0.05$). The authors calculated a relative risk of PROM for mothers colonized with GBS compared to non-colonized mothers of 1.66 (95% CI = 1.07 - 2.58). GBS carriers in whom the organism was also isolated from the cervix had a PROM prevalence of 41.7%, which was statistically higher than carriers with negative cervical cultures (only positive vaginal cultures) in whom the prevalence of PROM was 19%. (RR = 3.03, $\underline{X}^2$ = 4.04, 95% CI = 1.01 - 9.29). This group also had a statistically higher rate of PROM compared to non-carriers. The prevalence of PROM in non-carriers was 17.8%. ($\underline{X}^2$ = 10.16, p = 0.0018; RR = 3.31, 95% CI = 1.44 - 7.53). Carriers whose cervical culture was negative had a PROM prevalence similar to that of non-colonized mothers; 19.0% and 17.8% respectively, with a RR of 1.09 ($p > 0.05$). The authors concluded that the rate of PROM was statistically higher in women with vaginal and/or rectal colonization in whom GBS was isolated from the cervix, while the rate tended to be very similar to non-colonized mothers when the cervical culture was negative. From the definition of PROM used by the authors in this study; "...Spontaneous expulsion of amniotic fluid occurring 1 hour or longer prior to the onset of regular contractions...", it is apparent that they have included all cases of ruptured membranes, whether occurring preterm or at term, in addition to cases of prolonged rupture of the membranes in their outcome group.

SUMMARY:

The variations in the findings of these studies may have been due to several factors which include the differences in culture sites, culture media, and phase of the pregnancy at which culture was obtained. In addition, there were wide variations in the definition of PROM used by the various authors, such that some have included both preterm and term rupture cases in one group, while others have also included prolonged rupture cases with the preterm PROM cases regardless of the gestational age at which rupture occurred.

In most of the previously conducted studies there was no investigation of preterm PROM as an independent entity with a clear and strict definition as only those cases of preterm PROM occurring prior to 37 completed weeks of gestation; such that some authors have mixed the outcome of preterm PROM with PROM that occurs at a more advanced gestational age at which not much morbidity is expected from the rupture in any case. Furthermore, the differences of maternal culture sites and the gestational age at which cultures were obtained may have contributed to the discrepancies in these reports. Also, it is worthwhile to mention that some of the previously conducted studies had certain limitations of low power[18,24], which weakens these studies and raises questions on their conclusions.

The mechanism by which GBS infection triggers the rupture of the fetal membranes is still not clearly understood. Regan[26] suggested that GBS colonization of the cervix may alter the cervical mucous plug or may have a direct effect on the membranes overlying the cervical os leading to their rupture. There is still a need to investigate if, how and why GBS contribute to the preterm rupture of the membranes, and whether maternal or fetal factors or even factors which involve the microorganism itself may be responsible.

In my opinion, to draw an appropriate conclusion as to whether any association between maternal GBS colonization and preterm PROM exists, further analytical studies are required, in which strict definitions and criteria should be allocated for the outcome and each of the variables involved.

RATIONALE OF THE STUDY:

Some of the studies previously conducted to examine the association between maternal genital colonization by GBS during pregnancy and preterm PROM have supported the view that there is an association between colonization and preterm PROM, while other studies have not supported this view, which led to differences in opinions and the lack of a specific conclusion. There is still a need to investigate whether GBS contribute to the occurrence of preterm rupture of the fetal membranes, and consequently causing preterm labour and delivery.

In this study, I am interested in examining the prevalence of maternal GBS colonization, in addition to determining whether there is an association between maternal vaginal colonization with GBS during pregnancy and the occurrence of preterm premature rupture of the fetal membranes.

My hypothesis is that colonization of the female genital tract by GBS during pregnancy is associated with preterm PROM. The question I would like to answer is: Is cervical colonization by GBS at 28 weeks of gestation independently associated with preterm premature rupture of the fetal membranes?

RESEARCH OBJECTIVES:

1) To determine the prevalence of maternal Group B Streptococcal colonization at 28 weeks of gestation for women delivering at the Ottawa General Hospital during a study period of one year.

2) To determine whether vaginal colonization with Group B Streptococci at 28 weeks of gestation is independently associated with preterm premature rupture of the fetal membranes.

CHAPTER 2: TYPE OF STUDY AND METHODS:

2.1 STUDY DESIGN:

This study is composed of two main parts. The first part is a prevalence study, to determine the prevalence of Group B Streptococcal vaginal colonization at 28 weeks of gestation for eligible pregnant women delivering at the Ottawa General Hospital during a study period of one year. The second part of this study is a historical cohort study to investigate whether there is an association between vaginal colonization by Group B Streptococci at 28 weeks of gestation and preterm premature rupture of the fetal membranes.

In the cohort study, which is a follow up of the prevalence study population, the exposed group were mothers who had a positive high vaginal culture for Group B Streptococci at 28 weeks of gestation, while the non-exposed group were mothers who had a negative vaginal culture. The outcome, which was preterm premature rupture of the fetal membranes, was designated if it had occurred between 28 and 36 completed weeks of gestation.

2.2 STUDY POPULATION:

The study population was eligible women delivering at the Ottawa General Hospital during a period of one year, from the first of April 1990 until the end of March 1991, and who had been registered for antenatal care with any of the obstetrical specialists who had antenatal clinics at the hospital. This included both the mothers receiving antenatal care at the hospital clinics, and the mothers receiving antenatal care at the same obstetricians' clinics outside the hospital. Referrals from other tertiary care institutions and community hospitals were excluded from the study.

At the Ottawa General Hospital a high vaginal swab is routinely obtained for culture from all the pregnant women attending the antenatal clinics at both 28 and 36 weeks of gestation, specifically to detect Group B Streptococcal colonization. The swab is cultured on sheep blood agar plates, and no other specific culture medium is used. No antibiotic intervention is made if positive cultures are found, and this information is only used to identify infants at risk for Group B Streptococcal infection.

Criteria for eligibility for the prevalence study was that mothers had to have delivered at the Ottawa General Hospital at any time during the study period of one year, and had to have been registered for antenatal care before 25 weeks of gestation.

Criteria for eligibility for the cohort study, in addition to those mentioned above, were that mothers had to have a single pregnancy. Furthermore, mothers with conditions that could have independently predisposed to preterm premature rupture of the membranes (e.g. previous history of preterm rupture of the membranes, current pregnancy history of polyhydramnios, abruptio-placenta, and those undergoing cervical cerclage) were excluded from the cohort study. Women who had spontaneous preterm labour that was not preceded by rupture of the membranes during the current pregnancy were excluded from the cohort study. In addition, women who had spontaneous preterm labour that was resolved by tocolytic therapy during the current pregnancy, and who might have progressed to deliver at term, were also excluded because of their higher risk status. Women with severe obstetrical complications that had necessitated the induction of labour before term, were also excluded from the cohort study.

Data were not collected from the files of women who had registered for antenatal care after 25 weeks of gestation when they might have been cultured at the time of booking but not specifically at 28 weeks. Mothers who had not received any antenatal care throughout the pregnancy were also excluded apriori from data collection. Mothers who had preterm rupture of the membranes or preterm labour at any time before 28 weeks of gestation, thereby not getting the opportunity to be cultured at 28 weeks, were also excluded. Data were also not collected from cases found to be referrals from obstetricians or family practitioners who did not have antenatal clinics at the hospital if a referral letter or form was found in the chart.

2.3 DATA COLLECTION:

Data collected for both the prevalence and cohort parts of the study were obtained from the mother's files at the medical records department of the Ottawa General Hospital. A computer programme was specifically made for this study by the medical records department which allowed them to obtain the file numbers of all the eligible women. This programme allowed the inclusion of all the mothers who had delivered at the hospital during the study period, and who were registered with any of the obstetrical specialists who had antenatal clinics at the hospital, whether the mothers received their antenatal care at the hospital clinics or at the obstetricians' clinics outside the hospital. The programme also allowed the exclusion of all referrals from other tertiary care institutions and community hospitals, in addition to all the women who had received antenatal care from obstetricians or family practitioners who did not have antenatal clinics at the hospital.

Data extracted from the files of all the eligible women were recorded on a pre-prepared form (Appendix A). Data sources were the following:

- The Ontario Antenatal Record 1 (Appendix B): which is completed by both the antenatal nurse and the attending obstetrician on the first booking visit, and contains information on maternal personal and social history, past obstetric and gynecological history, past medical and surgical history, and family history, in addition to measurements of maternal height, pre-pregnancy weight, and blood pressure.

- The Ontario antenatal record 2 (Appendix C): which is completed by both the nurse and the obstetrician on each consecutive visit, and contains information on the gestational age at the first antenatal visit, maternal follow up of the mother during each visit, and any obstetrical or medical conditions, or complications arising during the pregnancy.

- The delivery record (Appendix D): which is completed by the nurse and attending obstetrician during labour and delivery, and contains information on maternal medical and obstetrical status during labour and delivery.

- Nurses antepartum record: which is completed by the nurse on admission of the expectant mother into hospital for labour and delivery.

Extracted information consisted of the following:

1) Maternal personal information: which included maternal age at the time of booking, maternal marital status, educational level, employment status, occupation, parity, gravidity, number of previous term deliveries, previous preterm deliveries, previous abortions, number of living children, and maternal height and weight, in addition to information on maternal social factors; smoking during the pregnancy, the number of cigarettes smoked per day, and alcohol intake during the pregnancy.

2) Maternal past medical history: which described the history of any medical condition that might have had an effect on the history or outcome of the current pregnancy. This included history of urinary tract infections, kidney disease, functional heart murmurs, heart disease, hypertension, diabetes mellitus, bronchial asthma, thyroid disease, and other medical disorders.

3) Past obstetrical and gynecological history: which described any condition which might have had an effect on the history or outcome of the current pregnancy. This included past history of preterm labour, premature rupture of membranes, sexually transmitted and pelvic inflammatory diseases, past history of gestational diabetes, pregnancy induced hypertension, antepartum hemorrhage, ectopic pregnancies, and previous intra-uterine fetal deaths or stillbirths.

4) History of the current pregnancy: which described any condition which might have influenced the outcome of the pregnancy; like the occurrence of early or late bleeding, amnio-centesis, urinary tract infections, sexually transmitted disease, gestational diabetes, diabetes mellitus, pregnancy induced hypertension, essential hypertension, pre-eclampsia, abruptio-

placenta, placenta previa, polyhydramnios, oligohydramnios, maternal anemia, Intra-uterine fetal growth retardation, and fetal RH-isoimmunization.

5) Status of high vaginal culture at 28 weeks of gestation: whether vaginal culture was done at 28 weeks, whether Group B Streptococci were isolated, degree of GBS colonization, and whether any other micro-organisms were found on culture.

6) Outcome of the pregnancy: which included: gestational age at delivery, type of labour, method of delivery, infant status; liveborn or stillborn, infant birth weight, gender of the infant, and outcome of the pregnancy. Information was obtained on the outcome of interest (preterm PROM), and the gestational age in weeks at which the rupture occurred. The main outcome of interest for the cohort study was the occurrence of preterm rupture of the fetal membranes prior to 37 weeks of gestation, whether the actual delivery occurred preterm or at term. Information was also collected on the occurrence of preterm labour, the gestational age at which it occurred, and whether it was resolved by tocolytic therapy or not. For the purpose of this study it was not important to indicate the length of time between rupture of the membranes

and the occurrence of labour or delivery, since the focus is on GBS colonization as the causal factor which precipitates the rupture.

The criteria defining each of these variables were as follows:

Maternal age: The age recorded on the mother's first visit on the Ontario Antenatal Record 1 (Appendix B).

Marital status: Maternal marital status was categorized into 6 categories; married, common-law, single, separated, divorced, and widowed. This information was also obtained from the antenatal record 1.

Maternal education: Information on maternal education was obtained from the Ontario antenatal record 1, and was categorized into 12 categories; less than grade 8, grade 8, grade 9, grade 10, grade 11, grade 12, grade 13, first year college or university, second year university, third year university, fourth year university, and post-graduate education.

Employment status: Information on whether the mother was employed or not at the beginning of the pregnancy.

Maternal occupation: Information on employment status and maternal occupation was obtained from the antenatal record 1, or the nurses' antepartum sheet. Occupation was classified into 14 categories based on the Standard Occupational Classification Manual (OCM)[51], which identifies most of the occupations in Canada. The classification serving the purposes of this study was based on the "... highest level of aggregation of occupations ..."[51] or the major groups of occupations according to the manual, as follows:

1. Managerial: Administrative and management positions, government administratives and officials.
2. Natural Sciences: Chemists, physicists, biologists, engineers, statisticians and computer workers.
3. Social Sciences: Sociologists, social workers, judges, lawyers, economists, psychologists, and librarians.
4. Teaching: Includes teachers of all levels of education, and teaching related occupations.
5. Medicine and health: Physicians, surgeons, nurses, dentists, dental assistants, pharmacists, and any health diagnosis or treating occupations.
6. Artistic and recreational: Painters, artists, interior designers, musicians, translators and

writers, in addition to sports occupations as coaches, trainers and athletes.

7. Clerical: Secretaries, typists, book-keepers, postal clerks, insurance, accountants, cashiers, receptionists, and hotel and personnel clerks.
8. Sales: Vendors, real estate, buyers, advertising and insurance sales, wholesale and retail trade.
9. Services: Armed forces and police officers, food and beverage preparation services, bar tenders, child care providers, housekeepers, hairdressers, travel guides, cleaners and janitors.
11. Other: Other occupations not listed above, which included occupations in religion, construction, farming, fishing, forestry, mining, machining, product fabricating, transport equipment operating, and other crafts.

Two other categories of occupations were added; students and home-makers. Students were defined as full time students at any level of education, and the homemakers category included both house-wives and non-employed mothers.

Maternal height and weight: was obtained from the antenatal record 1. Maternal height was that measured on the first antenatal visit, and maternal weight was the self reported pre-pregnancy weight.

Past medical history: was also obtained from the antenatal record 1. Information collected was the obstetrician's clinical diagnoses indicated on the form.

Past obstetric history: was obtained from both the Ontario antenatal record 1 and the Ontario antenatal record 2 (Appendix C) in the mothers' charts. Data collected were based on the obstetricians' clinical diagnoses indicated on the forms and in the charts.

History of the present pregnancy: was obtained from the Ontario antenatal record 2, from the obstetricians' admission notes, and from the delivery record (Appendix D). Early bleeding was defined as bleeding occurring prior to 16 weeks of gestation, and late bleeding was defined as that occurring after 16 weeks. Bleeding was designated only if it had been diagnosed by the attending obstetrician. Data collected on other clinical variables was based on the obstetricians' diagnoses indicated on the forms and in the charts.

Maternal smoking status: was obtained either from the antenatal record 1, the nurses antepartum notes, or from the obstetricians' notes in the chart. This was defined as maternal smoking at any time during the pregnancy. In addition, information on the number of cigarettes smoked per day was also collected.

Alcohol intake during pregnancy: was mainly obtained from the nurses antepartum notes. It was categorized into four categories; none, occasional, moderate, and heavy.

Culture status at 28 weeks: This information included whether culture was performed at 28 weeks of gestation or not, whether GBS were isolated, heaviness of GBS growth, and whether any other micro-organisms were also found on culture. This was obtained from the laboratory culture reports in the mother's charts.

The outcome; Preterm PROM: The main outcome of interest for the cohort study was the occurrence of preterm premature rupture of the fetal membranes. This was defined as rupture of the fetal membranes, as diagnosed by the attending obstetrician, prior to 37 completed weeks of gestation, whether the actual delivery occurred preterm or at term.

Gestational age at delivery: was defined as the gestational age in weeks at which delivery occurred, and was obtained from the Delivery Record (Appendix D).

Type of labour: The type of labour was defined as the method by which the mother went into labour, and was categorized into three categories; spontaneous, induced, and other. The "other" category mainly consisted of elective caesarian section cases. This information was also obtained from the delivery record.

Method of delivery: The method by which delivery occurred, whether vaginally or by caesarian section, was also obtained from the delivery record.

Infant status: Information on whether the infant was liveborn or stillborn was obtained from the delivery record.

Gender of the infant: whether male or female, was obtained either from the delivery record or the nurses' post-partum notes.

Infant birthweight: at delivery, in grams, was obtained from the delivery record or the nurses' postpartum notes.

Any missing information from any of the previously mentioned categories was recorded as missing by leaving a blank space on the data collection form.

2.4 SAMPLE SIZE:

The sample size needed for conducting this study was calculated based on a type I error of 0.05, and a power of 80% according to the formula given by Kelsey[52] for cohort studies. Calculation was based on 1989 data which indicated that the percentage of preterm births at Ottawa General Hospital for that year was 6.9%[53], and an estimated Relative Risk of 2. As the prevalence rate of maternal Group B Streptococcal colonization rates varied from previous studies, and ranged from 4% to 40%, a prevalence rate of 10% was assumed, which gives an exposed to non-exposed ratio of 1:9. Accordingly, the number required as the exposed group was calculated as 125 cases. The number of culture positive cases found after data collection was 131 cases, which were all used as the exposed group.

2.5 ETHICAL CONSIDERATIONS:

The study proposal was reviewed by the chairman of the ethical review committee who stated that it was acceptable to proceed without full committee review, due to its being a historical study fully based on chart review. Approval to access the obstetrical patient's charts was given by the head of the Department of Obstetrics and Gynecology.

2.6 QUALITY OF THE DATA:

The information recorded in the maternal charts was not assessed for validity. Data collected were purely based on the obstetricians' clinical diagnoses written in the charts. For example, if a diagnosis of gestational diabetes was written on the antenatal chart, then this diagnosis was taken as correct, without going back to the blood sugar analysis or other diagnostic tests, and so on. This is not expected to pose much of a problem, since it is assumed that the clinical and laboratory criteria for diagnosing the condition had to have been met, which consequently led the attending obstetrician into making the diagnosis and indicating it on the mothers' charts.

With regards to missing data, information found to be missing or not mentioned in a mother's chart, like maternal height, weight, smoking status, or alcohol intake was recorded as missing on the data collection form. Any missing information on a certain variable was not considered as a negative response. For example; if there was no mention of maternal smoking status in a certain chart, then the mother was not considered as a non-smoker, but as missing data.

Intra-observer reliability in chart abstraction was assessed in a pilot study on the first 80 cases, for which the charts were reviewed, data collected and entered into the computer using the Epi-Info computer programme. This was followed by a second review of the same files, data collection and entry. Both datasets were cross-validated to examine variations between them to assess intra-observer reliability in data collection. Discrepancies were found in three cases (3.75%); once in recording maternal height, and twice in recording infant birthweight.

After reviewing the first 80 charts, the form used for data collection was revised and extra variables on past obstetric history (namely past term pregnancies, previous abortions, and the number of living children) were added. This information was added to allow for comparison of cultured and non-cultured mothers in data analysis. In addition, variables pertaining to maternal and fetal complications arising during the current pregnancy (namely maternal anemia, intrauterine growth retardation and RH isoimmunization) were added to the form to allow control for these factors in data analysis.

On completion of chart review for all the eligible women, and after entry of the data into a first dataset, data were re-entered again into a second dataset. This was then cross-validated with the first set, to correct any errors that had occurred during data entry. Discrepancies were found in 97 cases (6.3%) as follows; 6 cases in maternal age, 11 cases in maternal occupation, 5 cases in maternal parity, 13 cases in maternal height, 9 cases in maternal weight, 7 cases in past medical history, 6 cases in past obstetric history, 11 cases in history of the present pregnancy, 21 cases in infant birthweight, and 8 cases in infant gender. Otherwise, no differences were noted between the two datasets. These discrepancies were resolved by re-examining each cases data collection form, then correcting the information in the main data set.

2.7 STATISTICAL ANALYSIS:

Data entry was done using the Epi-Info computer program, and data analysis was performed using both Epi-Info and the BMDP statistical package on the University of Ottawa AMDAHL mainframe computer.

The first step in statistical analysis of the data consisted of comparison of women found to be cultured at 28 weeks of gestation and women who were not cultured at that time or whose culture reports were not present in the chart.

The second step was analysis of the prevalence study, which mainly consisted of basic descriptive statistics, then calculation of the GBS colonization rate, and comparison of GBS positive and negative women.

The third step was analysis of the cohort study, which consisted of calculating the frequency rates of preterm PROM among the cohorts under study, and comparing them for those exposed and those non-exposed. Relative Risks were calculated to estimate the magnitude of the association along with confidence intervals. Chi-square testing was used to determine whether the differences in proportions between the study groups were statistically significant. Stratified analysis was carried out to find and to control for potential effect modifiers and confounders. Stepwise logistic regression analysis was performed to obtain an adjusted relative risk and confidence interval.

CHAPTER 3: RESULTS:

The total number of women delivering at the Ottawa General Hospital who were receiving antenatal care from any of the obstetricians who have antenatal clinics at the hospital during the study period of one year, from the first of April 1990 to the end of March 1991, was 2020. These files were reviewed, and 473 cases were excluded apriori from data collection. Those excluded cases included:

1. Women who had not received any antenatal care throughout the pregnancy.
2. Women who had booked for antenatal care at the Ottawa General Hospital at any time after 25 completed weeks of gestation because of their late starting of their antenatal care, and therefore being more likely to be cultured at their time of booking.
3. Women who had delivered at any time before 28 weeks of pregnancy, therefore not having the chance to be cultured at the appointed time.
4. Women who, after review of their charts, were found to be referrals from obstetricians or family physicians who did not have antenatal clinics at the hospital, when a referral form or letter was present in their files.

After excluding women with the previous conditions, the total number of cases for which data were collected was 1547.

3.1 THE TOTAL STUDY POPULATION:

The following section describes the total study population of 1547 cases for which data was collected.

3.1.1 CULTURE STATUS OF THE TOTAL POPULATION:

Reports of high vaginal cultures performed at 28 weeks of gestation were found in the files of 1039 women or 67.2% of the study population. Cultures were either not done or the results were missing from the files of 508 or 32.8% of the mothers. 288 files with missing cultures belonged to women registered with one of the obstetricians at the hospital who did not routinely obtain cultures from his patients at 28 weeks of gestation. For the rest of the files with missing culture reports (n = 220), it was presumed that either the cultures were not obtained, or the laboratory reports had not been returned to the mothers' charts. Table 3.1.1 describes the culture status of the total study population.

Table 3.1.1: Culture status of the total study population.

MATERNAL CULTURE STATUS	Number	Percent
Culture	1039	67.2%
No culture	508	32.8%
Total	1547	100.0%

3.1.2 DESCRIPTION OF THE TOTAL POPULATION:

The following section describes the characteristics of the total study population and compares cultured mothers with non-cultured mothers or those whose culture reports were missing from their files. This comparison was performed to investigate whether there were any significant differences between the two groups. For continuous variables, namely maternal age, maternal height and weight, and infant birth weight, comparison of the two groups was done by means of analysis of variance, under the assumptions that the two groups of women were independent random samples, that the variable to be compared was normally distributed and that the underlying variances were the same (Normality was assessed by examining the mean, median, mode, and histogram of each variable). The null hypothesis was H_0: $\underline{u}_1 = \underline{u}_2$ versus the alternate hypothesis H_1: $\underline{u}_1 \neq \underline{u}_2$. For categorical variables, comparison of the two groups was performed by chi-square testing.

A. Maternal personal and social characteristics:

1) Maternal age:

Table 3.1.2 describes the maternal age distribution of the total study population.

Table 3.1.2: Age distribution of total study population.

AGE GROUP	Cultured No.	%	Non-Cultured No.	%	Total No.	%
Under 20	31	3.0%	22	4.3%	53	3.4%
20 - 24	159	15.3%	79	15.6%	238	15.4%
25 - 29	408	39.3%	193	38.0%	601	38.8%
30 - 34	333	32.0%	147	28.9%	480	31.1%
35 - 39	90	8.7%	59	11.6%	149	9.6%
40 & over	18	1.7%	8	1.6%	26	1.7%
Total	1039	67.2%	508	32.8%	1547	100.0%
Mean	28.68		28.58			28.65
St. dev.	4.88		5.05			4.93

* F statistic = 0.137
** ANOVA p-value = 0.71

Maternal age ranged from 14 to 47 years. There were no missing data for maternal age. Mean age was 28.7 years and the standard deviation was 4.93 years. The largest group was 25 - 29 year old mothers, who comprised 38.8% of the total population, followed by 30 - 34 year olds who amounted to 31.1%. In cultured women the largest age group was the 25 - 29 year age group; 408/1039 (39.3%). The analysis of variance p-value indicates that the difference in mean maternal age between cultured and non-cultured mothers was not significant at the 5% level.

To allow generalizability of the results obtained, the data has to be comparable to the general population. In case of maternal age, the highest number of mothers were in the 25 - 29 year age group, which corresponds to a percentage of 37.8% obtained by the 1989 Physicians Notification of Birth (PNOB) data for Ottawa-Carleton,[53] in which this was also the largest age group. In this study the percentage of mothers under 20 years of age was 3.4%, which also corresponds to 3.6% in the PNOB. The percentage of 20 - 24 year old mothers was 15.4%, compared to 16.1% in the PNB. The percentage of 30 to 34 year olds was 31.0%, compared to 30.8% in the PNOB. That for mothers 35 - 39 year olds was 9.6%, which was slightly lower than the PNOB percentage of 10.3%, while that of mothers 40 years and over was 1.7%, compared to 1.4% in the PNOB. In a study of low birth weight currently being conducted by the Ottawa-Carleton Health Department (results unpublished, personal communication), the largest age group was also the 25 - 29 year group, who constituted 36.3% of the study population. The percentage of mothers under 20 was 4.0%, that for 20 - 24 year olds was 12.7%, the 30 - 34 year age group constituted 34.6%, the 35 - 39 age group constituted 10.8%, and mothers over 40 constituted 1.5% of the population. This indicates that maternal age for this study population is comparable to that for the general population.

2) <u>Marital status</u>:

Table 3.1.3 describes marital status of the total study population. Married women comprised the largest group of 1295/1547 cases or 83.8%, followed by the common-law group who amounted to 143/1547 cases or 9.2%. The "Other" category, which is comprised of single, separated, and divorced mothers, amounted to 7.0% of the study population. Chi-square p-value indicates that the difference of marital status between cultured and non-cultured women was not significant.

Table 3.1.3: Marital status of total study population.

MARITAL STATUS	Cultured		Non-Cultured		Total	
	No.	%	No.	%	No.	%
Married & Common-Law	972	93.6%	466	91.7%	1438	93.0%
Other	67	6.4%	42	8.3%	109	7.0%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 1.72
Degrees of freedom (df) = 1
P-value = 0.19

The percentage resulting from combining married and common-law mothers was found to be 93.0% which was slightly higher than that obtained in the PNOB, of 86.7%. On the other hand, the percentage of single mothers was 5.9%, which is much lower than the PNOB result of 12.6%. It is worthwhile to note that in the PNOB, common-law mothers are considered as single, and are included in the single mother group. In the low birth weight study, the percentage of married mothers was 82.5%, and common-law mothers constituted 10.9%. The percentage of single mothers was 5.1%, which is very similar to that obtained in this study. The percentage of separated and divorced mothers in this study is 0.6% and 0.5% respectively, and that for the low birth weight study was 0.8% and 0.6%. This indicates that the marital status of mothers in this study is comparable to that of the general population.

3) Maternal height:

Table 3.1.4 describes the height distribution of the total study population. Maternal height ranged from 120 to 179 centimeters, with a mean of 161.01 centimeters, and a standard deviation of 6.51. The analysis of variance p-value indicates that the difference in mean maternal height between cultured and non-cultured women was not significant at the 5% level.

Table 3.1.4: Height distribution of total population.

MATERNAL HEIGHT (cm)	Cultured No.	%	Non-cultured No.	%	Total No.	%
< 150	16	1.5%	10	2.0%	26	1.7%
150 - 159	373	36.2%	175	35.0%	548	35.8%
160 - 169	530	51.4%	260	52.0%	790	51.6%
170 & over	112	10.9%	55	11.0%	167	10.9%
Total	1031	100.0%	500	100.0%	1531	100.0%
Mean	161.03		161.00			161.01
St.dev.	6.59		6.34			6.51

* F statistic = 0.019
** Anova p-value = 0.88

4) <u>Maternal weight</u>:

Table 3.1.5 describes the weight distribution of the total study population.

Table 3.1.5: Weight distribution of total population.

MATERNAL WEIGHT (kgs)	Cultured No.	%	Non-cultured No.	%	Total No.	%
< 50	96	9.4%	64	12.8%	160	10.5%
50 - 59	481	47.1%	217	43.3%	698	45.8%
60 - 69	284	27.8%	142	28.3%	426	28.0%
70 - 79	102	10.0%	41	8.2%	143	9.4%
80 & over	59	5.7%	37	7.4%	96	6.3%
Total	1022	100.0%	501	100.0%	1523	100.0%
Mean	60.48		60.37			60.38
St.dev.	11.11		11.79			11.04

* F statistic = 0.031
** Anova P-value = 0.85

Maternal pre-pregnancy weight ranged from 40 to 127 kilograms, with a mean of 60.39 kg., and a standard deviation of 11.04. The difference in mean weight between cultured and non-cultured mothers was not significant.

5) Maternal parity:

Table 3.1.6 describes the parity of the total study population. Primiparous mothers amounted to 719 cases or 46.5%, and multiparous mothers amounted to 828 cases or 53.5% of the study population. The difference in maternal parity between cultured and non-cultured women was not significant at the 5% level.

Table 3.1.6: Parity of total study population.

PARITY	Cultured		Non-cultured		Total	
	No.	%	No.	%	No.	%
Primiparous	481	46.3%	238	46.9%	719	46.5%
Multiparous	558	53.7%	270	53.1%	828	53.5%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 0.04
df = 1
p-value = 0.84

6) Maternal gravidity:

Table 3.1.7 describes the gravidity of the total study population. Gravida 1 mothers comprised the largest group of 534 cases or 34.5%, followed by gravida 2 mothers who amounted to 527 cases or 34.1%. The gravida 1 and gravida 2 mothers together comprised over two-thirds of the study population. The difference in gravidity between cultured and non-cultured women was not significant.

Table 3.1.7: Gravidity of total study population.

GRAVIDITY	Cultured No.	%	Non-cultured No.	%	Total No.	%
G1	356	34.3%	178	35.0%	534	34.5%
G2	349	33.6%	178	35.0%	527	34.1%
G3	181	17.4%	94	18.5%	275	17.8%
G4	97	9.3%	38	7.5%	135	8.7%
G5 & over	56	5.4%	20	4.0%	76	4.9%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 3.31
df = 4
p-value = 0.51

7) <u>Employment status</u>:

Table 3.1.8 describes maternal employment status of the total population.

Table 3.1.8: Employment status of total study population

EMPLOYMENT STATUS	Cultured No.	%	Non-cultured No.	%	Total No.	%
Employed	685	65.9%	322	63.4%	1007	65.9%
Non-empl.	354	34.1%	186	36.6%	540	34.1%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 0.97
df = 1
P-value = 0.32

Employed mothers comprised 65.9% of the total study population, while non-employed mothers comprised 34.1%. Chi-square p-value indicates that the difference in employment status between cultured and non-cultured women was not significant at the 5% level. In the low birth weight study, the percentage of mothers who reported having a job other than looking after the family was 74.5%, compared to a percentage of employed mothers of 65.9% in this study. This higher percentage might have occurred because of the wording of the question in the low birth weight study, which is more likely to pick up a higher number, rather than the nurse or attending obstetrician asking the mother in the antenatal clinic whether she was employed or not.

8) Smoking status:

Table 3.1.9 describes the smoking status of the study population.

Table 3.1.9: Smoking status of total population

SMOKING STATUS	Cultured No.	%	Non-cultured No.	%	Total No.	%
Smokers	199	19.2%	111	21.9%	310	20.1%
Non-smokers	840	80.8%	397	78.1%	1237	79.9%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 1.55
df = 1
P-value = 0.21

The percentage of mothers who smoked during the pregnancy in this study was 20.1%, compared to 21.6% in the low birth weight study, which are very close. Non-smokers comprised 79.9% of the study population. The difference in smoking status between cultured and non-cultured women was not significant.

9) <u>Alcoholic intake during the pregnancy</u>:

Table 3.1.10 describes maternal alcoholic intake during the pregnancy. Most of the mothers or 71.9%, were reported as never drinking. Occasional drinkers amounted to 27.1%, moderate drinkers amounted to 0.8%, and only three cases or 0.2% were reported as heavy drinkers. The difference in alcohol intake between cultured and non-cultured mothers was not significant.

Table 3.1.10: Alcoholic intake during the pregnancy by the total study population.

ALCOHOLIC INTAKE	Cultured No.	%	Non-cultured No.	%	Total No.	%
No Intake	732	70.5%	378	74.7%	1110	71.9%
Intake	306	29.5%	128	25.3%	434	28.1%
Total	1038	100.0%	506	100.0%	1544	100.0%

* Chi-square = 2.95
df = 1
p-value = 0.09

The percentage of mothers who reported any alcohol intake during the pregnancy in this study was 28.1%, compared to 39.1% in the low birth weight study. This difference might have been due to under-reporting of drinking habits by the mothers when asked by the nurse in the prenatal clinic, and better reporting in the anonymous questionnaire of the low birth weight study.

B. MATERNAL MEDICAL AND OBSTETRICAL HISTORY:

1) Past medical history:

Table 3.1.11 describes the presence of history of any medical condition affecting mothers of the total study population. The total number of women with any past medical condition was 260 cases or 16.8%, while those with no past medical history was 1287 cases or 83.24%. The difference in past medical history between cultured and non-cultured mothers was not significant.

Table 3.1.11: Past medical history of total study population.

Past Medical History (PMH)	Cultured No.	Cultured %	Non-cultured No.	Non-cultured %	Total No.	Total %
PMH	183	17.6%	77	15.2%	260	16.8%
No PMH	856	82.4%	431	84.8%	1287	83.2%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 1.47
df = 1
P-value = 0.23

2) Previous term deliveries:

Table 3.1.12 describes the history of previous term deliveries, which is the previous history of the mother having pregnancies and deliveries which progressed to term or 40 weeks of gestation. The difference in the history of previous term deliveries between cultured and non-cultured women was not significant.

Table 3.1.12: History of previous term deliveries of the total study population.

PREVIOUS TERM DELIVERIES	Cultured No.	%	Non-cultured No.	%	Total No.	%
0	514	49.5%	248	48.8%	762	49.3%
1	363	34.9%	174	34.2%	537	34.7%
2	112	10.8%	60	11.8%	172	11.1%
3 & over	50	4.8%	26	5.1%	76	4.9%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 0.47
df = 3
P-value = 0.93

3) Previous abortions:

Table 3.1.13 describes the history of previous abortions of the total study population. The difference in history of previous abortions between cultured and non-cultured women was not significant at the 5% level.

Table 3.1.13: History of previous abortions of the total study population.

PREVIOUS ABORTIONS	Cultured No.	%	Non-cultured No.	%	Total No.	%
History	366	35.2%	194	38.2%	560	36.2%
No history	673	64.8%	314	61.8%	987	63.8%
Total	1039	100.0%	330	100.0%	1547	100.0%

* Chi-square = 1.30
df = 1
P-value = 0.25

4) <u>Previous preterm deliveries</u>:

Table 3.1.14 describes the history of previous preterm deliveries of the total study population. This variable describes the occurrence of any previous preterm births, and it is unknown whether these preterm births had occurred as a result of spontaneous preterm labour, or had been induced due to any complication to either mother or infant, and whether preceded by preterm rupture of the membranes or not. There was a significant difference in the history of previous preterm deliveries between cultured and non-cultured women at the 5% level, being higher in cultured women. This might have occurred because, as the OGH is a referral center for high risk cases, mothers who had preterm labour in a previous pregnancy, or mothers who had any medical or obstetrical condition that necessitated the termination of a previous pregnancy before term were more likely to have been referred to the OGH for obstetrical care, and accordingly more likely to continue their obstetrical care at the same hospital in a following pregnancy, and are therefore likely to be cultured at 28 weeks of gestation.

Table 3.1.14: History of previous preterm deliveries of the total study population.

PREVIOUS PRETERM DELIVERIES	Cultured No.	%	Non-cultured No.	%	Total No.	%
History	62	6.0%	15	3.0%	77	7.6%
No history	977	94.0%	493	97.0%	936	92.4%
Total	1039	100.0%	508	100.0%	1013	100.0%

* Chi-square = 6.56
df = 1
P-value = 0.01

5) <u>Number of living children</u>:

Table 3.1.15 describes the number of living children of the total study population. The difference in the number of living children born to cultured and non-cultured women was not significant.

Table 3.1.15: Number of living children of the total study population.

NUMBER OF LIVING CHILDREN	Cultured No.	%	Non-cultured No.	%	Total No.	%
0	495	47.6%	241	47.4%	736	47.6%
1	372	35.8%	181	35.6%	553	35.7%
2	123	11.8%	60	11.8%	183	11.8%
3	39	3.8%	16	3.2%	55	3.6%
4 & over	10	1.0%	10	2.0%	20	1.3%
Total	1039	100.0%	508	100.0%	1013	100.0%

* Chi-square = 3.03
df = 4
P-value = 0.55

6) History of the current pregnancy:

Table 3.1.16 describes the history of the current pregnancy of the total study population. The number of women with uneventful pregnancies was 1065 cases (68.8%), while the number who had any event, i.e. any medical or obstetrical complications to either the mother or the fetus (eg. antepartum hemorrhage, placenta previa, gestational diabetes, pregnancy induced hypertension, intrauterine fetal growth retardation, etc.) occurring during the current pregnancy was 482 cases (31.2%). The difference in history of the current pregnancy between cultured and non-cultured women was not significant at the 5% level.

Table 3.1.16: History of the current pregnancy of the total study population.

HISTORY OF THE CURRENT PREGNANCY	Cultured No.	%	Non-cultured No.	%	Total No.	%
Any event	338	32.5%	144	28.3%	482	31.2%
Uneventful	701	67.5%	364	71.7%	1065	68.8%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 2.79
  df = 1
  P-value = 0.09

C. OUTCOME OF THE PREGNANCY:

1) Premature rupture of the membranes and spontaneous preterm labour:

Spontaneous preterm labour occurred in 60 cases or 3.9% of the total study population, 15 (25.0%) of whom were resolved by tocolytic therapy and progressed to deliver at term. 45 cases (75.0%) were not resolved and progressed to preterm delivery. 27 cases (60.0%) of the women who had preterm labour and delivery had associated preterm rupture of the fetal membranes. Table 3.1.17 describes the frequency of preterm labour and delivery in the total study population. The difference in spontaneous preterm labour and delivery between cultured and non-cultured women was not significant.

Table 3.1.17: Frequency of preterm labour and delivery in the total study population.

PRETERM DELIVERY	Cultured No.	%	Non-cultured No.	%	Total No.	%
Pret. delivery	34	3.3	11	2.2	45	2.9
No Pret. delv.	1005	96.7	497	97.8	1502	97.1
Total	1039	100.0	508	100.0	1547	100.0%

* Chi-square = 1.48
df = 1
P-value = 0.22

Of the total population studied, there were 40 cases (2.6%) who had preterm PROM, 27 (67.5%) of whom also had associated spontaneous preterm labour, and in 13 cases (32.5%) labour was induced by obstetrical intervention whether for fetal or maternal welfare. Table 3.1.18 describes the frequency of premature rupture of the fetal membranes in the total study population. The frequency of preterm PROM was higher in cultured women, and the difference was statistically significant at the 5% level.

Table 3.1.18: Frequency of preterm PROM in the total study population.

STATUS OF THE FETAL MEMBRANES	Cultured No.	%	Non-cultured No.	%	Total No.	%
PROM	34	3.3%	6	1.2%	40	2.6%
No PROM	1005	96.7%	502	98.8%	1507	97.4%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 5.92
df = 1
P-value = 0.01

2) <u>Gestation at delivery</u>:

Table 3.1.19 describes gestational age at delivery of the total study population, whether the delivery occurred spontaneously or was induced because of any maternal or fetal cause. The number of women who delivered at any time between 28 and 36 completed weeks of gestation was 77 cases or 5.0%, while the number delivering at 37 or more weeks was 1470 cases or 95.0%. The difference in gestational age at delivery between cultured and non-cultured women was not significant.

Table 3.1.19: Gestation at delivery for total population.

GESTATION IN WEEKS	Cultured No.	%	Non-cultured No.	%	Total No.	%
Under 37	57	5.5%	20	3.9%	77	5.0%
37 & over	982	94.5%	488	96.1%	1470	95.0%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 1.73
df = 1
p-value = 0.19

The 77 cases or 5.0% who delivered before 37 weeks of gestation includes all preterm births, whether they occurred spontaneously, or were induced for either maternal or fetal reasons. This rate is slightly lower than the PNOB rate for 1989, which was 6.9%, as this rate does not include preterm births occurring before 28 weeks of gestation, in addition to the criteria of eligibility for inclusion of mothers into this study, i.e. the exclusion of referrals from other centers who were most likely to be higher risk cases.

3) Type of labour:

Table 3.1.20 describes the type of labour of the total study population. Spontaneous labour occurred in 1146 (74.1%) cases, and was induced in 274 (17.7%) cases. Other methods of labour, namely elective caesarian section, occurred in 127 cases or 8.2% of the total population. The difference in type of labour between cultured and non-cultured mothers was not significant.

Table 3.1.20: Type of labour of total population.

TYPE OF LABOUR	Cultured No.	%	Non-cultured No.	%	Total No.	%
Spontaneous	778	74.9%	368	72.4%	1146	74.1%
Induced	176	16.9%	98	19.3%	274	17.7%
Other	85	8.2%	42	8.3%	127	8.2%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 1.34
Df = 2
p-value = 0.51

3) Method of delivery:

Table 3.1.21 describes the method of delivery of the total study population. Vaginal delivery occurred in 1260 cases or 81.4%, and caesarian section occurred in 287 cases or 18.6%. The difference in the method of delivery between cultured and non-cultured women was not significant.

Table 3.1.21: Method of delivery of total population.

METHOD OF DELIVERY	Cultured No.	%	Non-cultured No.	%	Total No.	%
Vaginal	844	81.2%	416	81.9%	1260	81.2%
Caesarian	195	18.8%	92	18.1%	287	18.6%
Total	1039	100.0%	508	100.0%	1547	100.0%

* Chi-square = 0.1
df = 1
p-value = 0.75

4) Infant status:

Table 3.1.22 describes the status of infants born to mothers of the total study population. 1561 infants or 99.6% of the infants were liveborn, and 6 or 0.4% were stillborn. Fisher exact p-value indicates that the difference in the occurrence of stillbirths between cultured and non-cultured mothers was not significant.

Table 3.1.22: Status of Infants born to total population

INFANT STATUS	Cultured No.	%	Non-cultured No.	%	Total No.	%
Liveborn	1035	99.6%	906	99.8%	1561	99.6%
Stillborn	4	0.4%	2	0.2%	6	0.4%
Total	1039	100.0%	908	100.0%	1567	100.0%

* Chi-square = 0.43
df = 1
p-value = 0.51
** Fisher exact p-value = 0.41

5) <u>Infant birthweight</u>:

Table 3.1.23 describes the birthweights of infants born to the total study population. Data for birthweight were present for 1342 infants (85.6%) and were missing for 225 (14.4%). The difference in mean birthweights of infants born to cultured and non-cultured mothers showed borderline statistical significance.

Table 3.1.23: Birthweights of infants born to total population.

INFANT BIRTHWEIGHT (in grams)	Culture		Non-cultured		Total	
	No.	%	No.	%	No.	%
Less than 2500	41	4.5%	26	6.0%	67	5.0%
2500 and over	868	95.5%	407	94.0%	1275	95.0%
Total	909	100.0%	433	100.0%	1342	100.0%
Mean	3431.75		3367.90		3411.14	
St. deviation	547.02		577.15		557.50	

* F statistic = 3.86
** ANOVA p-value = 0.05

From the above findings we conclude that there were not many significant differences between mothers who had a high vaginal culture at 28 weeks of gestation, and mothers who did not have one. In case of maternal history of previous preterm deliveries, which was higher in cultured women, this might have occurred because, as previously mentioned, the hospital is a referral center for high risk cases, and mothers who had preterm labour or any complication necessitating preterm termination of a previous pregnancy were more likely to have been referred to the Ottawa General Hospital for obstetrical care, and therefore more likely to continue their obstetrical care at the same hospital in a following pregnancy. Also, in case of the occurrence of preterm rupture of the fetal membranes in the current pregnancy, which was higher in cultured women, this might have occurred as a result of the exclusion criteria, and the exclusion of patients of the single obstetrician who did not obtain cultures routinely from his patients. However, it remains that the difference in the occurrence of preterm deliveries during the current pregnancy (table 3.1.17), and the difference in gestational age at delivery (table 3.1.19) between cultured and non-cultured mothers of the total study population were not significant. In case of infant birthweight, the difference in mean birthweight of infants born to cultured and non-cultured women showed borderline statistical significance.

3.2 THE PREVALENCE STUDY:

3.2.1 CULTURE STATUS AT 28 WEEKS:

High vaginal cultures done at 28 weeks of gestation revealed group B streptococcal colonization in 131/1039 cases, which gives a prevalence "rate" of 12.6%. Group B Streptococcal positivity was determined by the reported presence of the micro-organism in the high vaginal culture performed at 28 weeks of gestation. Table 3.2.1 describes GBS colonization status.

Table 3.2.1: Group B Streptococcal colonization status.

GBS CULTURE STATUS	Number	Percent
GBS positive	131	12.6%
GBS negative	908	87.4%
Total	1039	100.0%

Table 3.2.2 describes the degree of colonization in GBS positive women. 66 women or 50.4% of the cultured population had moderate growth, 28.2% had light growth, and 21.4% had heavy growth of Group B Streptococci.

Table 3.2.2: Degree of colonization of GBS positive women.

DEGREE OF COLONIZATION	Number	Percent
Light	37	28.2%
Moderate	66	50.4%
Heavy	28	21.4%
Total	131	100.0%

Table 3.2.3 describes all other micro-organisms cultured at 28 weeks of gestation. Of these, the most common micro-organisms cultured were Yeast (in 98 cases or 9.4%), and Gardenerella vaginalis (in 62 cases or 6.0%). Staphylococci were isolated in 5 cases (0.5%), Chlamydia was found in 2 cases (0.2%), Coliform organisms also in 2 cases (0.2%), and Trichomonas vaginalis were found in 1 case (0.1%).

Table 3.2.3: Other micro-organisms cultured at 28 of weeks of gestation.

OTHER MICRO-ORGANISMS CULTURED	Number	Percent
Yeast	98	9.4%
Gardenerella vaginalis	62	6.0%
Staphylococci	5	0.5%
Chlamydia	2	0.2%
Coliform	2	0.2%
Trichomonas vaginalis	1	0.1%
Total	170	16.4%

3.2.2 DESCRIPTION OF CULTURED WOMEN:

A. MATERNAL PERSONAL AND SOCIAL CHARACTERISTICS:

The following section describes the personal and social characteristics of mothers cultured at 28 weeks of gestation, and compares GBS positive and negative mothers. Under the assumption that the samples are normally distributed, analysis of variance was carried out for comparison of continuous variables (ANOVA p-value is equivalent to that for the student's t-test since there are only two samples), and chi-square testing was done for categorical variables.

1) Maternal age:

Table 3.2.4 describes maternal age distribution of cultured women. The largest group was 25 to 29 year old mothers, who comprised 408 cases or 39.3% of the population, followed by 30 to 34 year olds who amounted to 333 cases or 32.1%. There were 31 (3.0%) mothers under 20, and 18 mothers (1.7%) in the 40 years and over age group.

Table 3.2.4: Age distribution of cultured women.

AGE GROUP	GBS +ve No.	GBS +ve %	GBS -ve No.	GBS -ve %	TOTAL
Under 20	7	22.6%	24	77.4%	31
20 - 24	27	17.0%	132	83.0%	159
25 - 29	40	9.8%	368	90.2%	408
30 - 34	42	12.6%	291	87.4%	333
35 - 39	14	15.6%	76	84.4%	90
40 & over	1	5.5%	17	94.4%	18
Total	131	12.6%	908	87.4%	1039
Mean	28.22		28.75		28.65
St.dev.	5.35		4.80		4.93

* F statistic = 1.34
** ANOVA p-value = 0.25

The percentage of GBS positivity was highest among mothers under 20, followed by 20 to 24 year old mothers, and was lowest in mothers over 40. Analysis of variance p-value was not significant, which indicates that the difference in mean maternal age between GBS positive and negative women was not significant at the 5% level.

2) <u>Marital status</u>:

Table 3.2.5 describes the marital status of cultured women by culture status. GBS positivity was higher in the "other" category, which consisted of single, separated and divorced women, but the difference in marital status between GBS positive and negative mothers was not significant at the 5% level.

Table 3.2.5: Marital status of cultured women.

MARITAL STATUS	GBS +ve No.	%	GBS -ve No.	%	Total
Married & Common-Law	119	12.2%	853	87.8%	972
Other	12	17.9%	55	82.1%	67
Total	131	12.6%	908	87.4%	1039

* Chi-square = 1.83
df = 1
p-value = 0.18

3) <u>Maternal height</u>:

Table 3.2.6 describes the height distribution of cultured women. GBS positivity was highest in women under 150 cms. in height, and lowest in women in the 160-169 cms. height range. The difference in mean height between GBS positive and negative women was statistically significant at the 5% level.

Table 3.2.6: Height distribution of cultured women

MATERNAL HEIGHT (cms)	GBS +ve No.	%	GBS -ve No.	%	Total
< 150	5	31.3%	11	68.7%	16
150 - 159	52	13.9%	321	86.1%	373
160 - 169	57	10.8%	473	89.2%	530
170 & over	15	13.4%	97	86.6%	112
Total	129	12.5%	902	87.5%	1031
Mean	159.81		161.20		161.03
St.dev.	7.14		6.49		6.59

* F statistic = 5.04
** ANOVA p-value = 0.02

4) Maternal weight:

Table 3.2.7 describes the weight distribution of cultured women. There were not much difference between the weight distributions of GBS positive and negative women, although GBS positivity was slightly higher in women under 50 kgs. in weight. The difference in mean maternal weight between GBS positive and negative women was not statistically significant.

Table 3.2.7: Weight distribution of cultured women

MATERNAL WEIGHT (kgs)	GBS +ve No.	%	GBS -ve No.	%	Total
< 50	17	16.8%	84	83.2%	101
50 - 59	60	12.5%	421	87.5%	481
60 - 69	35	12.3%	249	87.7%	284
70 - 79	10	9.7%	93	90.3%	103
80 & over	6	10.3%	52	89.7%	58
Total	128	12.5%	899	87.5%	1027
Mean	59.46		60.62		60.39
St.deviation	11.76		11.01		10.65

* ANOVA p-value = 0.27
** F statistic = 1.22

5) Maternal parity:

Table 3.2.8 describes the parity of cultured women. The percentage of GBS positive mothers was higher in primiparous women. Chi-square p-value indicates that the difference in parity between GBS positive and negative women was not significant at the 5% level.

Table 3.2.8: Parity of cultured women

PARITY	GBS +ve No.	%	GBS -ve No.	%	Total
Primiparous	68	14.1%	413	85.9%	481
Multiparous	63	11.3%	495	88.7%	558
Total	131	12.6%	908	87.4%	1039

* Chi-square = 1.90
df = 1
p-value = 0.17

6) Maternal gravidity:

Table 3.2.9 describes the gravidity of cultured women. The percentage of GBS positive mothers was highest in gravida 4 women, followed by the gravida 1 group. There was no significant difference in the prevalence of GBS positivity across gravidity levels.

Table 3.2.9: Gravidity of cultured women

GRAVIDITY	GBS +ve No.	%	GBS -ve No.	%	Total
G1	54	15.2%	302	84.8%	356
G2	39	11.2%	310	88.8%	349
G3	14	7.7%	167	92.3%	181
G4	16	16.5%	81	83.5%	97
G5 & over	8	14.3%	48	85.7%	56
Total	131	12.6%	908	87.4%	1039

* Chi-square = 8.14
df = 4
p-value = 0.09

7) <u>Employment status</u>:

Table 3.2.10 describes employment status of cultured mothers. The percentage of GBS positivity was higher in non-employed mothers, but the difference in employment status between GBS positive and negative mothers was not significant at the 5% level.

Table 3.2.10: Employment status of cultured women.

EMPLOYMENT STATUS	GBS +ve No.	GBS +ve %	GBS -ve No.	GBS -ve %	Total
Employed	79	11.5%	606	88.5%	685
Non-employed	52	14.7%	302	85.3%	354
Total	131	100.0%	908	100.0%	1039

* Chi-square = 2.11
df = 1
p-value = 0.15

8) <u>Maternal occupation</u>:

Table 3.2.11 describes the occupations of cultured mothers (this table includes students). The percentage of GBS positive mothers was highest among students, social occupations, teaching and occupations of medicine and health. The difference in occupations of GBS positive and negative mothers was not significant at the 5% level.

Table 3.2.11: Occupations of cultured women

OCCUPATION	GBS +ve No.	%	GBS -ve No.	%	Total
Clerical & Managerial	29	9.7%	271	90.3%	300
Medicine	21	16.9%	103	83.1%	124
Sales & Services	8	8.0%	92	92.0%	100
Teaching	8	17.4%	38	82.6%	46
Natural Sciences	3	6.5%	43	93.5%	46
Social Sciences	4	17.9%	20	82.1%	24
Arts & Recreation	1	9.4%	16	90.6%	17
Students	7	16.7%	32	83.3%	39
Other	5	17.9%	23	82.1%	28
Total	86	11.9%	638	88.1%	724

* Chi-square = 11.90
df = 8
p-value = 0.16

9) <u>Smoking status</u>:

Table 3.2.12 describes smoking status of cultured women. The rate of GBS positivity was slightly higher in smoking mothers, but was not statistically significant.

Table 3.2.12: Smoking status of cultured women.

SMOKING STATUS	GBS +ve No.	%	GBS -ve No.	%	Total
Smokers	27	13.6%	172	86.4%	199
Non-smokers	104	12.4%	736	81.6%	840
Total	131	12.6%	908	87.4%	1039

* Chi-square = 0.21
df = 1
p-value = 0.65

Table 3.2.13 describes the number of cigarettes smoked per day for mothers who smoked during the pregnancy. The rate of GBS positivity was highest in mothers smoking less than 10 cigarettes per day. The difference in the number of cigarettes smoked per day by GBS positive or GBS negative smoking mothers was not significant at the 5% level.

Table 3.2.13: Number of cigarettes smoked per day

NUMBER OF CIGARETTES SMOKED / DAY	GBS +ve		GBS -ve		Total
	No.	%	No.	%	
less than 10	11	18.3%	49	81.7%	60
10 - 19	11	12.5%	77	87.5%	88
20 & over	5	10.0%	45	90.0%	50
Total	27	13.6%	171	86.4%	198

* Chi-square = 1.78
df = 2
p-value = 0.41

10) <u>Alcohol intake during the pregnancy</u>:

Table 3.2.14 describes alcohol intake during the pregnancy by cultured women.

Table 3.2.14: Alcohol intake during the pregnancy.

ALCOHOL INTAKE	GBS +ve		GBS -ve		Total
	No.	%	No.	%	
None	97	13.3%	635	86.7%	732
Occasional	31	10.4%	267	89.6%	298
Moderate to heavy	3	37.5%	5	62.5%	8
Total	131	100.0%	907	100.0%	1038

* Chi-square = 6.08
Df = 2
p-value = 0.05

GBS positivity was highest in mothers who reported moderate to heavy alcoholic intake, and was lowest in mothers who reported no alcoholic intake during the pregnancy. The difference in alcohol intake between GBS positive and GBS negative mothers showed borderline statistical significance.

B. MATERNAL MEDICAL AND OBSTETRICAL HISTORY:

The following section reports GBS prevalence rates in terms of past medical history, past obstetrical and gynecological history, and in relation to events occurring during the current pregnancy. For chi-square calculations, to compare between GBS positive and negative mothers, the reference category for each disease group was absent disease, for example no UTI for UTI positive mothers, no kidney disease for mothers with kidney disease and so on.

1) Past medical history:

Table 3.2.15 describes the past medical history of cultured mothers. The total number of women with no past medical history was 856 cases (82.4%), 106 (12.4%) of whom were GBS positive, and 750 (87.6%) were negative. There were not much differences in the prevalence of GBS positivity between women with any past medical history and women with no past medical conditions. GBS positivity was highest in mothers with medical history of Diabetes mellitus (4/12 cases or 33.3%) and, when compared with mothers with no history of diabetes, this difference was statistically significant at the 5% level. This was followed by mothers with history of kidney disease (6/27 cases or 22.2%), but was not statistically significant. The category "other" (which describes other past medical conditions not stated in this table) is described in appendix E.

Table 3.2.15: Past medical history of cultured women.

PAST MEDICAL HISTORY	GBS+ve No.	GBS+ve %	GBS-ve No.	GBS-ve %	Ttl.	Chi-sqr.	p-val.	*p-val.
None	106	80.9	750	82.6	856	0.22	0.64	-
UTI	2	1.5	14	1.5	16	0.00	0.99	0.67
Kidney dis	6	4.6	21	2.3	27	2.32	0.13	0.11
Func. hrt murmurs	2	1.5	21	2.3	23	0.33	0.57	0.43
Heart dis.	1	0.8	10	1.1	11	0.13	0.72	0.59
Hypertens.	0	0.0	14	1.5	14	2.05	0.15	0.15
Diabetes	4	3.1	8	0.9	12	4.73	0.03	-
Thyroid	3	2.3	24	2.6	27	0.06	0.81	0.55
Asthma	5	3.8	23	2.5	28	0.72	0.40	0.27
Other	4	3.1	35	3.9	39	0.20	0.65	0.44

* Fisher exact p-value is demonstrated for variables in which chi-square was not applicable due to small cell values.

** UTI = Urinary tract infection.
Func. heart murmurs = Functional heart murmurs
Hypertens. = Hypertension.

*** For chi-square calculations the reference category for each disease group was absent disease.

2) <u>Past Obstetrical and Gynecological history</u>:

Table 3.2.16 describes the past obstetrical and gynecological history of cultured mothers. The number of women with no significant past obstetrical history was 854 cases (82.2%), 104 (12.2%) of whom were positive for GBS, and 750 (87.8%) were negative.

Table 3.2.16: Past obstetrical and gynecological history of cultured women.

PAST OBSTETRIC HISTORY	GBS+ve No.	GBS+ve %	GBS-ve No.	GBS-ve %	Ttl.	Chi-sqre	p-val	*p-val
None	104	79.4	750	82.6	854	0.81	0.37	-
Preterm labour	8	6.1	33	3.6	41	1.85	0.17	-
PROM	3	2.3	16	1.8	19	0.18	0.67	0.44
STD/PID	6	4.6	30	3.3	36	0.56	0.46	0.30
PIH	2	1.5	28	3.1	30	0.99	0.32	0.25
Gest.diab.	2	1.5	21	2.3	23	0.33	0.57	0.43
Ectopic pregnancy	3	2.3	11	1.2	14	1.00	0.32	0.25
IUFD & stillbirth	3	2.3	16	1.8	19	0.18	0.67	0.44

* Fisher exact p-value is demonstrated for variables in which chi-square was not applicable due to small cell values.
** STD = Sexually transmitted disease.
PID = Pelvic inflammatory disease.
PIH = Pregnancy induced hypertension.
Gest.diab = Gestational diabetes.
IUFD = Intra-uterine fetal deaths.
*** For chi-square calculations the reference category for each disease group was absent disease.

The difference in the rate of GBS positivity between mothers who had a history of any previous obstetric or gynecological complication when compared with mothers who did not was not significant. The rate of GBS positivity was higher among women who had previous history of ectopic pregnancy (3/14 cases or 21.4%), women with past history of preterm labour (8/41 cases or 19.5%), women with past history of sexually transmitted or pelvic inflammatory disease (6/36 cases or 16.7%), and women with past history of PROM (3/19 cases or 15.8%) when compared to women who did not have any of the above complications, but the differences were not statistically significant ($p > 0.05$).

3) <u>History of the present pregnancy</u>:

Table 3.2.17 describes the history of the present pregnancy for cultured women. This includes all medical and obstetrical events that occurred during the current pregnancy prior to 28 weeks of gestation. The rate of GBS positivity was highest among women who had diabetes mellitus during the current pregnancy (4/11 cases or 36.4%), and the difference was statistically significant at the 5% level when compared with women who did not. Also, the rate of GBS positivity was high in women who complained of early bleeding (13/57 cases or 22.8%), and the difference was statistically significant when compared with women who did not. The rates of GBS positivity were also high in mothers who had UTI (4/16 cases or 25.0%), late bleeding (5/30 cases or 16.7%), gestational diabetes (8/49 cases or 16.3%), oligohydramnios (2/13 cases or 15.4%), and in those undergoing amniocentesis (10/64 cases or 15.6%), but the differences were not significant.

3.2.17: History of the present pregnancy of cultured women.

HISTORY OF PRESENT PREGNANCY	GBS+ve No.	%	GBS-ve No.	%	Ttl	Chi-sqr.	p-val	*p-val
Normal	70	53.4	631	69.5	701	13.50	0.00	-
Early bld.	13	9.9	44	4.8	57	5.69	0.02	-
Late bld.	5	3.8	25	2.8	30	0.46	0.50	0.32
Amnio-centesis	10	7.6	54	5.9	64	0.56	0.45	-
UTI	4	3.1	12	1.3	16	2.26	0.13	0.13
Diabetes	4	3.1	7	0.8	11	5.69	0.02	0.04
Gest.Diab.	8	6.1	41	4.5	49	0.65	0.42	-
PIH	7	5.3	53	5.8	60	0.05	0.82	-
Abruptio-placenta	1	0.8	10	1.1	11	0.13	0.72	0.59
Oligo-hydramnios	2	1.5	11	1.2	13	0.09	0.76	0.50
Mult.pregn	0	0.0	15	1.7	15	2.19	0.14	0.13
Anemia	1	0.8	9	1.0	10	0.06	0.80	0.63

* Fisher exact p-value is demonstrated for variables in which chi-square was not applicable due to small cell values.

** UTI = Urinary tract infection.
Gest.Diab = Gestational diabetes.
PIH = Pregnancy induced hypertension.
Mult.pregn = Multiple pregnancy.

*** For chi-square calculations the reference category for each disease group was absent disease.

SUMMARY OF THE PREVALENCE STUDY:

High vaginal cultures obtained at 28 weeks of gestation revealed a Group B Streptococcal colonization prevalence of 12.6%. The rate of GBS positivity was highest among mothers under 20, and lowest among mothers over 40 years of age. The prevalence was higher among unmarried mothers (single, separated and divorced), primiparous women, and those of higher gravidity (gravida 4 and over), but was not statistically significant. Maternal height showed a significant difference between positive and negative women, the prevalence being higher among mothers under 150 centimeters in height.

The rate of GBS positivity was slightly higher among smoking mothers, especially those smoking less than 10 cigarettes per day, but this was not statistically significant. The rate was also higher among mothers who reported moderate to heavy alcoholic intake, and lowest among mothers who reported no alcoholic intake during the pregnancy. The difference in alcohol intake between GBS positive and negative mothers showed borderline statistical significance.

In terms of maternal employment status, the rate of GBS positivity was higher among non-employed mothers. In case of employed mothers, the rate was highest among students, those in social occupations, teachers, and those in medical and health occupations, but were not statistically significant.

In terms of maternal medical history, GBS positivity was highest among mothers who had a history of diabetes mellitus, which was statistically significant, and in mothers who had a history of kidney disease, but was not statistically significant.

In case of past obstetric and gynecologic history, the rate of GBS positivity was higher among women who had previous history of ectopic pregnancy, preterm labour, sexually transmitted or pelvic inflammatory disease, and previous history of premature rupture of the membranes, but the difference was not statistically significant.

With regards to maternal conditions arising during the current pregnancy, the rate of GBS positivity was highest among women with diabetes mellitus, followed by those with early bleeding, and the difference was statistically significant. The rates of GBS positivity were also high in mothers who had UTI, late bleeding, gestational diabetes, oligohydramnios, and in those undergoing amniocentesis, but were not significant.

3.3 THE COHORT STUDY:

The total number of cultured women was 1039, 77 of whom were excluded from the cohort study according to the eligibility criteria. Those excluded cases included: women with past history of PROM (19 cases), since it was not indicated in the maternal charts whether rupture of the membranes was preterm or at term; women having multiple pregnancies (15 cases); women who had certain complications during the current pregnancy like abruptioplacenta (11 cases), poly-hydramnios (5 cases), cervical circulage (1 case), spontaneous preterm labour not preceded by ruptured membranes (12 cases) and women who had preterm PROM that was preceded by preterm labour but was resolved by tocolytic therapy (2 cases; one of whom had preterm labour at 29 weeks of gestation which was resolved by tocolytic therapy, then had preterm PROM and preterm labour at 33 weeks. The other had resolved preterm labour at 30 weeks, followed by ruptured membranes and preterm labour at 35 weeks). Also, an additional number of 12 cases were excluded from the cohort study; these were mothers who had certain complications during the current pregnancy and had to be induced before term because of these complications, thereby not getting them the chance to reach term. These cases included two women induced at 33 and 34 weeks because of intrauterine fetal death, one case of systemic lupus erythematosus induced at 36 weeks, one case of polyhydramnios and RH-isoimmunization induced at 34 weeks, 2 cases of diabetes mellitus complicated by pregnancy induced hypertension (PIH); both induced at 36 weeks, one case of gestational diabetes and PIH induced at 35 weeks, 3 cases of diabetes mellitus; one induced at 35 weeks, and two induced at 36 weeks, one case of PIH induced at 35 weeks, and one case of PIH complicated by pre-eclampsia, who was induced at 36 weeks. The total number of women eligible for inclusion in the cohort study was 962 cases.

3.3.1 UNIVARIATE ANALYSIS:

1) GBS COLONIZATION AND PRETERM PROM:

The total number of exposed women was 120, and the total number of non-exposed women was 842. The number of women whose pregnancy was complicated by preterm premature rupture of the fetal membranes (PPROM) prior to 37 weeks of gestation (whether delivery occurred preterm or at term) was 29 women, and the number who delivered at term (Non-PPROM) was 933. The "Non-PPROM" group consists of all term deliveries, including those preceded by rupture of the fetal membranes occurring at or after 37 weeks of gestation. The number of exposed women whose pregnancy ended with preterm PROM was 17/120 women or 14.2%, and the number non-exposed who developed preterm PROM was 12/842 women or 1.4%. The number of exposed women who delivered at term was 103/120 women or 85.8%, and the number non-exposed who delivered at term was 830/842 or 98.6%. The association between vaginal GBS colonization and preterm premature rupture of the fetal membranes is described in table 3.3.1.

Table 3.3.1: The association between vaginal GBS colonization and preterm PROM.

GBS STATUS	Preterm PROM	Non PPROM	Total
GBS positive	17 (14.2%)	103 (85.8%)	120
GBS negative	12 (1.4%)	830 (98.6%)	842
Total	29 (3.0%)	933 (97.0%)	962

Relative Risk = 9.94
95% Confidence Interval = 4.87 < RR < 20.30
Uncorrected Chi-square = 58.32 p-value < 0.0001
Yates Corrected Chi-square = 54.04 p-value < 0.0001
Fisher exact: 1-tailed p-value = 0.0000000
2-tailed p-value = 0.0000000

2) <u>OUTCOME OF THE CURRENT PREGNANCY</u>:

a. <u>Preterm rupture of membranes and preterm labour</u>:

In the cohort study, the number of women who had preterm PROM was 29 cases or 3.0%. The number of colonized mothers who had preterm PROM was 17 (14.2%), and the number of non-colonized mothers who had preterm PROM were 12 (1.4%). Table 3.3.2 describes the gestational age at which preterm PROM occurred. This table includes all the cases who had preterm PROM, whether it was also followed by preterm delivery (prior to 37 weeks of gestation), or delivery occurred at term. (Details on the exact week of pregnancy at which delivery occurred, whether preterm or term, for women who had preterm PROM are in appendix F).

Table 3.3.2: Gestational age at which preterm PROM occurred.

GEST. IN WKS.	28		33		34		35		36		Ttl
	No.	%	No.	%	No.	%	No.	%	No.	%	
GBS+ve	1	5.9	2	11.8	1	5.9	7	41.2	6	35.3	17
GBS-ve	0	0.0	2	16.7	2	16.7	1	8.3	7	58.3	12
Total	1	3.4	4	13.8	3	10.3	8	27.6	13	44.8	29

* Chi-square = 5.20
Df = 4
p-value = 0.27
** Chi-square may not be valid because of small cell numbers.

Most cases of preterm PROM occurred at 36 weeks of gestation (13 cases or 44.8%). The number of GBS positive women who had preterm PROM before 35 weeks of gestation was 4 (23.5%), the number who had preterm PROM at 35 weeks was 7 (41.2%), and 6 (35.3%) had preterm PROM at 36 weeks. In case of women whose pregnancy was complicated by preterm PROM, the difference in the gestational age at delivery between GBS positive and negative women was not significant.

b. Gestation at delivery:

Table 3.3.3 describes gestational age at delivery of all women in the cohort study. This table includes women who had preterm PROM before 37 weeks of gestation, women who had to be induced before term due to any complication arising during the pregnancy to either mother or fetus, in addition to women delivering at term (which includes cases in which rupture of the fetal membranes occurred at or after 37 weeks of pregnancy).

Table 3.3.3: Gestation at delivery.

GESTATION (in weeks)	Under 34 No.	%	34 - 36 No.	%	37 & over No.	%	Total
GBS +ve	3	2.5	12	10.0	105	87.5	120
GBS -ve	1	0.1	8	1.0	833	98.9	842
Total	4	0.4	20	2.1	938**	97.5	962

* Chi-square = 57.11
Df = 2
p-value = 0.00
** This includes 5 cases who had preterm PROM but who delivered at term.

Among GBS positive women, 12.5% delivered before 37 weeks of gestation, compared to 1.1% of negative mothers. The difference in the gestational age at delivery between

GBS positive and negative women was highly significant at the 5% level.

c. Type of labour:

Table 3.3.4 describes the type of labour of all women in the cohort study. Spontaneous labour occurred in 76.1%, was induced in 15.9%, and occurred by elective caesarian section in 8.0%. There was a higher percentage of GBS positive women whose labour was induced or had elective caesarian sections. The difference in the type of labour between positive and negative mothers was statistically significant at the 5% level.

Table 3.3.4: Type of labour.

TYPE OF LABOUR	Spontaneous		Induced		Elective Caesarian		Total
	No.	%	No.	%	No.	%	
GBS +ve	81	67.5	22	18.3	17	14.2	120
GBS -ve	651	77.3	131	15.6	60	7.1	842
Total	732	76.1	153	15.9	77	8.0	962

* Chi-square = 8.34
Df = 2
p-value = 0.02

d. Method of delivery:

Table 3.3.5 describes the method of delivery of all women in the cohort study. Spontaneous vaginal delivery occurred in 82.6%, and delivery by caesarian section occurred in 17.4%. The percentage of GBS positive women delivering by caesarian section was higher than that of GBS negative women. The difference in the method of delivery between GBS positive and negative women was statistically significant at the 5% level.

Table 3.3.5: Method of delivery.

METHOD OF DELIVERY	Vaginal No.	%	Caesarian No.	%	Total
GBS +ve	91	75.8	29	24.2	120
GBS -ve	704	83.6	138	16.4	842
Total	795	82.6	167	17.4	962

* Chi-square = 4.43
df = 1
p-value = 0.04

e. <u>Infant birthweight</u>:

Table 3.3.6 describes the birthweights of infants born to women in the cohort study. The mean birthweight of infants born to GBS positive women was lower than that of those born to negative mothers, and there was a higher percentage of infants with birthweights under 2500 grams born to positive mothers. Analysis of variance p-value indicates that there was a highly significant difference in mean infant birthweight between the two groups.

Table 3.3.6: Birthweights of infants born to women in the cohort study.

INFANT BIRTHWEIGHT (in grams)	< 2500 No. %	2500 & over No. %	Ttl	Mean	St.dev
GBS +ve	4 3.6	107 96.4	111	3319.03	500.8
GBS -ve	21 2.9	711 97.1	732	3486.17	512.3
Total	25 3.0	818 97.0	843	3402.60	506.6

* F statistic = 10.32
** ANOVA p-value = 0.001

3) <u>COMPARISON BETWEEN GBS POSITIVE AND NEGATIVE WOMEN</u>:

Comparison between GBS positive and negative women in the cohort study was performed to pick up variables that showed differences between the two groups. The results obtained were very similar to those of comparing GBS positive and negative women in the prevalence study (Details are in appendix G). Significant differences were observed for the following variables: maternal height (p-value = 0.05), marital status (p-value = 0.05), gravidity (p-value = 0.03), and current pregnancy history of early bleeding (p-value = 0.004), and urinary tract infection (p-value = 0.05).

4) COMPARISON BETWEEN WOMEN WITH PRETERM PROM AND WOMEN WITH NO PROM:

Comparison between women whose pregnancy was complicated by preterm PROM and women whose pregnancy was not complicated by preterm PROM was performed to pick up variables that showed differences between the two groups, and to identify other maternal factors associated with preterm PROM.

A) Maternal personal and social characteristics:

Table 3.3.7 compares maternal personal and social characteristics between mothers whose pregnancy ended by preterm premature rupture of the fetal membranes and mothers with no preterm premature rupture of the membranes.

Table 3.3.7: Comparison of personal & social characteristics between women with preterm PROM and women with no PPROM.

MATERNAL PERSONAL CHARACTERISTICS	PPROM rate		Chi-square	p-value
Maternal age:				
Under 20 (n=28)	3	10.7%	6.48	0.09
20 - 29 (531)	14	2.6%		
30 - 39 (386)	12	3.1%		
40 & over (17)	0	0.0%		
Maternal height:				
Under 155 (137)	5	3.6%	1.36	0.51
155 - 164 (492)	17	3.5%		
165 & over (327)	7	2.1%		
Maternal weight:				
Under 55 (277)	9	3.2%	4.83	0.18
55 - 64 (422)	10	2.4%		
65 - 74 (167)	9	5.4%		
75 & over (86)	1	1.2%		
Marital Status:				
Married/C.L (904)	25	2.8%	3.18	0.07
Other (58)	4	6.9%		*(0.09)
Maternal parity:				
Primiparous (458)	18	3.9%	2.51	0.11
Multiparous (504)	11	2.2%		
Maternal gravidity:				
Gravida 1 (342)	16	4.7%	8.57	0.04
Gravida 2 (320)	4	1.3%		
Gravida 3 (168)	3	1.8%		
G.4 & over (132)	6	4.5%		
Employment:				
Yes (632)	22	3.5%	1.37	0.24
No (330)	7	2.1%		
Smoking status:				
Yes (182)	8	4.4%	1.46	0.23
No (780)	21	2.7%		
Alcohol intake:				
Yes (285)	6	2.1%	1.15	0.28
No (676)	23	3.4%		

* Fisher exact 1-tailed p-value.

Table 3.3.7 shows that there were no significant differences in mean age, height, or weight between the two groups at the 5% level. The differences in maternal marital status, parity, employment, smoking status and alcohol intake between women who had PPROM and women with no PPROM were not statistically significant. Only maternal gravidity showed a significant difference between the two groups with a chi-square p-value of 0.04.

B) <u>Past Medical History</u>:

Table 3.3.8 reports the rates of Preterm PROM in women with various past medical conditions. There were no significant differences in past medical conditions between the analyzed groups.

Table 3.3.8: Comparison of Past Medical History between women with preterm PROM and women with no PPROM.

PAST MEDICAL HISTORY	PPROM rate	Chi-square	P-value	*P-value
Kidney Disease:				
Yes (n=24)	1 4.2%	0.11	0.74	0.52
No (938)	28 3.0%			
Functional Heart Murmurs: Yes (21)	1 4.8%	0.22	0.64	0.48
No (941)	28 3.0%			
Other Medical Condition:				
Yes (36)	1 2.8%	0.01	0.93	0.70
No (926)	28 3.0%			

* Fisher exact 1-tailed p-value.

C) Past Obstetric and Gynecological History:

Table 3.3.9 compares the rate of PPROM in women with various past obstetrical and gynecological conditions. There was a significant difference between the two groups in past history of preterm labour (p-value = 0.04).

Table 3.3.9: Comparison of Past Obstetrical and Gynecological History between women with preterm PROM and women with no PPROM.

PAST OBSTETRIC OR GYNECOLOGICAL CONDITION	PPROM rate	Chi-square	P-value	*P-value
Preterm Labour:				
Yes (n=25)	3 12.0%	7.09	0.008	0.04
No (937)	26 2.8%			
STD &/or PID:				
Yes (32)	1 3.1%	0.00	0.97	0.63
No (930)	28 3.0%			
Uterine Anomalies				
Yes (7)	1 14.3%	3.06	0.08	0.19
No (955)	28 2.9%			

* Fisher exact 1-tailed p-value.

D) History of the Current Pregnancy:

Table 3.3.10 shows the rates of PPROM related to the history of the current pregnancy. The highest rate of preterm PROM occurred in women who had late bleeding during the current pregnancy (20.0%), which was statistically significant at the 5% level when compared with women who did not. Women who had early bleeding also showed a significantly higher rate of PPROM (9.6%). The rate of PPROM was also high in women who had UTI (8.3% compared to 2.9%), but this difference was not statistically significant. On the other hand, the rate of PPROM was lower in women who underwent amniocentesis (1.9% compared to 3.1%), and in mothers who had gestational diabetes (2.3% compared to 3.0%), but these differences were not significant at the 5% level.

Table 3.3.10: Comparison of the History of the current pregnancy between women with preterm PROM and women with no PPROM.

HISTORY OF THE CURRENT PREGNANCY	PPROM rate	Chi-square	P-value	*P-value
Early Bleeding:				
Yes (n = 52)	5 9.6%	8.19	0.004	0.02
No (910)	24 2.6%			
Late Bleeding:				
Yes (20)	4 20.0%	20.15	0.000	0.00
No (942)	25 2.7%			
Amniocentesis:				
Yes (54)	1 1.9%	0.26	0.61	0.51
No (908)	28 3.1%			
UTI: Yes (12)	1 8.3%	1.18	0.28	0.31
No (950)	28 2.9%			
Gestational Diabetes:				
Yes (43)	1 2.3%	0.07	0.79	0.62
No (919)	42 3.0%			

* Fisher exact 1-tailed p-value.

From the univariate analysis, both maternal gravidity and current pregnancy history of early bleeding were found to be significantly associated with both exposure to GBS and the outcome of preterm PROM, and therefore may be considered as potential confounders. Late bleeding during the current pregnancy, although found to be significantly associated with exposure to GBS but not to preterm PROM, may be considered as a potential confounder, since bleeding during the pregnancy is a known risk factor for preterm PROM[8]. Past history of preterm labour should also be considered as a potential confounder, as it is known to increase the risk for preterm PROM[15].

Since a confounder can affect the magnitude of the association even if it did not reach statistical significance in its relationship with either the exposure or the outcome[54], certain other variables in this study may be considered as potential confounders. The presence of uterine anomalies, medical history of diabetes mellitus, kidney disease, and urinary tract infections during the current pregnancy should all be considered as potential confounders, since previous studies have shown that all these conditions are associated with an increased risk for preterm PROM[8]. Also, maternal smoking during the pregnancy should be considered as a potential confounder, since it is known to increase the risk of preterm PROM[9].

3.3.2 MULTIVARIATE ANALYSIS:

1) STRATIFIED ANALYSIS:

Stratified analysis was carried out as the first step in multivariate analysis of the cohort study, to find out and control for potential effect modifiers and confounders.

Selection of variables for the stratified analysis was based on clinical basis and statistical significance testing. Stratified analysis was carried out for all the main variables, namely; maternal age, marital status, parity, gravidity, height, weight, employment status, past medical history, past obstetric history, smoking, and alcohol intake. Stratified analysis was also carried out for variables which were found to be statistically significant at the 5% level in the univariate analysis, namely past medical history of kidney disease, past history of preterm labour, current pregnancy history of early bleeding, current history of late bleeding, and the presence of uterine anomalies.

a. <u>Maternal age</u>:

Table 3.3.11 describes the association of maternal GBS colonization and preterm PROM stratified by maternal age. By observing the stratum-specific relative risks it appears that there is some effect modification by age, in spite of Woolf's test showing an insignificant p-value. This may have been due to the small numbers which would have given the test low power to detect heterogeneity.

Table 3.3.11: The association of GBS colonization and preterm PROM stratified by maternal age.

MATERNAL AGE		PROM +	PROM -	Total	RR	MH$\underline{X}^2$	p-val.
Under 20	GBS+ve	2	4	6	7.33	3.94	0.0472
	GBS-ve	1	21	22			
		3	25	28			
20 - 24	GBS+ve	3	22	25	15.24	10.18	0.0014
	GBS-ve	1	126	127			
		4	148	152			
25 - 29	GBS+ve	6	30	36	14.29	30.39	0.0000
	GBS-ve	4	339	343			
		10	369	379			
30 & over	GBS+ve	6	47	53	6.60	14.67	0.0001
	GbS-ve	6	344	350			
		12	391	403			
	Crude RR =						9.94
	95% CI =				4.82 < RR < 20.92		
	M-H Chi Square =						51.78
	P value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 1.02 *						
	P value = 0.80						

* Test did not suggest multiplicative interaction.

b. Marital Status:

Table 3.3.12 describes the association of maternal GBS colonization and preterm PROM stratified by maternal marital status. The relative risk of the "other" category (which consisted of single, separated and divorced mothers), and Woolf's test for heterogeneity were not computed due to zero cell values.

Table 3.3.12: The association of GBS colonization and preterm PROM stratified by marital status.

MARITAL STATUS		PROM +	PROM -	Total	RR	MH$\underline{X}^2$	p-val.
Married & common-law	GBS+ve	13	95	108	7.98	39.17	0.000
	GBS-ve	12	784	796			
		25	879	904			
Other	GBS+ve	4	8	12	Undefined	6.19	0.000
	GBS-ve	0	46	46			
		4	54	58			
	Crude RR =						9.94
	95% CI =						4.82 < RR < 20.92
	M-H Chi Square =						51.78
	P value =						0.000000

* Woolf's test for heterogeneity was not done due to zero cell values.

c. <u>Maternal Parity</u>:

Table 3.3.13 describes the association of maternal GBS colonization and preterm PROM stratified by maternal parity. There is no effect modification by maternal parity and no confounding. Woolf's test for heterogeneity gave an insignificant p-value, and did not suggest multiplicative interaction.

Table 3.3.13: The association of GBS colonization and preterm PROM stratified by maternal parity.

PARITY		PROM +	PROM −	Total	RR	MH$\underline{X}^2$	p-val
Primiparous	GBS+ve	11	54	65	9.50	33.80	0.000
	GBS-ve	7	386	393			
		18	440	458			
Multiparous	GBS+ve	6	49	55	9.80	21.98	0.000
	GBS-ve	5	444	449			
		11	493	504			

Crude RR =	9.94
Summary RR =	9.61
95% CI =	4.82 < RR < 20.92
M-H Chi Square =	51.78
P value =	0.000000
Woolf's test for heterogeneity:	
Woolf's Chi-square =	0.00 *
P value =	0.97

* Test did not suggest multiplicative interaction.

d. Maternal Gravidity:

Table 3.3.14 describes the association of maternal GBS colonization and preterm PROM stratified by maternal gravidity, which was composed of 3 strata; "Gravida 1", "Gravida 2", and "Gravida 3 & over". Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be some effect modification by maternal gravidity, especially in mothers gravida 3 and over.

Table 3.3.14: The association of GBS colonization and Preterm PROM stratified by maternal gravidity.

GRAVIDITY		PROM +	PROM -	Total	RR	$MH\underline{X}^2$	p-val.
G1	GBS+ve	9	44	53	7.01	21.23	0.000
	GBS-ve	7	282	289			
		16	326	342			
G2	GBS+ve	2	31	33	8.70	6.88	0.009
	GBS-ve	2	285	287			
		4	316	320			
G3 & over	GBS+ve	6	28	34	15.65	28.18	0.000
	GBS-ve	3	263	266			
		9	291	300			
	Crude RR =						9.94
	95% CI =						4.46 < RR < 18.28
	M-H Chi Square =						48.76
	P-value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 0.85 *						
	P value = 0.65						

* Test did not suggest multiplicative interaction.

e. <u>Maternal Height</u>

Table 3.3.15 describes the association of maternal GBS colonization and preterm PROM stratified by maternal height. Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be effect modification by maternal height.

Table 3.3.15: The association of GBS colonization and Preterm PROM stratified by maternal height.

MATERNAL HEIGHT		PROM +	PROM -	Total	RR	$MH\underline{X}^2$	p-val.
Under 155	GBS+ve	3	21	24	7.13	6.51	0.037
	GBS-ve	2	112	114			
		5	138	138			
155 - 159	GBS+ve	5	24	29	33.45	26.84	0.000
	GBS-ve	1	193	194			
		6	217	223			
160 - 164	GBS+ve	5	27	32	6.17	12.28	0.005
	GBS-ve	6	231	237			
		11	258	269			
165 & over	GBS+ve	4	30	34	11.49	16.73	0.003
	GBS-ve	3	290	293			
		7	320	327			
	Crude RR =						9.98
	95% CI =				4.81 < RR < 20.20		
	M-H Chi Square =						52.78
	P-value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 1.97 *						
	P value = 0.58						

* Test did not suggest multiplicative interaction.

f. Maternal Weight:

Table 3.3.16 describes the association of maternal GBS colonization and preterm PROM stratified by maternal weight. Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be some effect modification by maternal weight.

Table 3.3.16: The association of GBS colonization and Preterm PROM stratified by maternal weight.

MATERNAL WEIGHT		PROM +	PROM -	Total	RR	MHX^2	p-val.
Under 50	GBS+ve	3	14	17	5.29	5.53	0.048
	GBS-ve	3	78	81			
		6	92	98			
50 - 59	GBS+ve	5	50	55	8.89	15.84	0.002
	GBS-ve	4	387	391			
		9	437	446			
60 - 69	GBS+ve	7	28	35	15.27	28.99	0.000
	GBS-ve	3	226	229			
		10	254	264			
70 & over	GBS+ve	2	11	13	10.85	9.12	0.036
	GBS-ve	2	139	141			
		4	150	154			
	Crude RR =						10.11
	95% CI =				4.74 < RR < 19.59		
	M-H Chi Square =						52.19
	P-value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 1.23 *						
	P value = 0.75						

* Test did not suggest multiplicative interaction.

g. Employment Status:

Table 3.3.17 describes the association stratified by maternal employment status. Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be effect modification by maternal employment status.

Table 3.3.17: The association of GBS colonization and preterm PROM stratified by Employment Status.

EMPLOYMENT STATUS		PROM +	PROM -	Total	RR	MH$\underline{X}^2$	p-val.
Employed	GBS+ve	12	59	71	9.48	42.81	0.001
	GBS-ve	10	551	561			
		22	610	632			
Non-employed	GBS+ve	5	44	49	14.34	18.05	0.000
	GBS-ve	2	279	281			
		7	323	330			
	Crude RR =						9.94
	95% CI =				5.11 < RR < 21.57		
	M-H Chi square =						56.43
	P value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 0.13 *						
	P value = 0.72						

* Test did not suggest multiplicative interaction.

h. Smoking Status:

Table 3.3.18 describes the association stratified by maternal smoking status. Woolf's test for heterogeneity was not calculated due to zero cell values.

Table 3.3.18: The association of GBS colonization and preterm PROM stratified by smoking status.

SMOKING STATUS		PROM +	PROM -	Total	RR	$MH\underline{X}^2$	p-val.
Smoking	GBS+ve	8	17	25	Undefined	52.26	0.000
	GBS-ve	0	157	157			
		8	174	182			
Non-smoking	GBS+ve	9	86	95	5.41	18.96	0.003
	GBS-ve	12	673	685			
		21	759				
	Crude RR =						9.94
	95% CI =						4.85 < RR < 21.16
	M-H Chi Square =						53.21
	P value =						0.000000

* Woolf's test for heterogeneity was not done due to zero cell values.

i. <u>Alcohol Intake</u>:

Table 3.3.19 describes the association stratified by alcohol intake. Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be effect modification by maternal alcohol intake during the pregnancy.

Table 3.3.19: The association of GBS colonization and preterm PROM stratified by alcohol intake.

ALCOHOL INTAKE		PROM +	PROM -	Total	RR	MHχ^2	p-val.
Any Intake	GBS+ve	4	27	31	16.39	19.61	0.002
	GBS-ve	2	252	254			
		6	279	285			
No Intake	GBS+ve	13	76	89	8.57	39.09	0.000
	GBS-ve	10	577	587			
		23	653	676			
	Crude RR =						9.93
	95% CI =				4.76 < RR < 19.69		
	M-H Chi Square =						52.75
	P value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 0.41 *						
	P value = 0.52						

* Test did not suggest multiplicative interaction.

j. Past Medical History:

Table 3.3.20 describes the association stratified by maternal past medical history (PMH). Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be effect modification by past medical history.

Table 3.3.20: The association of GBS colonization and preterm PROM stratified by past medical history.

PAST MEDICAL HISTORY		PROM +	PROM −	Total	RR	MHχ^2	p-val.
Any PMH	GBS+ve	1	22	23	3.11	0.97	0.326
	GBS-ve	2	141	143			
		3	163	166			
No PMH	GBS+ve	16	81	97	11.53	61.10	0.000
	GBS-ve	10	689	699			
		26	770	796			
	Crude RR =						9.94
	95% CI =						4.90 < RR < 20.28
	M-H Chi Square =						54.72
	P value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 1.21 *						
	P value = 0.27						

* Test did not suggest multiplicative interaction.

k. <u>Medical History of Kidney Disease</u>:

Table 3.3.21 describes the association stratified by past medical history of kidney disease, which was classified into two strata; "positive", and "negative". Relative risk for the stratum of positive history of kidney disease and Woolf's test for heterogeneity were not calculated due to zero cell values.

Table 3.3.21: The association of GBS colonization and preterm PROM stratified by history of Kidney disease.

KIDNEY DISEASE		PROM +	PROM -	Total	RR	MHX^2	p-val.
Positive	GBS+ve	0	6	6	0.00	0.33	0.564
	GBS-ve	1	17	18			
		1	23	24			
Negative	GBS+ve	17	97	114	11.17	63.68	0.000
	GBS-ve	11	813	824			
		28	910	938			
	Crude RR =						9.94
	95% CI =						4.70 < RR < 18.85
	M-H Chi Square =						53.40
	P value =						0.000000

* Woolf's test for heterogeneity was not done due to zero cell values.

1. <u>Past Obstetric History</u>:

Table 3.3.22 describes the association stratified by past obstetric and gynecological history. By observing the stratum-specific relative risks there appears to be effect modification by past obstetric history, but Woolf's test for heterogeneity gave a borderline p-value, and did not suggest multiplicative interaction.

Table 3.3.22: The association of GBS colonization and preterm PROM stratified by past obstetric history.

PAST OBSTETRIC HISTORY		PROM +	PROM -	Total	RR	MH$\underline{X}^2$	p-val.
Any History	GBS+ve	1	20	21	1.55	0.16	0.532
	GBS-ve	4	126	130			
		5	146	151			
No History	GBS+ve	16	83	99	14.38	68.36	0.000
	GBS+ve	8	704	712			
		24	787	811			

Crude RR = 9.94
95% CI = 4.79 < RR < 19.75
M-H Chi Square = 53.79
P value = 0.000000

Woolf's test for heterogeneity:
Woolf's Chi-square = 3.74 *
P value = 0.05

* Test did not suggest multiplicative interaction.

m. <u>Past History of Preterm Labour</u>:

Table 3.3.23 describes the association stratified by past history of preterm labour, which was classified into two strata; "positive" and "negative". The relative risk for the stratum of mothers with positive past history of preterm labour, and Woolf's test for heterogeneity could not be calculated due to zero cell value.

Table 3.3.23: The association of GBS colonization and preterm PROM stratified by history of preterm labour.

PAST PRETERM LABOUR		PROM +	PROM -	Total	RR	MHX^2	p-val.
Positive	GBS+ve	0	4	4	0.00	0.62	0.430
	GBS-ve	3	18	21			
		3	22	25			
Negative	GBS+ve	17	99	116	13.37	69.19	0.000
	GBS-ve	9	812	821			
		26	911	937			
	Crude RR =						9.94
	95% CI =				4.62 < RR < 18.88		
	M-H Chi Square =						52.61
	P value =						0.000000

* Woolf's test for heterogeneity was not done due to zero cell values.

n. Current History of Early Bleeding:

Table 3.3.24 describes the association stratified by current pregnancy history of early bleeding, which was classified into two strata; "positive" and "negative". Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be effect modification by current pregnancy history of early bleeding.

Table 3.3.24: The association of GBS colonization and preterm PROM stratified by current history of early bleeding.

EARLY BLEEDING		PROM +	PROM -	Total	RR	MHX²	p-val.
Positive	GBS+ve	4	9	13	12.00	8.75	0.003
	GBS-ve	1	38	39			
		5	47	52			
Negative	GBS+ve	13	94	107	8.87	42.68	0.000
	GBS-ve	11	792	803			
		24	886	910			
	Crude RR =						9.94
	95% CI =				4.62 < RR < 19.28		
	M-H Chi Square =						50.26
	P value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 0.18 *						
	P value = 0.67						

* Test did not suggest multiplicative interaction.

o. Current History of Late Bleeding:

Table 3.3.25 describes the association stratified by current pregnancy history of late bleeding. Although Woolf's test for heterogeneity gave an insignificant p-value, by observing the stratum-specific relative risks there appears to be effect modification by current pregnancy history of late bleeding.

Table 3.3.25: The association of GBS colonization and preterm PROM stratified by current history of late bleeding.

LATE BLEEDING		PROM +	PROM -	Total	RR	MHX^2	p-val.
Positive	GBS+ve	3	1	4	12.00	8.98	0.003
	GBS-ve	1	15	16			
		4	16	20			
Negative	GBS+ve	14	102	116	9.06	45.34	0.000
	GBS-ve	11	815	826			
		25	917	942			
	Crude RR =						9.94
	95% CI =				4.62 < RR < 19.28		
	M-H Chi Square =						50.26
	P value =						0.000000
	Woolf's test for heterogeneity:						
	Woolf's Chi-square = 0.86 *						
	P value = 0.35						

* Test did not suggest multiplicative interaction.

p. <u>Uterine anomalies</u>:

Table 3.3.26 describes the association of maternal GBS colonization and preterm PROM stratified by the presence of uterine anomalies. Woolf's test for heterogeneity was not calculated due to zero cell values.

Table 3.3.26: The association of GBS colonization and preterm PROM stratified by the presence of uterine anomalies.

UTERINE ANOMALIES		PROM +	PROM -	Total	RR	MHX^2	p-val.
Positive	GBS+ve	0	2	2	0.00	0.40	0.527
	GBS-ve	1	4	5			
		1	6	7			
Negative	GBS+ve	17	101	118	10.96	62.23	0.000
	GBS-ve	11	826	837			
		28	927	955			
	Crude RR =						9.94
	Summary RR =						9.06
	95% CI =						4.54 < RR < 18.07
	M-H Chi Square =						51.64
	P value =						0.000000

* Woolf's test for heterogeneity was not done due to zero cell values.

2) LOGISTIC REGRESSION ANALYSIS:

Stepwise logistic regression analysis was performed as the second step of multivariate analysis. Selection of variables for the logistic regression was based on both clinical basis and statistical significance. All the variables found to be significant from the univariate analysis on both relationships to GBS colonization and preterm PROM were used in the logistic regression analysis. A higher significance level of 15% was used to determine which variables to enter into the logistic regression analysis. This level was designated as the level of significance because of the small cell numbers. Maternal smoking status during the pregnancy was also included in the logistic regression analysis because of its known association with preterm rupture of the fetal membranes.

Logistic regression was done with the dependent variable being preterm PROM and controlling for the following variables: marital status categorized into two groups (married & common-law, other), employment status, maternal parity, maternal height, maternal smoking status, medical history of kidney disease, past obstetric history of preterm labour, maternal history of uterine anomalies, in addition to conditions occurring during the current pregnancy, which included: early bleeding, late bleeding, urinary tract infection, diabetes mellitus, hypertension, pre-eclampsia, and GBS colonization status.

The first variable to be entered in step 1 was GBS colonization status. The variable entered in step 2 was late bleeding during current pregnancy, followed by past history of preterm labour in step 3, and finally maternal employment status was entered in step 4. Table 3.3.27 describes the result of stepwise logistic regression analysis.

Table 3.3.27: Result of Stepwise Logistic Regression.

Variable	Coef.	SE	Coef/SE	$e^{(coef.)}$	95% CI Lower	95% CI Upper
Constant	-5.22	0.53	-9.86			
GBS	2.59	0.41	6.27	13.40	5.93	30.10
Lt.bld.	2.39	0.70	3.41	10.90	2.76	43.20
Pret.lbr	2.29	0.72	3.16	9.90	2.38	41.10
Empl.	0.93	0.49	1.91	2.53	0.98	6.58

Empl. = Employment status.
Pret.lbr = Preterm labour.
Lt.bld. = Late bleeding.

Table 3.3.27 indicates that the relative risk of preterm PROM for GBS positive women is 13.4, with a 95% confidence interval ranging from 5.93 to 30.1. Late bleeding showed a relative risk of 10.9, and past history of preterm labour showed a relative risk of 9.9. The only variable which confidence interval included 1 was employment status, which showed a relative risk of 2.53, and a confidence interval ranging from 0.976 to 6.58.

SUMMARY OF THE COHORT STUDY:

The total number of women who had preterm PROM was 29 cases (3.0%). The number of colonized mothers who had preterm PROM was 17 (14.2%), and the number non-colonized was 12 (1.4%). The association between maternal vaginal GBS colonization and preterm PROM showed a Relative Risk of 9.94 (95% CI = 4.87 < RR < 20.30).

The difference in the gestational age at delivery between GBS positive and negative women was highly significant. The percentage of positive women was highest among women delivering before 34 weeks of gestation (75.0%), followed by those delivering between 34 to 36 weeks of gestation (60.0%).

With regards to labour and delivery, there was a higher percentage of positive women whose labour was induced or had elective caesarian sections. The mean birthweight of infants born to positive women was lower than that of those born to negative mothers. The differences in labour and delivery, and mean infant birthweight between GBS positive and negative women were statistically significant.

When GBS positive and negative women were compared, significant differences were found in case of maternal height, marital status, gravidity, in addition to current pregnancy history of early bleeding, and urinary tract infection. When women whose pregnancy ended by preterm PROM and women who did not have preterm PROM were compared, significant differences were also found between the two groups in case of maternal gravidity, past history of preterm labour, and current pregnancy history of early bleeding and late bleeding.

Stratified analysis indicated effect modification by maternal age, gravidity, height, weight, employment status, alcohol intake during the pregnancy, in addition to current pregnancy history of early bleeding and late bleeding.

Stepwise logistic regression analysis indicated an adjusted relative risk of preterm PROM for GBS positive women of 13.4 (CI = 5.93 < RR < 30.1). Late bleeding during the pregnancy showed a relative risk of 10.9 (CI = 2.76 < RR < 43.2), and past history of preterm labour showed a relative risk of 9.9 (CI = 2.38 < RR < 41.1).

CHAPTER 4: DISCUSSION:

4.1 THE PREVALENCE STUDY:

Previously reported rates for maternal genital colonization by Group B Streptococci during pregnancy have varied widely from 2.3%[22] to 32-41%[27]. The prevalence rates of maternal GBS colonization have been reported to be influenced by many factors, like maternal age, parity, gravidity, geographical location, maternal socio-economic status, and ethnic background. Colonization rates have also varied according to the number of sites cultured, and the distance of the cultured site from the cervix.

In this study, high vaginal cultures at 28 weeks of gestation revealed the prevalence of maternal Group B Streptococcal colonization to be 12.6%. This "rate" is quite similar to that obtained from previous studies, and points to the importance or significance of colonization on the general population. The closest reported rates was that reported by Bobbitt and co-workers[28], who reported the incidence of at least one positive culture during pregnancy to be 11.3%. Regan and associates[26], who obtained cultures from the cervix, indicated a slightly higher maternal colonization rate of 13.4%. Baker and associates[24], obtained cultures from the throat and vagina of pregnant women, and reported a colonization rate of 14.8% during the second trimester of pregnancy.

Other Canadian studies of maternal GBS colonization reported higher rates. Macdonald and Mackenzie[29] reported a maternal colonization rate at delivery of 20%, which is relatively high, and may be attributed to the collection of swabs from both vaginal and rectal sites in the mother. Allardice and co-workers[30] reported an antenatal colonization rate of 10.3%, and a lower rate of 7.6% during labour. Joshi, Chen, and Turnell[22], reported a much lower colonization rate of 2.3%. These different rates may be attributed to differences in the cultured sites, the distance of the cultured site from the cervix, and the stage of pregnancy at which culture was obtained in each of these studies.

Comparatively, much higher or lower rates have been reported by other authors. Hastings and associates[27] reported an overall colonization rate of 28.4%, while Yow and Leeds[31] reported a vaginal colonization rate of 20.4%. On the other hand, lower rates were reported by Lewin and Amstey[21], who reported a colonization rate of 7% to 8% in any trimester of pregnancy. Ancona, Ferrieri and Williams[25] reported a rate of 8.0%, and Minkoff and associates[18] reported a rate of 9.9%. It might have been beneficial to have performed meta-analysis of the results of previously conducted studies, so as to obtain a summary prevalence figure, but this was not done because of time limitations and inaccessibility of the data.

The rate of GBS positivity was found to be highest among mothers under 20 years, and lowest in mothers over 40 years of age. This is consistent with the findings of previous studies that colonization rates are higher in pregnant teenagers, and in mothers under 20 years of age. With regards to marital status, the rate of colonization was higher in unmarried mothers, although this was not statistically significant but it may suggest that women with one partner are less likely to harbour the micro-organism. In case of parity, GBS positivity was higher in primiparous women, but was not statistically significant, which may support the findings of Hastings and associates[27] who found no association between maternal parity and GBS colonization during pregnancy. With regards to maternal gravidity, which has never been investigated in previous studies, the rate of maternal GBS colonization was found to be higher in women with higher gravidity (gravida 4 and over), but was also not statistically significant. GBS positivity was highest in women under 150 centimeters in height and in mothers who were under 50 kilograms in weight.

With regards to maternal social characteristics, the rate of GBS positivity was higher among non-employed mothers. The rate of GBS positivity was also higher in mothers who smoked, especially those smoking less than 10 cigarettes per day, but was not significant. With regards to alcoholic intake during the pregnancy, the rate of GBS positivity was higher in mothers who reported moderate to heavy alcoholic intake, but was lowest in mothers who reported no alcoholic intake during the pregnancy, and this showed borderline statistical significance.

Although previous studies of GBS colonization during pregnancy did not report on maternal medical conditions, in this study GBS positivity was found to be highest in mothers with a past medical history of Diabetes mellitus, and was statistically significant. This may have occurred because of the higher susceptibility of women with diabetes for infections, thereby making them more likely to harbour the organism.

In case of past obstetric and gynecological history, the rate of GBS positivity was higher in women who had previous history of ectopic pregnancy and sexually transmitted or pelvic inflammatory disease, although the difference was not statistically significant. Since these conditions are related to maternal genital infection and colonization by offending micro-organisms, then this may suggest that women with history of any of the above conditions may be more likely to harbour GBS in their genital tracts. Also, the rate of GBS positivity was higher in women who had previous history of preterm labour, and premature rupture of the membranes, which is consistent with the findings of previous studies.

The prevalence of GBS colonization was significantly higher among women with current pregnancy history of diabetes mellitus, which may be explained by their higher susceptibility for infections. Also, the rate of GBS colonization was significantly higher in women who had early bleeding during the current pregnancy. The prevalence rate of GBS positivity were also high among mothers who had UTI, late bleeding, gestational diabetes, oligohydramnios, and in those undergoing amniocentesis, but the differences were not significant.

4.2 <u>THE COHORT STUDY</u>:

High vaginal cultures were obtained at 28 weeks of gestation, and the positive outcome group included only preterm PROM cases who had ruptured their membranes prior to 37 completed weeks of gestation. The association between high vaginal GBS colonization and preterm PROM showed a relative risk of 9.94, with a 95% Confidence Interval lower limit of 4.87 and upper limit of 20.30. This relative risk is higher than that obtained in other previously conducted studies, but is likely to be more accurate in reflecting the true association, because of the strict criteria of eligibility applied in including women in this study. Only women with preterm PROM (i.e. only those occurring prior to 37 weeks of gestation) are included in the outcome group, whereas almost all of the previous studies have included PROM cases occurring after 37 weeks, in addition to those occurring at term, which may have diluted the effect, since 80% of term deliveries are preceded by rupture of the fetal membranes. The only study in the literature that investigated preterm PROM occurring before 37 weeks of gestation was that conducted by Alger and co-workers[49] where they also obtained a high relative risk of 8.04, which is close to that obtained in this study.

The total number of cultured women was 1039 cases, 77 of which were excluded from entry into the cohort study. These excluded cases were women with high risk pregnancies like those with previous history of preterm labour and preterm rupture of the fetal membranes. Although most previous studies did not exclude women with these conditions, they were excluded in this study because they had known risk factors of preterm PROM in a consequent pregnancy. Also, women with current pregnancy history of multiple pregnancy, amniocentesis, cervical circulage, and polyhydramnios, were excluded from the cohort study as they have been shown in previous studies to increase the risk of preterm rupture of the membranes. Furthermore, mothers who had spontaneous preterm labour that had been resolved by tocolytic therapy to bring their pregnancies closer to term, were also excluded from the cohort study since they are considered as high risk cases, and may be more susceptible to have preterm labour or preterm PROM. On the other hand, had any of these high risk cases been included in the cohort study, the Relative Risk would have decreased, since we expect a prevalence rate of about 10-12%, and because of the small number of GBS positive women in these high risk groups, most of them are likely to be negative to GBS.

Comparison between women who had preterm PROM and women who did not, showed a significant difference between the two groups in past history of preterm labour, which is comparable to the findings of previous studies. In addition, there were significant differences between the two groups in the occurrence of early and late bleeding during the current pregnancy, indicating that women who have early or late bleeding during the pregnancy are significantly more likely to have preterm PROM, which is consistent with previous studies.

When outcome of the pregnancy was compared between GBS positive and negative women in the cohort study, there was a highly significant difference in the occurrence of preterm PROM, being higher in positive women. There was a significant difference in gestational age at delivery between positive and negative mothers, with a much higher percentage of positive women delivering earlier in the pregnancy than negative mothers, especially those delivering before 34 weeks of gestation, followed by those delivering between 34 to 36 weeks. This indicates that women positive for GBS are more likely to deliver before term as a result of the higher occurrence of preterm PROM. With regards to the type of labour, there was a higher percentage of induced labour and elective caesarian sections in GBS positive mothers, which suggests that GBS colonization in pregnant women may be associated with more complications during labour, that might necessitate instrumental or surgical interference. In addition, the mean infant birthweight of those born to GBS positive mothers was lower than that of infants born to negative mothers, which also points to the adverse consequences of GBS colonization during the pregnancy on the infant.

Stratified analysis showed effect modification by current pregnancy history of early and late bleeding, which are known risk factors for preterm PROM. Also, maternal gravidity, employment status, and alcohol intake during the pregnancy were found to be effect modifiers. Stepwise logistic regression analysis indicated an adjusted relative risk of preterm PROM for GBS positive mothers of 13.4 with a 95% confidence interval lower limit of 5.93 and upper limit of 30.1. Related factors in the logistic regression included both past obstetrical history of preterm labour and current pregnancy history of late bleeding, which have been shown in previous studies to increase the risk for preterm PROM.

4.3 STRENGTHS AND WEAKNESS OF THE STUDY:

This study is a historical cohort study based on reviewing hospital charts, and has both the advantages and disadvantages of any historical study, being less expensive, and requiring a shorter time to complete than prospective studies. In addition, information on both past exposure and disease status are available in the hospital charts, which were likely to contain adequate information on both maternal exposure status of vaginal colonization by GBS at 28 weeks of gestation, and the outcome of preterm PROM. The charts also included additional information on maternal social, demographic and lifestyle factors that are likely to affect the association.

On the other hand, in historical cohort studies in general, data which were collected for purposes other than investigating the hypothesis of interest may be incomplete or incomparable in some cases. In this study this possibility is minimal, because the information in the mothers charts is most likely to be accurate and comparable, as it was obtained for the purpose of obstetrical care of the mothers during pregnancy for early detection of problems arising during the pregnancy for the benefit of both the mother and the infant. Therefore any problem detected during the pregnancy is likely to be treated, followed up, and well documented in each mother's chart. With regards to the completeness of socio-demographic details in the charts, complete information was found for most of the variables. Absence of information on a certain variable in the chart was recorded as missing during data collection, and was not indicated as negative history of that variable. Missing data were not incorporated in subsequent analysis. Information on maternal age, marital status, parity, gravidity, employment status, occupation, past history of term and preterm deliveries, in addition to the number of living children was recorded for 100% of the cases. Maternal height and weight was recorded for almost 99% of the total study population. Maternal smoking status was documented for 100.0% of cases, and the percentage of smoking mothers (20.0%) was comparable to that of the general population. With regards to alcoholic intake during the pregnancy, information was found in 99.8% of the charts, and was missing in only 3 charts. The only socio-demographic variable that was not well documented in the charts was maternal educational level, which was found in only 501/1547 charts (32.4%) and, consequently, this variable was excluded from the analysis.

In selecting women for the study, we expected maternal exposure to GBS in at least 5% of the population under study, so a large number was expected to be exposed. Reasonably accurate data on exposure status of each of the eligible women was expected to be found in the laboratory culture reports in each of the mothers charts. An appropriate comparison group was identified as non-exposed mothers by means of the same laboratory reports, which insures the comparability of GBS negative and GBS positive mothers. One of the possible limitations of historical cohort studies is obtaining sufficient exposure data. In this study exposure status is well documented by means of the laboratory reports present in each mothers chart, which gives good quality to the data collected. In case of measuring maternal exposure, the laboratory reports indicate whether mothers were colonized at 28 weeks of gestation or not, and the heaviness of growth of the micro-organism on culture, which is likely to be comparable in both exposed and non-exposed mothers as the swabs are examined and cultured at the same hospital laboratory. The swabs were collected from all the mothers and examined beforehand, without prior knowledge of the underlying hypothesis to this study. On the other hand, the laboratory reports from which maternal exposure status was determined can not indicate how long each mother was exposed. This might have been a real limitation to the study, since, with a prospective study it could have been decided to culture more often during the pregnancy, and consequently gain a better idea of the natural history of maternal colonization by the organism, and whether women with prolonged colonization were at an even higher risk.

Another draw back to historical cohort studies is that under-ascertainment of the status of disease or outcome of the cohorts under study decreases the precision in estimating the association between exposure and disease. In this study, data on disease status or the outcome of preterm PROM were obtained from the delivery record in each mothers chart. This information was mainly dependent on the obstetricians' clinical diagnosis written in the chart and the gestational age at which rupture of the membranes occurred that was documented on the record. The same information on the ascertainment of disease status was used for both exposed and non-exposed mothers. Data on the outcome were complete for all the cases and most likely to be accurate. Since the delivery record contains a section on maternal antenatal GBS colonization status, the obstetrician attending the delivery is most likely to have known the colonization status. But it is unlikely that knowledge of maternal GBS colonization status would have affected the obstetricians diagnosis of preterm PROM, firstly because this information is indicated on the delivery record only to identify infants at risk for perinatal GBS infection, secondly because the obstetrician confirms rupture of the fetal membranes by nitrazine testing before making the diagnosis, and thirdly because preterm PROM had to have occurred before 37 weeks of gestation.

Another of the draw-backs of historical cohort studies is obtaining sufficient information on confounding variables that may affect the association between exposure and disease. In this study adequate information on confounding variables is likely to be documented and present in the mothers charts equally for both exposed and non-exposed mothers. As previously mentioned, information on maternal age, marital status, parity, and gravidity was documented in 100% of the charts. Maternal smoking status was documented for 100.0% of cases, and alcoholic intake during the pregnancy was found in 99.8% of the charts. Information on maternal past history of preterm labour, preterm PROM, in addition to events occurring during the current pregnancy like bleeding, are likely to be accurate and complete. On the whole, the quality of the information indicated in the maternal charts was quite accurate and complete. For example, as I have previously mentioned, maternal smoking status was documented in 100.0% of the charts, 20.0% of whom smoked during the pregnancy. This percentage is similar to the rate of maternal smokers in the general population, which indicates that the chart accurately reflected what smoking status really was. If there had been under-reporting in any of the variables it is likely to have been the same in both GBS positive and negative mothers. In any case, the attending obstetrician would not have known the culture status when recording the information on any of the variables under study, firstly because most of the information on socio-demographic and past medical and obstetrical history were obtained from the mother at the first prenatal visit, and secondly because all women who registered for prenatal care after 25 weeks of gestation (i.e. around the gestational age when culture is taken), were excluded from the study.

A possible point of weakness in this study is that occurring in certain parts of the stratified analysis. In spite of some of the variables showing a large difference in relative risks between strata, Woolf's tests for heterogeneity showed insignificant p-values (e.g tables 3.3.15, 3.3.16, 3.3.17, 3.3.19, 3.3.20, 3.3.22, 3.3.23). This may have occurred as a result of the small number of cases of preterm PROM in the study, which in turn resulted in some cells having very small numbers. This would have given the test low power to detect heterogeneity. In fact, this opinion is supported by table 3.3.22 where, in spite of there being a huge difference in stratum-specific relative risks (1.55 and 14.38), the test for heterogeneity only gave a borderline p-value of 0.05.

Another possible point of weakness in the study is the danger of limitations of multiple testing, since quite a few tests of significance were made.

4.4 SOURCES OF BIAS:

The most important issue in the interpretation of historical cohort studies is the role of bias. As both the exposure and the disease or outcome of interest have occurred in the past, knowledge of the study hypothesis by the person collecting the data on the disease status can affect the selection of exposed and non-exposed individuals, and selection bias could result. In this study this possibility is minimal, first because all the women delivering at the OGH during a period of one year were selected by means of the computer program formulated by the department of medical records, and second because strict criteria for eligibility, were adhered to. In addition, the outcome status of each mother was not known prior to data collection, and was obtained on chart review at the same time that information on exposure status was obtained. Also, knowledge of the outcome status of mothers in this study does not affect the investigation of exposure status, as the information on whether the mother was exposed to GBS at 28 weeks of gestation was documented in the laboratory culture report, and if the report was missing from the mother's chart, then the mother was not included into the study.

Another potential source of bias in historical cohort studies arises from the degree of accuracy with which the study subjects are classified, with respect to their exposure and outcome status. A number of those exposed may be considered non-exposed, and a number of those truly non-exposed may be classified as exposed. This is not likely to have occurred in this study, because data on exposure status of mothers to GBS were obtained from the laboratory culture reports found in the mothers' charts, which clearly indicate whether GBS were present on culture, the heaviness of growth of the micro-organism, and the presence of any other organisms on culture. These laboratory reports are most likely to reflect the true status of maternal exposure, and to be accurate for all the study population regardless of their disease status. As previously mentioned, mothers whose culture report was not found in the chart were excluded from the study. A source of error that might have occurred in case of exposure status, was if the swab was not taken from the same vaginal site in all the mothers, but there is no way of detecting this possibility at this stage of chart review. If this had occurred, the result might have been under-reporting (i.e. more cases being identified as controls), and diminishing of the true effect difference, but will not have discounted the effect found in this study.

In terms of ascertaining the outcome of interest, data obtained are likely to be comparable regardless of maternal exposure status. The outcome information was obtained from the same source (the delivery record) in each the mother's chart. This information was completely dependent on the obstetricians' clinical evaluation and diagnosis. The gestational age at which preterm PROM occurred was documented on the forms, and would have been easily calculated from the date of the mother's last menstrual period documented in the record.

Non-differential misclassification occurs if there were inaccuracies in categorizing the study subjects by their exposure or disease status, and these inaccuracies occurred in similar proportions in each of the study groups[54]. When this type of misclassification is present it results in making both the exposed and non-exposed groups more similar to each other, and any true association between the exposure and the outcome will be diluted. Non-differential misclassification of the outcome might have occurred in this study if errors were found in the delivery record in terms of the gestational age at which preterm PROM occurred. This information was strictly obtained from the obstetricians' clinical diagnosis on the delivery record, and if any error was found in documenting the gestational age at which rupture of the membranes occurred, such that a woman with the outcome be classified as her rupture not being preterm, then this was likely to occur randomly. On the other hand, there is no possibility of random misclassification in case of maternal exposure status, because this information was obtained from the laboratory culture reports, which are expected to be accurate. It should be mentioned that non-differential misclassification may diminish the association between exposure and disease, but can not be responsible to cause an association if one did not exist.[54]

Differential or non-random misclassification, on the other hand, results when errors in the classification of women in the study by exposure or disease produce a differential accuracy or quality of information among the groups under study[54], is also unlikely to have occurred in this study. First, because both the exposed and non-exposed women are similar in their seeking antenatal care at the same hospital, and have no control on either their exposure or outcome status. Secondly, because it is unlikely that there is more diagnosis of preterm PROM in

GBS positive women. Information on the outcome was obtained from the delivery record that is filled by the attending obstetrician, who confirms rupture of the membranes by nitrazine testing before making the diagnosis, and whose knowledge of maternal GBS colonization status is unlikely to have affected his diagnosis, since this information is indicated on the delivery record only to identify infants at risk for perinatal GBS infection. Also, both the vaginal culture that determined exposure status, and the diagnosis of preterm PROM were made without prior knowledge of the underlying hypothesis to this study. If any error had occurred it would have occurred equally in both positive and negative women.

The validity of the data of historical studies is affected by both the accuracy and completeness of the information on which the classifications of the study population were based, and also by the degree to which the errors were made differentially between the study groups.[54] It is not expected that the validity of the data in this study was affected, because of the strict criteria for classifying mothers whether exposed or not, and whether they developed preterm PROM, that were adhered to prior to data collection.

4.5 ESTIMATION OF A CAUSE-EFFECT RELATIONSHIP:

Since it has been statistically proven that there is an association between maternal exposure to group B streptococci and the occurrence of preterm premature rupture of the fetal membranes, now it is needed to consider whether the relationship can be judged as one of cause and effect. The presence of a cause-effect relationship between the exposure and the outcome of interest may be ascertained by different factors; the strength of the association, the biologic credibility of the hypothesis, consistency of the findings with previous investigations, in addition to the presence of an appropriate time sequence to the association and the presence of a dose-response relationship.[54]

With regards to strength of the association, the stronger the association between exposure and outcome the more likely is the association to have a cause-effect relationship. In this study there was a strong association between exposure to GBS and preterm PROM showing a relative risk of 9.94, which remained and even increased to 13.4 after control of potential confounding variables.

With regards to biologic credibility, although there is no scientifically proven biologic mechanism by which Group B Streptococci precipitate preterm PROM, it has been postulated that micro-organisms ascending from the mother's lower genital tract into the uterus invade the fetal membranes and cause a local inflammatory reaction, thus weakening the membranes at the area of inflammation, and causing their preterm rupture.

With regards to consistency of the findings with previously conducted studies, although there is a controversy in the literature, most studies supported the hypothesis that maternal genital colonization by GBS was associated with preterm PROM, and the findings in this study support that view.

With regards to an appropriate time sequence, it is clear in this study that the exposure of interest preceded the outcome of preterm PROM by a reasonable period of time.

With regards to the presence of a dose-response relationship, by means of observing a gradient of risk associated with the degree of exposure, it remains to be investigated whether maternal exposure to different colonization levels of GBS increases the risk of preterm premature rupture of the fetal membranes.

CONCLUSION:

The prevalence of maternal Group B Streptococcal colonization at 28 weeks of gestation was found to be 12.6%. This is a relatively high and significant rate, which demonstrates the importance of the problem. The percentage of mothers exposed to Group B Streptococcal colonization at 28 weeks of gestation whose pregnancy was complicated by preterm rupture of the membranes was 14.2%, compared to 1.4% in non-exposed mothers.

The crude relative risk of preterm premature rupture of the fetal membranes for mothers with vaginal Group B Streptococcal colonization at 28 weeks of gestation was 9.94, with a 95% Confidence Interval lower limit of 4.87 and higher limit of 20.30. After adjusting for potential confounders by means of stepwise logistic regression an adjusted relative risk of preterm rupture of the membranes for GBS positive mothers was found to be 13.4 with a 95% confidence interval lower limit of 5.93 and higher limit of 30.1.

Stratified analysis showed effect modification by past obstetrical history of preterm labour, the presence of uterine anomalies, and current pregnancy history of early and late bleeding which are all known risk factors for preterm PROM. Furthermore, there was effect modification by medical history of kidney disease, which is a known risk factor for intra-uterine fetal growth retardation, and low infant birth weight.

The high prevalence of maternal GBS colonization, the much higher rate of preterm PROM in positive compared to negative women, and the high relative risk of preterm rupture of the membranes for positive mothers, all combine to signify a very important factor associated with preterm PROM, which is vaginal colonization of pregnant women by Group B Streptococci during the pregnancy.

The results of this study support the hypothesis that maternal genital colonization by Group B Streptococci during pregnancy increases the risk of preterm rupture of the fetal membranes and subsequent preterm birth. Therefore, this is a significant health problem that is worthy of future research to explore what can be done to bring down this high prevalence rate and identify how to decrease it's impact, in addition to methods of prevention of preterm premature rupture of the fetal membranes for GBS positive mothers.

REFERENCES:

1. Baker CJ, Barrett FF. Transmission of Group B Streptococcus among parturient women and their neonates. J Pediatr 1973; 82:707.
2. Youmans, Patterson, and Sommers. The biologic and clinical basis of infectious diseases. W.B. Saunders Co., 1975.
3. Anthony BF, Okada DM, Hobel CJ; Epidemiology of group B streptococcus: Longitudinal observations during pregnancy. J Infect Dis 1978; 137:524.
4. Scott JR, DiSaia PJ, Hammond CB, Spellacy WN. Danforth's Obstetrics and Gynecology. 6th edition. 1990.
5. World Health Organisation: prevention of perinatal mortality and morbidity: A report. Public Health Pap 42, 1972, pp 1-97.
6. Statistics Canada, National Data for Livebirths, 1991.
7. 1991 Physicians notification of birth data for Ottawa-Carleton, Ottawa, Canada.
8. U.S Department of Health and Human Services. Public Health Service. Vital Statistics of the United States. 1982. Vol.I (Natality). Hyattsville, Maryland: National Centre for Health Statistics, 1986.

9. Main DM. The Epidemiology of Preterm Birth. Clinical Obstetrics and Gynecology, 1988; 31,521.

10. Meis PJ, MacErnest J, Moore ML. Causes of low birth-weight births in public and private patients. Am J Obstet Gynecol 1987; 156:1165.

11. Abramowicz M, Kass EH. Pathogenesis and prognosis of prematurity. N Eng J Med 1966; 275: 878, 938, 1001, 1053.

12. US Department of Health and Human Services. Report of the Secretary's Task Force on Black and Minority Health, Publication 0-487-637(QL3). Vol.6 (Infant mortality and low birthweight). Hyattsville, Maryland, National Centre for Health Statistics, 1985.

13. Miller HC, Hassanein K, Henslight PA. Maternal factors in the incidences of low birthweight infants among black and white mothers. Pediatr Res. 1978; 12:1016.

14. MacGregor SN, Keith LG, Chasnoff IJ, et al. Cocaine use during pregnancy: Adverse perinatal outcome. Am J Obstet Gynecol 1987; 157:686.

15. Fedrick J, Anderson A. Factors associated with spontaneous preterm birth. Br J Obstet Gynecol 1976; 83:342.

16. Stillman RJ. In utero exposure to diethylstil-bestrol; Adverse effects on the reproductive tract

and reproductive performance in male and female offspring. Am J Obstet Gynecol 1982; 142:905.

17. Artal JP, Sokol RJ, Neuman M, et al. The mechanical properties of prematurely and non-prematurely ruptured membranes. Am J Obstet Gynecol 1976; 125: 655.

18. Minkoff H, Grunebaum AN, Schwarz RH, et al. Risk factors for prematurity and premature rupture of membranes. A prospective study of the vaginal flora in pregnancy. Am J Obstet Gynecol 1984; 150:965.

19. Youmans, Paterson and Sommers. The Biologic and Clinical Basis of Infectious Diseases. W.B. Saunders Co., 1975.

20. Baker CJ, Barrett FF. Transmission of group B streptococci among parturient women and their neonates. J Pediatr 1973; 83:919.

21. Lewin EB, Amstey MS. Natural history of group B streptococcus colonization and it's therapy during pregnancy. Am J Obstet Gynecol 1981; 139:512.

22. Joshi KJ, Chen CI, Turnell RW. Prevalence and significance of group B streptococcus in a large obstetric population. Can Med Assoc J 1987; 137:209.

23. Badri MS, Zawaneh S, Cruz AC, et al. Rectal colonization with Group B Streptococcus: Relation to vaginal colonization of pregnant women. J Infect Dis 1977; 135:308.

24. Baker CJ, Barrett FF, Yow MD. The influence of advancing gestation on group B streptococcal colonization in pregnant women. Am J Obstet Gynecol 1975; 122:820.

25. Ancona RJ, Ferrieri P, Williams PP. Maternal factors that enhance the acquisition of group B streptococci by newlyborn infants. J Med Microbiol 1980; 13:273.

26. Regan JA, Chao S, James LS. Premature rupture of membranes, preterm delivery, and group B streptococcal colonization of mothers. Am J Obstet Gynecol 1981; 141:184.

27. Hastings MJG, Easmon CSF, Neill J, Bloxham B, Rivers RP. Group B streptococcal colonization and the outcome of pregnancy. J Infect 1986; 12:23.

28. Bobitt JR, Damato JD, Sakakini J. Perinatal complications in group B streptococcal carriers: A longitudinal study of prenatal patients. Am J Obstet Gynecol 1985; 151:711.

29. Macdonald NE, Mackenzie AMR, Maternal and neonatal colonization with group B streptococci in Ottawa. Can Med Assoc J 1979; 120:1110.

30. Allardice JG, Baskett TF, Seshia MMK, Bowman N, Malazdrewicz R. Perinatal group B streptococcal colonization and infection. Am J Obstet Gynecol 1982; 142:617.

31. Yow MD, Leeds LJ, Thompson PK, Mason EO, Clark DJ,

Beachler CW. The natural history of group B streptococcal colonization in the pregnant woman and her offspring. I Colonization studies. Am J Obstet Gynecol 1980; 137:34.

32. Boyer KM, Gadzala CA, Kelly PD, Burd LI, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal Group B Streptococcal early-onset disease II. Predictive value of prenatal cultures. J Infect Dis 1983; 148:802.

33. Baker CJ. Summary of the workshop in perinatal infections due to group B streptococcus. J Infect Dis 1977; 136:137.

34. Franciosi RA, Knostman JD, Zimmerman RA. Group B streptococcal neonatal and infant infections. J Pediatr 1973; 82:707.

35. Eickoff TC, Klein JO, Daly AK, Ingall D, Finland M. Neonatal sepsis and other infections due to group B beta-hemolytic streptococci. N Engl J Med 1964; 271:1221.

36. From the National Institute of Allergy and Infectious Diseases. Summary of the National Institutes of Health Workshop on Group B Streptococcal Infection. J Infect Dis 1983; 148:163.

37. Boyer KM, Gadzala CA, Burd LI, Fisher DE, Paton JB, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease.

I. Epidemiologic rationale. J Infect Dis 1983; 148:795.

38. Pass MA, Gray BM, Khare S, Dillon HC Jr. Prospective studies of group B streptococcal infections in infants. J Pediatr 1979; 95;437.

39. Pyatti SP, Pildes RS, Jacobs NM, et al. Penicillin in infants weighing two kilograms or less with early onset group B streptococcal disease. N Engl J Med 1983; 308:1383.

40. Gerards LJ, Cats BP, Hoogcamp-Korstanje AA; Early neonatal group B streptococcal disease: degree of colonization as an important determinant. J Infect 1985; 11:119.

41. Hoogkamp-Korstanje JAA, Gerards LJ, Cats BP. Maternal carriage and neonatal acquisition of group B streptococci. J Infect Dis 1982; 145:800.

42. Naeye RL: Factors that predispose to premature rupture of the fetal membranes. Obstet Gynecol 1982; 60:93.

43. Rudd EG: Premature rupture of the membranes; a review. J Rep Med 1985; 30:841.

44. Kaltreider DF, Kohl S: Epidemiology of preterm delivery. Clin Obstet Gynecol 1980; 23:17.

45. Skinner SJM, Campos GA, Liggins GC: Collagen content of human amniotic membranes: Effect of gestational length and premature rupture. Obstet Gynecol 1981;

57:487.

46. Perkins RP: The neonatal significance of selected perinatal events among infants of low birth weight. II. The influence of ruptured membranes. Am J Obstet Gynecol 1982; 142:7.

47. Gunn GC, Mishell DR Jr, Morton DG. Premature rupture of the fetal membranes. Am J Obstet Gynecol 1970; 106:469.

48. Burcell RC. Premature spontaneous rupture of membranes. Am J Obstet Gynecol 1964; 88:252.

49. Alger LS, Lovchik JC, Hebel JR, Blackmon LR, Crenshaw MC. The association of Chlamydia trachomatis, Neisseria gonorrhoea, and group B streptococci with preterm rupture of the membranes and pregnancy outcome. Am J Obstet Gynecol 1988; 159:397.

50. Matorras R, Garcia Perea A, et al.; Group B Streptococcus and premature rupture of the membranes and preterm delivery. Gynecol Obstet Invest 1989; 27:14.

51. 1980 Standard occupational classification manual.

52. Kelsey JL, Thompson WD, Evans AS. Methods in observational epidemiology.

53. 1989 Physicians notification of birth data for Ottawa-Carleton, Ottawa, Canada.

54. Hennekens CH, Buring JE. Epidemiology in Medicine, Little, Brown and company, 1987.

APPENDIX:

APPENDIX A: **Form used for data collection**:

DATE OF BIRTH: ____________ MATERNAL AGE ----

EDUCATIONAL LEVEL:

--- <Grade 8	--- Grade 11	--- Univ.2
--- Grade 8	--- Grade 12	--- Univ.3
--- Grade 9	--- Grade 13	--- Univ.4
--- Grade 10	--- Univ.1	--- Postgrad.

MARITAL STATUS:

--- Married	--- Common-law	--- Divorced
--- Single	--- Separated	--- Widowed

OCCUPATION:

--- Unemployed --- Employed

--- Homemaker	--- Managerial	--- Med.& Health
--- Sales	--- Natural Sci.	--- Arts & Recr.
--- Services	--- Social Sci.	--- Sports
--- Transport	--- Teaching	--- Clerical
--- Student	--- Other	

DATE OF LMP: ____________ EDC: ____________

PARITY: PRIMIPAROUS ______________

MULTIPAROUS ______________

GRAVIDITY ______________

Term ____________

preterm ___________

Abortions ___________

Living ___________

MATERNAL HEIGHT _______ft.____in. ___________cm.

PRE-PREGNANCY WEIGHT _________lb. ___________kg.

<u>PAST MEDICAL HISTORY</u>:

---- Irrelevant

---- Kidney Disease

---- Heart Disease

---- Functional Murmurs

---- Hypertension

---- Diabetes

---- Thyroid Disease

---- Other Explain_______________________

PAST OBSTETRIC & GYNAECOLOGIC HISTORY:

---- Uneventful

---- Preterm Labour

---- PROM

---- STD or PID

---- Cervical Incompetence

---- Uterine Anomalies

---- Multiple Pregnancies or Births

---- Antepartum Hemorrhage

---- Pregnancy Induced Hypertension

---- Toxemia

---- Gestational Diabetes

---- Previous Uterine Surgery

---- Hydramnios

---- Previous Ectopic Pregnancy

---- IUFD or Stillbirths

HISTORY OF PRESENT PREGNANCY:

---- Uneventful

---- Early Bleeding (before 16 weeks)

---- Late Bleeding (after 16 weeks)

---- Amniocentesis

---- UTI

---- STD & PID

---- Diabetes

---- Gestational Diabetes

---- Hypertension

---- PIH

---- Toxemia

---- Abruptio Placenta

---- Placenta Praevia

---- Cervical Circulage

---- Oligohydramnios

---- Polyhydramnios

---- Multiple Pregnancy

---- Anemia

---- IUGR

---- RH isoimmunization

---- PROM ---- wks.

---- Preterm lbr. ---- wks.

---- Resolved

---- Unresolved

SMOKING: No ------ Yes ------

Number _____ cigs/day

ALCOHOL: ---- No

---- Occasionally

---- Moderately

---- Heavy

RESULT OF CULTURE at 28 weeks:

- GBS: ------- Negative ------- Moderate

  ------- Few ------- Abundant

- Others: ________________________(Which?)

  ____

GESTATION AT DELIVERY: From LMP or U/S ___________ wks.

TYPE OF DELIVERY: Spontaneous -------

Induced -------

Other -------

METHOD OF DELIVERY: Vaginal -------

Caesarian -------

INFANT: ---- Liveborn

---- Stillborn

BIRTH WEIGHT ___________gms. GENDER ---- Male

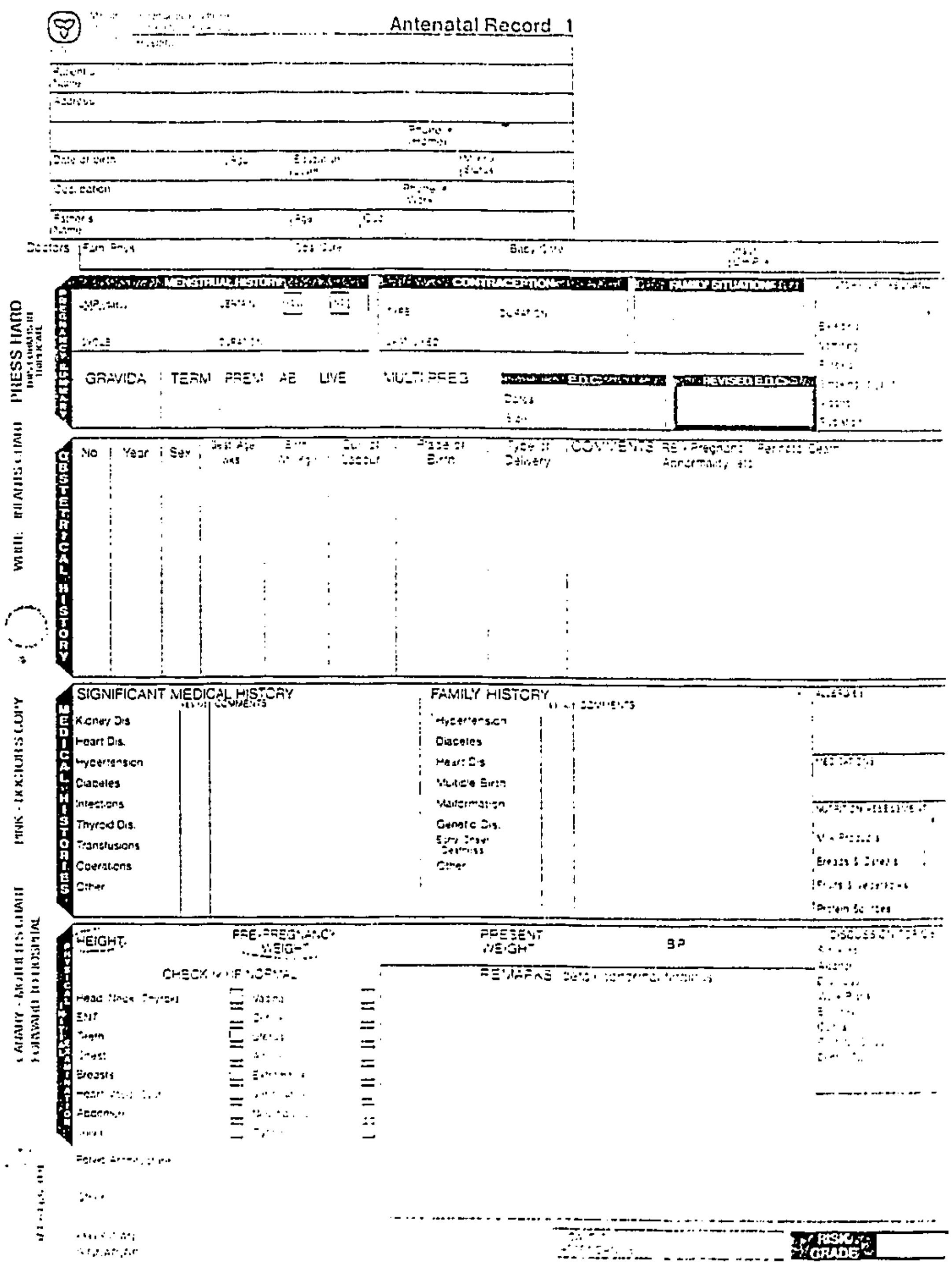
---- Female

OUTCOME OF PREGNANCY: PROM -------

Preterm -------

Term -------

APPENDIX B: Ontario Antenatal Record 1:



Antenatal Record 1

Address

Date of birth | Age | Occupation

Doctors

PRESS HARD

MENSTRUAL HISTORY | CONTRACEPTION | FAMILY SITUATION

GRAVIDA | TERM | PREM | AB | LIVE | MULTI PREG | E.D.C. | REVISED E.D.C.

OBSTETRICAL HISTORY

No | Year | Sex | Place of Birth | Type of Delivery | COMMENTS

MEDICAL HISTORIES

SIGNIFICANT MEDICAL HISTORY: Kidney Dis, Heart Dis., Hypertension, Diabetes, Infections, Thyroid Dis., Transfusions, Operations, Other

FAMILY HISTORY: Hypertension, Diabetes, Heart Dis, Multiple Birth, Malformation, Genetic Dis., Other

PHYSICAL EXAMINATION

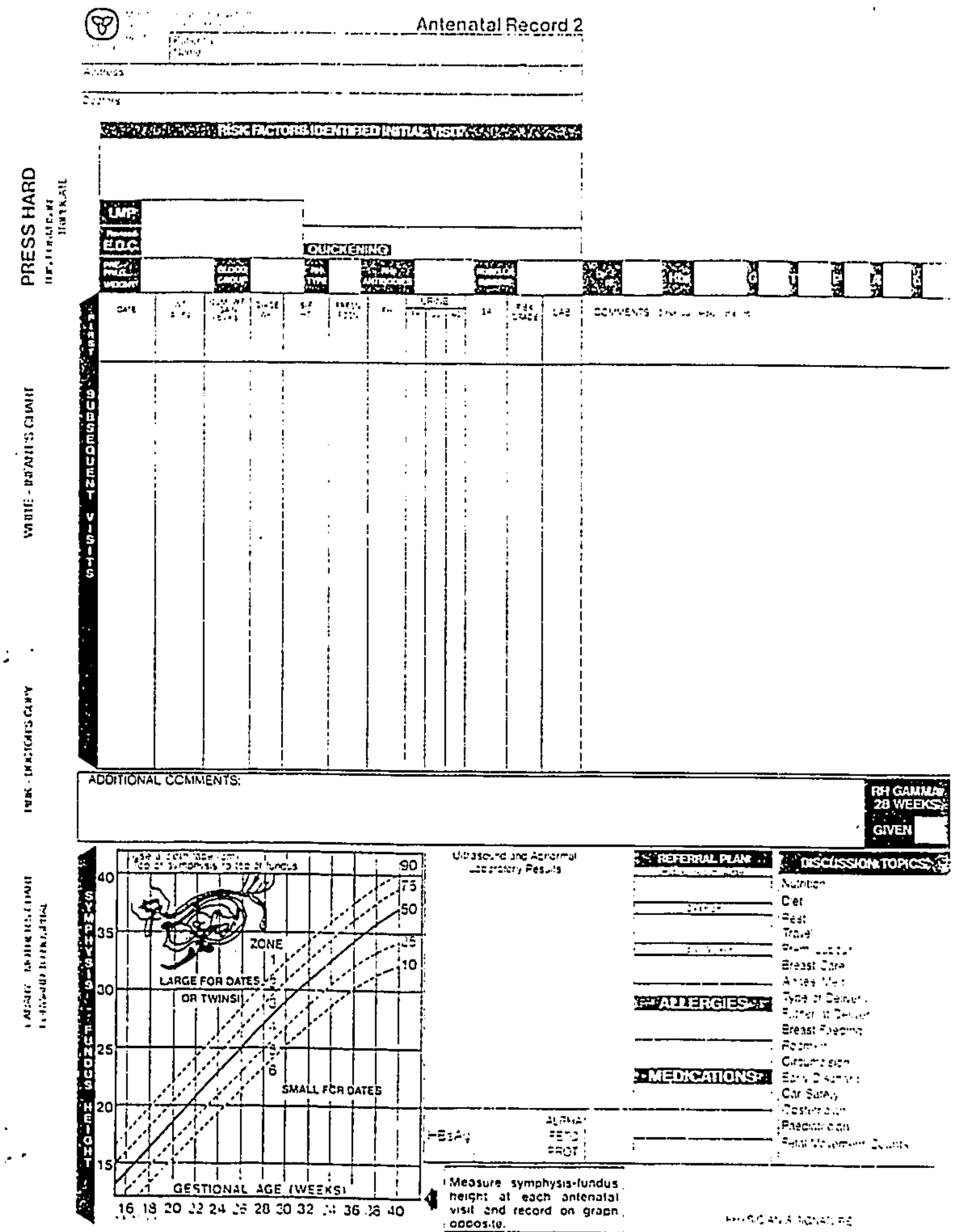
HEIGHT | PRE-PREGNANCY WEIGHT | PRESENT WEIGHT | BP

CHECK IF NORMAL | REMARKS

Head, Neck, Thyroid; ENT; Teeth; Chest; Breasts; Abdomen

RISK GRADE

APPENDIX C: Ontario Antenatal Record 2:


Antenatal Record 2

PRESS HARD

RISK FACTORS IDENTIFIED INITIAL VISIT

LMP

E.D.C.

QUICKENING

FIRST

SUBSEQUENT VISITS

ADDITIONAL COMMENTS:

RH GAMMA 28 WEEKS

GIVEN

SYMPHYSIS - FUNDUS HEIGHT

ZONE

LARGE FOR DATES OR TWINS

SMALL FOR DATES

GESTIONAL AGE (WEEKS)

16 18 20 22 24 26 28 30 32 34 36 38 40

Ultrasound and Abnormal Laboratory Results

HBsAg

REFERRAL PLAN

ALLERGIES

MEDICATIONS

DISCUSSION TOPICS

Nutrition

Diet

Rest

Travel

Breast Care

Type of Delivery

Breast Feeding

Circumcision

Car Safety

Measure symphysis-fundus height at each antenatal visit and record on graph opposite.

APPENDIX D: Delivery Record:

HÔPITAL GÉNÉRAL D'OTTAWA
OTTAWA GENERAL HOSPITAL

RAPPORT D'ACCOUCHEMENT
DELIVERY RECORD

Encerclez ou cochez où nécessaire-Circle or check where necessary.

G	T	P	A	L	Accouchement-Delivery Date

Transféré de l'hôpital-Transferring hospital

Référé par-Referring physician

Âge de gestation prévu (semaines complétées) Estimated gestation age (completed weeks)

DMN-LNMP ☐ 1-certain-sure ☐ 2-incertain-unsure | j-d | m-m | a-y

Catégorie des risques (Ontario Antenatal Record) Énumérez les facteurs
Risk category (Ontario Antenatal Record) List factors

Antepartum A B C

Intrapartum A B C

Group B hemolytic streptococcus carrier
☐ 1-Oui-Yes ☐ 2-Non-No ☐ 3-Inconnu-Unknown

TYPE DE TRAVAIL-TYPE OF LABOR
☐ 1-Spontané-Spontaneous ☐ 2-Provoqué-Induced
☐ 3-Stimulé-Augmentation

MÉTHODE D'INDUCTION-METHOD OF INDUCTION ☐ 0-Nul-Nil
☐ 1-Amniotomie-Amniotomy ☐ 2-Prostin
☐ 3-Oxytocin ☐ 4-Autre-Other

MONITEUR CARDIAQUE FÉTAL-FETAL HEART RATE MONITORING
☐ 0-Nul-Nil ☐ 1-Interne-Internal
☐ 2-Externe-External ☐ 3-Les deux-Both

Manométrie-Manometry ☐ 1-Oui-Yes ☐ 2-Non-No

Épreuve de cicatrice-Trial of scar ☐ 1-Oui-Yes ☐ 2-Non-No

ANESTHÉSIE-ANESTHESIA
☐ 0-Nul-Nil ☐ 1-Locale-Local
☐ 2-Général-General ☐ 3-Bloc Honteux-Pudendal
☐ 4-Epidurale-Epidural ☐ 5-Inhalation
☐ 6-Autre-Other (Précisez-Specify)

PRÉSENTATION-PRESENTATION
☐ 1-Vertex ☐ 2-Siège-Breech
☐ 3-Autre-Other (Voir commentaires-See comments)

ACCOUCHEMENT-DELIVERY
☐ 1-Spontané-Spontaneous ☐ 2-Low-Forceps
☐ 3-Mid-forceps ☐ 4-Mid-forceps rotation
☐ 5-Césarienne Primaire-Primary C/S
☐ 6-Césarienne répétée sans essai-Repeat C/S no-trial
☐ 7-Césarienne après essai de travail-Repeat C/S after trial
☐ 8-Ventouse-Vacuum extractor
☐ 9-Forceps sur tête suivante-Forceps to after coming head

Indication(s) pour la césarienne-Cesarean section indication(s)

Incision: ☐ 1-Segment inférieur-Low segment ☐ 2-Classique-Classic

Numéro dossier de l'enfant
Infant chart number

Description	Heures minutes / Hours minutes	Date j-d m-m a-y	Stade du travail / Stage of labour / Durée-Duration
Début du travail / Start of labour	:	| |	
Dilatation complète / Fully Dilated	:	| |	1 ST.
Accouchement / Delivery	:	| |	2 ST.
Placenta	:	| |	3 ST.
Membranes rompues / Ruptured membranes	:	| |	

SITE D'ACCOUCHEMENT-BIRTH SITE
☐ 1-Salle d'accouchement-Delivery Room
☐ 2-Salle de travail-Labor room ☐ 3-Autre-Other

ÉPISIOTOMIE-EPISIOTOMY
☐ 0-Non-No ☐ 1-Médiane-Median
☐ 2-Mediolateral

PERTE DE SANG-BLOOD LOSS
☐ 1-Moyenne-Average ☐ 2-Excessive

TRANSFUSION DE SANG-BLOOD TRANSFUSION
☐ 1-Oui-Yes ☐ 2-Non-No

DEGRÉ DE LACÉRATION-LACERATION DEGREE 0 1 2 3 4

COMPLICATIONS DU TROISIÈME STADE-THIRD STAGE PROBLEMS
☐ 1-Oui-Yes ☐ 2-Non-No
Décrire-Describe:

Médecin accoucheur-Delivering Physician

Médecin-Physician (antepartum)

Médecin (enfant)-Physician (infant) (à l'accouchement-At delivery)

Médecin (résident-interne)-Physician (resident-intern)

Poids à la naissance-Birth weight. g Sex: ☐ M ☐ F

Mesures de réanimation / Resuscitative measures (Décrire-Describe)	☐ 1-Non-No ☐ 2-Oui-Yes	MIN	1	5	10
		APGAR			

	Oui Yes	Non No	Inconnu Unknown	Val.
ph antenatal-Scalp ph	☐ 1	☐ 2	☐ 3	
ph cordon omb.-Cord ph	☐ 1	☐ 2	☐ 3	
Détresse fétale-Fetal distress	☐ 1	☐ 2	☐ 3	
Meconium	☐ 1	☐ 2	☐ 3	
Anomalies-Abnormalities	☐ 1	☐ 2	☐ 3	

Vagin examiné pour éponges
Vagina inspected for sponges ☐ 1-Oui-Yes ☐ 2-Non-No

Infirmière
Nurse

Commentaires-Comments

Médecin accoucheur responsable-Delivering Staff Physician Signature | Date (j d-m m-a y)

5805(08.90)Cat:410830 1- DOSSIER CHART 2- MÉDECIN ACCOUCHEUR-DELIVERING PHYSICIAN 3- ENTRÉE DES DONNÉES DATA ENTRY 4- POUPONNIÈRE NURSERY

APPENDIX E: Other Past Medical Conditions:

The following table describes "other" past medical history of cultured women.

Other past medical history of cultured women.

MEDICAL CONDITION	GBS+ve	GBS-ve	Total
Anemia	0	4	4
Arthritis	0	2	2
Crohn's disease	0	4	4
Epilepsy	2	10	12
Gastric ulcer	0	2	2
HIV positive	0	1	1
Hypoglycemia	0	1	1
Myasthenia gravis	0	1	1
Myotonic dystrophy	1	0	1
Pulmonary embolism	0	1	1
Reiter's syndrome	0	1	1
Scoliosis	0	1	1
Sickle cell disease	0	1	1
Systemic lupus erythematosus	1	1	2
Thrombocytopenia	0	1	1
Ulcerative colitis	0	4	4
Total	4	35	39

APPENDIX F: Weeks of pregnancy at which delivery occurred for women who had preterm PROM:

WEEKS OF PREGNANCY AT WHICH PRETERM PROM OCCURRED	WEEKS OF PREGNANCY AT WHICH DELIVERY OCCURRED									Total
	28	33	34	35	36	37	38	39	40	
28	1									1
33		3					1			4
34			3							3
35				6	1	1				8
36					10	1		1	1	13
Total	1	3	3	6	11	2	1	1	1	29

APPENDIX G: Comparison of GBS positive and GBS negative women in the cohort study:

A. MATERNAL PERSONAL AND SOCIAL CHARACTERISTICS:

The following section describes and compares the personal and social characteristics of GBS positive and negative mothers in the cohort study.

a. Continuous variables:

Table 1 compares continuous variables of maternal personal and social characteristics between GBS positive and negative women in the cohort study.

Table 1: Comparison of continuous variables of personal characteristics between GBS positive and GBS negative mothers.

MATERNAL PERSONAL CHARACTERISTICS	GBS positive	GBS negative	F stat.	ANOVA p-val.
Age : Mean	28.33	28.69	0.55	0.53
St.dev.	5.31	4.80		
Height: Mean	160.00	161.24	3.92	0.05
St.dev.	6.60	6.32		
Weight: Mean	59.41	60.86	1.73	0.19
St.dev.	11.27	11.18		

b. Categorical variables:

Table 2 compares categorical variables of maternal characteristics between GBS positive and negative women.

Table 2: Comparison of categorical variables of personal characteristics between GBS positive and GBS negative mothers.

Maternal Personal Characteristics	Chi-square	p-value
Marital status	3.82	0.05
Maternal parity	2.36	0.12
Maternal gravidity	9.11	0.03
Maternal employment	2.59	0.11
Smoking status	0.33	0.57
Alcohol intake	0.96	0.33

B) PAST MEDICAL HISTORY:

Table 3 compares the past medical history between GBS positive and negative women in the cohort study.

Table 3: Comparison of Past Medical History between GBS positive and negative women in cohort study.

PAST MEDICAL HISTORY	Chi-square	P-value	Fisher exact P-value
UTI	0.01	0.91	0.58
Kidney Disease	3.54	0.06	0.07
Functional Murmur	0.17	0.68	0.50
Heart Disease	0.00	0.99	0.66
Hypertension	2.02	0.15	0.15
Diabetes	1.67	0.19	0.21
Thyroid Disease	0.00	0.99	0.59
Bronchial Asthma	0.93	0.33	0.24
Other Condition	0.06	0.80	0.53

* For chi-square calculations the reference category for each disease group was absent disease.

C) <u>PAST OBSTETRIC AND GYNECOLOGICAL HISTORY</u>:

Table 4 compares past obstetric and gynecological history between GBS positive and GBS negative women.

Table 4: Comparison of Past Obstetrical and Gynecological History between GBS positive and negative women in cohort study.

PAST OBSTETRIC OR GYNECOLOGIC CONDITION	Chi-square	P-value	*P-value
Preterm Labour	0.29	0.59	0.38
STD	1.19	0.27	0.20
Cervical Incompetence	0.14	0.70	0.87
Uterine Anomalies	1.67	0.19	0.21
Multiple Pregnancies	1.16	0.28	0.26
Antepartum Hemorrhage	0.02	0.90	0.69
Pre-eclampsia	0.57	0.45	0.59
Gestational Diabetes	0.17	0.68	0.50
Uterine Surgery	1.20	0.27	0.33
Hydramnios	0.57	0.45	0.59
Ectopic Pregnancy	1.36	0.24	0.21
IUFD/Stillbirths	0.42	0.51	0.36

* Fisher exact p-value.

** For chi-square calculations the reference category for each disease group was absent disease.

D) <u>HISTORY OF THE CURRENT PREGNANCY</u>:

Table 5 compares history of the current Pregnancy between GBS positive and negative women.

Table 5: Comparison of the History of the current pregnancy between GBS positive and negative women in cohort study.

HISTORY OF THE CURRENT PREGNANCY	Chi-square	P-value	* P-value
Any Event	14.84	0.000	-
Early Bleeding	7.90	0.004	-
Late Bleeding	1.06	0.30	0.23
Amniocentesis	1.91	0.17	-
UTI	4.84	0.03	0.05
STD	1.67	0.19	0.21
Diabetes	2.41	0.12	0.16
Gestational Diabetes	0.60	0.44	-
Hypertension	1.29	0.26	0.30
PIH	0.05	0.82	-
Pre-eclampsia	2.41	0.12	0.16
Placenta Praevia	0.14	0.70	0.87
Oligohydramnios	0.19	0.66	0.55
Anemia	0.02	0.90	0.69
IUGR	0.47	0.49	0.42
RH-isoimmunization	0.14	0.70	0.87

* Fisher exact p-value.
** For chi-square calculations the reference category for each disease group was absent disease.