Study of consanguinity and premature rupture of membranes in gestating women and their association with neonatal outcome.

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A thesis submitted in partial fulfillment of the requirements for the degree of

MASTERS OF PHILOSOPHY

IN

Human Genetics

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Declaration

I hereby declare that the work accomplished in this thesis is the result of my own research carried out in Human Genetics lab, Department of Animal Sciences, Quaid-i-Azam University Islamabad.

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This dissertation "Study of Consanguinity and Premature Rupture of Membranes in Gestating Women and their Association with Neonatal Outcome" submitted by **Ms. Saima Khan** is accepted in its present form by the Department of Animal Sciences, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad as satisfying the thesis requirement for the degree of Master of Philosophy in Human Genetic.

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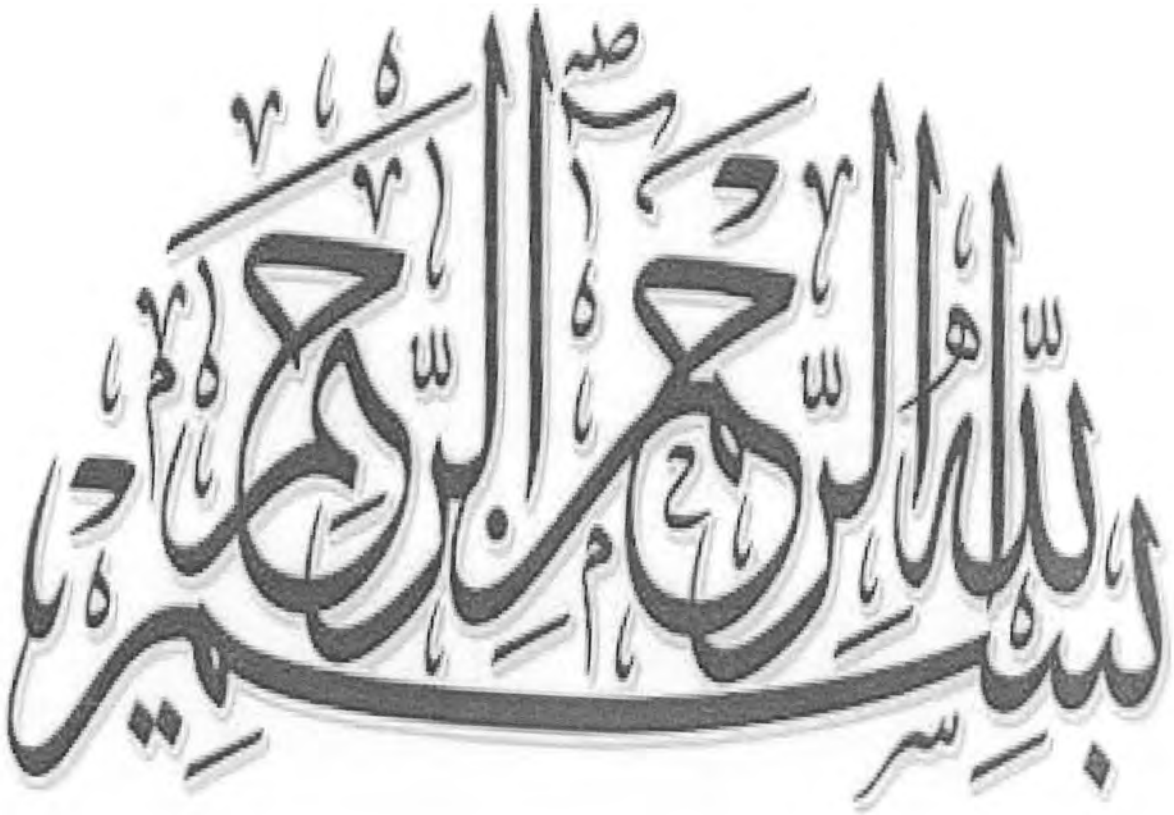
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I dedicate this humble effort to my parents.

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Abstract

Premature rupture of membrane (PROM) is a complicating factor in as many as one-third of premature births. During preterm premature rupture of membranes, both the mother and the fetus are at greater risk of complications. This study was a cross sectional study and it was conducted to examine the socio-demographic factors affecting maternal and neonatal health with respect to premature rupture of membranes. The main focus of the study was to find out the association of consanguinity with premature rupture of membranes. The data were collected from Pakistan Institute of Medical Sciences Islamabad. Though the major proportion of the subjects was from urban areas but one cannot overlook its occurrence in rural and underdeveloped areas due to lack of awareness and the women are underprivileged to get maximum health care facilities. The results showed a significant association of premature rupture of membranes with consanguinity, pregnancy related parameters, language and family types of the subjects whereas no association was found with the origin, caste, literacy, occupation, province and age group of the subjects. The association of the neonatal outcome with this pregnancy related condition was also evaluated and analyzed; it was observed to be significantly associated with the distribution of neonates but no significant association was obtained with the gender, birth weight, single or multiple gestation and congenital anomalies in neonates of subjects exposed to premature rupture of membranes. Further studies are required to fully understand the combined effect of premature rupture of membranes and other maternal factor on pregnancy outcome

CHAPTER 1

INTRODUCTION

1.1 Why studying premature rupture of membranes?

Premature rupture of membrane (PROM) is a complicating factor in as many as one-third of premature births. A significant risk of PROM is that most babies are born within a week of the membrane rupture. Another major risk of PROM is development of a serious infection of the placental tissues called chorioamnionitis. This can be very dangerous for mother and baby. Other complications that may occur with PROM include placental abruption (early detachment of the placenta from the uterus), compression of the umbilical cord, cesarean birth, and postpartum (after delivery) infection (Brian et al. 2010).

Premature rupture of membranes (PROM), or pre-labor rupture of membranes, is one of the conditions that can occur during pregnancy. The membranes surrounding the fetus known as fetal membranes (chorion and amnion) are actually the target tissues in PROM. PROM is defined as splitting or breakage of the amniotic sac .It starts one hour before the onset of labor and lasts for many hours. The "membranes" contain amniotic fluid which surrounds and protects the fetus in the womb. After rupture, the amniotic fluid leaks out of the uterus through the vagina. This is informally known as one's "water breaking" (Vadillo et al. 1990).

Preterm Premature rupture of membrane (PPROM) is another case of PROM in which the rupture of fetal membrane occurs at less than 37 completed weeks of gestation (Uma et al., 2007). About 3.0-10.0% of all deliveries have an incidence of PPROM (Kaur et al., 2009). It complicates approximately 3% of pregnancies and leads to 1/3 of preterm births (Medina et al., 2006). Preterm delivery affects one in 10 births, 11% in USA and the ratio is even greater in developing countries and causes 40-75% neonatal deaths (Uma et al., 2007).

During preterm premature rupture of membranes, both the mother and the fetus are at greater risk for complications. The major complication is prematurity which can sometimes lead to death. Open membranes can also put both the mother and the fetus at risk of life threatening infections because they provide an entry to bacteria to infect the womb (McGregor et al. 1987). If the fluid level is low around the fetus, it can increase the risk of having umbilical cord compression and the fetus lungs and body formation gets affected by this during early pregnancy (Mckeen et al., 2014).

Usually Women with PROM experience a painless gush of fluid leaking out from the vagina, but sometimes a steady and slow leakage can also occur. The risk to fetus minimizes if the premature rupture of membranes occurs around 37 weeks completed gestational age (at term) and labor typically starts soon after.

Approximately 8%-10% of all pregnancies experience prolonged rupture of membranes that lasts for more than 18 hours before the onset of labor (Popowski et al., 2011). This condition of membrane rupture has also been found to be an important risk factor for both early onset neonatal sepsis (EONS) and preterm births. It is considered to be a continuous major cause of mortality and morbidity among neonates (Boskabadi et al., 2011).

1.2 Fetal membranes:

The membranes surrounding the amniotic cavity (chorion and amnion) are actually the layers which are closely adherent with each other. These layers are composed of many cell types including epithelial cells, mesenchymal cells and trophoblast cells, embedded in a collagenous matrix. The functions of fetal membranes are to retain amniotic fluid, secrete substances both into the amniotic fluid and toward the uterus, and guard the fetus against infection ascending the reproductive tract. The membranes normally rupture during labor and this rupture is traditionally attributed to physical stress, particularly which is associated with labor. However, more recent evidence suggests that membrane rupture is also related to biochemical processes and programmed death of cells in the fetal membranes (Samuel et al., 1998).

1.3 Fetal membrane structure:

The human amnion is made up of five distinct layers (Schmidt, 1992). It contains no blood vessels or nerves; the amniotic fluid supplies all the nutrients for its growth and maintenance. These layers are amniotic epithelium, basement membrane, compact layer, fibroblast layer and intermediate (spongy) layer. The innermost layer, nearest the fetus, is the amniotic epithelium. These layers secrete various types of collagens and non-collagenous glycoproteins. The main fibrous skeleton of the amnion is its compact layer. The thickest layer of the amnion is its fibroblast layer (Malak et al., 1993). The last layer of amnion also known as intermediate layer (spongy layer or zona spongiosa) lies between the amnion and the chorion. This layer

absorbs physical stresses by permitting the amnion to slide over the underlying chorion, which is firmly adherent to the maternal decidua. The chorion is thicker than the amnion but the amnion has greater tensile strength. The three layers of chorion are reticular layer, basement membrane and trophoblast layer. Although there is no evidence of preset weak points where the membranes break as these membranes show regional variations (Leppert et al., 1996), care must be taken to avoid overlooking localized changes in the membrane structure and composition in studies of premature rupture of the membranes.

1.4 Types of premature membrane rupture:

The rupture of amniotic sac or fetal membranes has been classified into different types (depending upon the gestational age of the fetus) which are as follows:

1. Premature rupture of membranes (PROM): When the amniotic sac ruptures one hour before the labor has started (Beckman et al., 2014).

2. Prolonged PROM: In this case of premature rupture of membranes, the rupture lasts for more than 18 hours before the onsets of labor (DeCherney et al., 2013).

3. Preterm Premature Rupture of Membranes (PPROM): This condition occurs before 37 completed weeks of gestation (Tucker et al., 1991).

4. Mid-trimester PPROM: it occurs before 24 completed weeks of gestation. The fetus cannot survive outside of the mother's womb before this age (Beckmann et al., 2014).

1.5 Symptoms of PROM:

Most women experience a constant painless leaking or a gush of watery fluid from the vagina (Beckmann et al., 2014). The color and consistency of fluid may also change and through ultrasound testing, the decreased size of uterus may also be observed (DeCherney et al., 2013).

1.6 Risk factors:

As stated earlier, rupture of the membranes (at term) near pregnancy may be caused by natural weakening of the membranes or by physical stretching of the membrane itself. In summary the following risk factors have been shown to increase

the chance of its happening: infections in the uterus (Offenbacher et al., 1996), smoking during pregnancy (Schectman et al., 1989), previous pregnancies with preterm births, woman with two or more fetuses at one time, vaginal bleeding, nutritional deficiencies (Wideman et al., 1964; Artal et al., 1979), low socioeconomic status (women with such status are less likely to get proper prenatal care), being underweight (Beckmann et al., 2010), sexually transmitted diseases (chlamydia and gonorrhea), presence of excessive amniotic fluid, a condition known as hydro-amnion, and the extra amount of fluid exerts pressure on the fetal membrane (DeCherney et al., 2013).

1.7 Role of genes:

There is a role of genes behind every activity in our body. Many genes are involved in inflammation and collagen production, therefore alteration in gene function may play a role in predisposing a pregnant woman to PROM.

Genetic factors contribute to the risk of PROM because familial clustering and ethnic differences are seen in the incidence of PPROM (Hoffman et al., 1999). In one of the studies, it was previously reported that polymorphisms in *MMPs* promoters that increases promoter activity are linked with PPROM, highlighting that genetic variation in *MMP* genes can contribute to the risk of adverse obstetrical outcomes (Fujimoto et al. 2002; Ferrand et al., 2002). *MMP8* gene variation has a role in fetal membrane rupture (Vadillo et al., 1996). Patients with intra-amniotic infections, preterm labor and PPROM have high concentrations of *MMP8* in their amniotic fluid (Angus et al., 2001). These high concentrations of *MMP8* are also strongly associated with neonatal death and other adverse neonatal outcomes (Maymon et al., 2001).

Chorion layer is also a rich source of *MMP8*. Some past studies have indicated that in African-Americans, discrete polymorphisms in the *MMP1* and *MMP9* promoters are associated with risk of PPROM (Fujimoto et al. 2002; Ferrand et al. 2002). The more recent study suggests that the haplotype with three minor alleles of the *MMP8* promoter is also associated with PPROM (Hongyan et al., 2004). This haplotype induces greater promoter activity only when the constructs were introduced into cells resembling the chorion cytotrophoblasts. In this experiment, three SNPs in the *MMP8* gene 50 regions and a haplotype that confers increased *MMP8* promoter activity in chorion-like cytotrophoblast-like cell lines have been identified. It can be

concluded from these findings that genetic variation at the *MMP8* locus contributes to adverse events associated with extra cellular matrix breakdown and fetal membrane rupture.

1.8 Consanguinity:

One of the most significant complications observed during pregnancy is the preterm birth. Preterm births involve several genetic factors (Jennifer et al., 2009). Consanguinity is defined as a blood relation among individuals or close relationship by descent from a common ancestor. Consanguinity increases the chances of homozygosity of recessive alleles. It is often interchangeably used with the term inbreeding. In human, the amount of inbreeding is largely controlled by traditional and cultural practices. In any disease in which the inheritance pattern is not known or certain, the geneticist can use consanguinity to investigate the recessive component of genes. In a study, it was shown that the infants of consanguineous parents had a significant 1.6-fold increased risk of being born preterm at less than 33 weeks' gestation compared to the infants of unrelated parents (Mumtaz et al., 2010). Each year, many hundreds of children are born before they reach their full term. The exact cause of this large percentage is still doubtful although there are medical, social and environmental factors involved. The preterm delivery also runs in families. The condition is prevalent in certain human races which show that there must be some factors that aggregate in such families. This recurrence of preterm birth shows that there can be a genetic cause for this condition (Hoffmann et al., 1999). The fetus inherits several mutant genes which can predispose it to preterm birth. If the sequence variation of the mutant genes is analyzed, it can reveal polymorphisms that may contribute to susceptibility to preterm births. (Anuma et al., 2009). Preterm delivery, low birth weight of neonates, birth asphyxia assisted ventilation are associated with risk of neonatal sepsis. The consanguinity among parents does not increase the risk for developing septicemia (infection) (Maya et at., 1992).

1.9 Preventory measures:

Women who already experienced premature rupture of membrane in their previous pregnancies are more likely to experience it again in future pregnancies (Goldenberg et al., 2008). There is still not enough data available to recommend a better way to prevent future PROM. However, progesterone supplementation is

recommended for such women to prevent preterm birth recurrence (DeCherney et al., 2013). Women experiencing PROM should be regularly evaluated in the hospital to determine if a rupture of membranes has indeed occurred and to be treated appropriately to avoid infection and other complications.

1.10 Neonatal outcomes:

As stated earlier that there are different types of PROM depending upon the gestational age of the fetus (Beckmann et al., 2010).

- PROM at term: In this case, PROM followed by the onset of labor and delivery. The women give birth soon after the membrane rupture without any intervention (Goldenberg et al., 2008).
- Opening in the fetal membranes at any age provides a route for the microbes to cause an infection which can either be milder if diagnosed and treated earlier or life threatening for both women and her baby, e.g. chorioamnionitis (Beckmann, Charles). The longer the membranes remain open, the greater is the risk of getting infections. The chances of infection are greater at earlier gestational age and women with preterm PROM have 15-20% more chances of infections. (Goldenberg et al., 2008)
- Before 37 weeks: It is one of the leading causes of preterm birth. Many complications associated with prematurity such as respiratory distress, infection, brain injury, muscle dysfunction, and death can happen in this case (Beckmann et al., 2010). Prematurity from any cause leads about 50% of all long term morbidity and 75% of perinatal mortality (Hosli et al., 2014). PROM is responsible for 20% of all fetal deaths between 24 and 34 weeks gestation (Cunninghum et al., 2014).
- Before 24 weeks: Before 24 weeks the fetus is still developing its organs, and the amniotic fluid at this stage is important for protecting the fetus against infection, physical impact. It also prevents the umbilical cord compression. The fetal movement and breathing is necessary for the development of the lungs, chest, and bones (Beckmann et al., 2010). Low levels of amniotic fluid due to mid-trimester or previable PPROM (before 24 weeks) can result in fetal deformity (ex: Potter-like face), limb contractures, underdeveloped lungs, umbilical cord compression and placental abruption (DeCherney et al., 2013).

- After second trimester amniocentesis: The risk of PROM is 1% in women undergoing a second trimester amniocentesis for prenatal diagnosis of genetic disorders. The chances of the membranes healing on their own and the amniotic fluid returning to normal levels is much higher in this case than spontaneous PROM. 70% of women will have normal amniotic fluid levels within one month, and about 90% of babies will survive as compared to women with spontaneous PROM (Goldenberg et al., 2008).

1.11 Research objectives:

The objectives of this study were:

1. To determine the etiological factors concerning premature rupture of membranes.
2. To examine the socio-demographic parameters affecting maternal health and fetal growth.
3. To determine the association of maternal morbidities and neonatal outcome with PROM .
4. To evaluate its effects on neonatal mortality.
5. To evaluate its relation with consanguinity.

CHAPTER 2

MATERIALS AND METHODS

2.1: Study area:

To achieve the defined objectives, Pakistan Institute of Medical Sciences (PIMS) was selected for a cross-sectional study. The data were collected from MCH (maternal and child health center) of PIMS.

2.2: Study subjects:

Study subjects included both mothers and neonates from General Ward. The mothers were both normal and morbid and the information about their health parameters was obtained after delivery. Neonates were also categorized as morbid and normal. This definition was based on the assessment made by the medical officer.

2.3: Ethical approval:

The project was first reviewed and approved by Review Committee of Department of Animal Sciences, Quaid-i-Azam University (QAU), Islamabad. Research proposal was further reviewed by the Ethical Review Committee of PIMS, Islamabad. Director and Incharge of General ward and Nursery (PIMS) approved the project. The mothers were also asked before data collection and permission was granted.

2.4: Initial phase of study:

To learn the data collection, subject examination, questionnaire filling, viewing and analyzing filed medical records, I visited the MCH Department of PIMS with my senior lab fellows who were already working on some other concerns of maternal health. This step was necessary to meet the defined aims and objectives.

2.5: Data collection span:

The data of the same parameters were collected during August 2010 to December 2013. During this time span 5,363 mother and their neonates were recruited and their information was recorded in the designed Performa. Data were collected on working days only. I joined the project in its final stages of data collection.

2.6: Research team:

Research team included two researchers, me and one of on duty staff members of PIMS (doctors/nurses).

2.7: Questionnaire design:

The questionnaire was designed according to the aims and objectives of the project. There were two parts of the questionnaire. The first part covered the parameters related to maternal health and the second part was about the neonatal health parameters. Socio-demographic parameters (age, language, caste, origin, residence), consanguinity, parent's age, parental consanguinity, anomalies, previous pregnancy record, marriage year, blood tests reports, Hb level, LFT, mode of delivery, neonatal outcome were included in the first part of questionnaire.

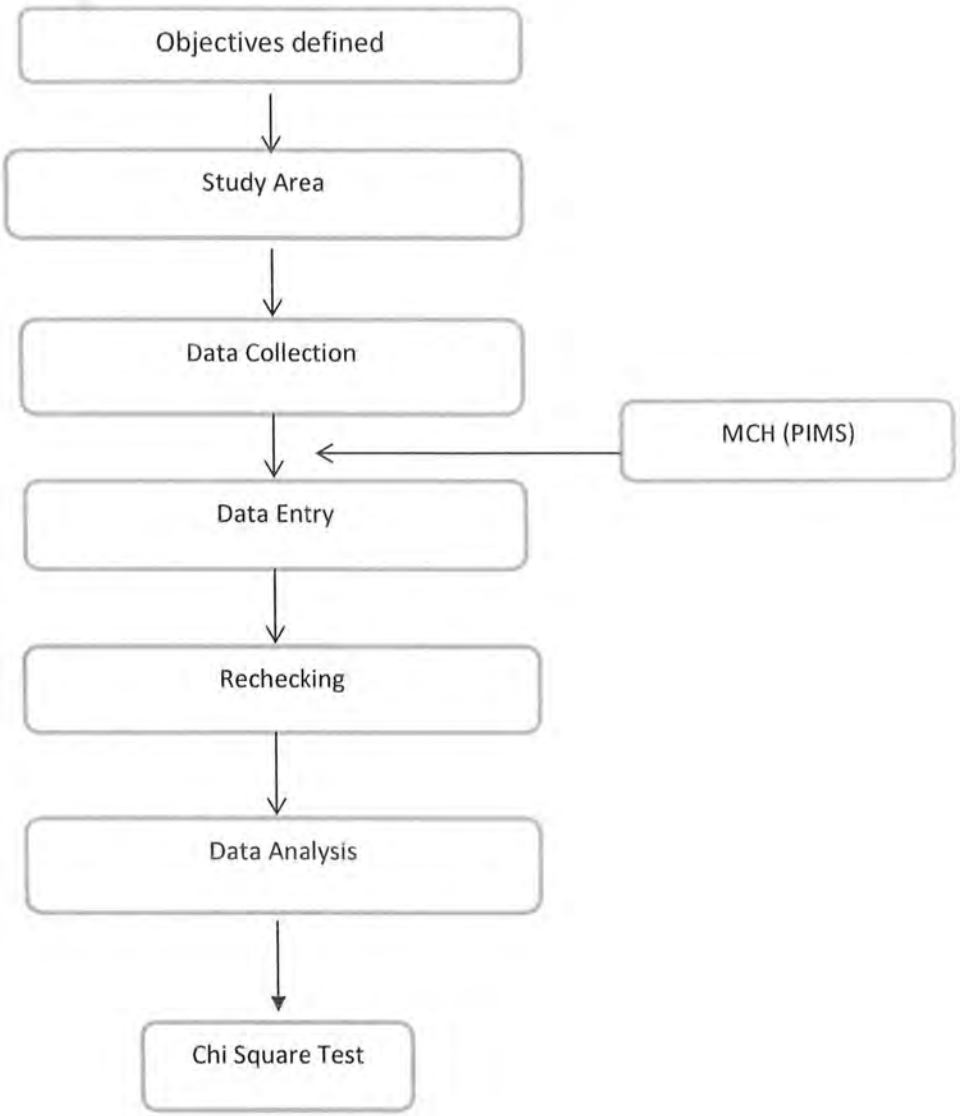
In the second part of questionnaire, medical records or discharge slips were consulted for anthropometric measurements (length, weight, OFC (occipital-frontal-circumference) and APGAR (appearance-pulse-grimace-activity-respiration) score.

Questionnaires were filled by interviewing mothers and consulting medical records.

2.8: Data entrance and analysis:

MS Excel (ver. 7) was used for data entry and storage. Graph-pad Prism (Ver. 5) was used for statistical analysis. Chi-square test was applied to check association of demographic variables and maternal and neonatal parameters with PROM/ preterm PROM.

Summary of the methodology is shown in the following Figure.



CHAPTER 3

RESULTS

The data was recruited from MCH-PIMS (2010-2013). All the results have been presented in four sections: 3.1—3.4.

3.1 Association between demographic variables and premature rupture of membranes:

A total of 617 women with PROM were included and a corresponding control subjects without PROM were also taken (n=617).

3.1.1 Origin of subjects:

The distribution of subjects with PROM and normal was established in rural/urban areas. The rural representatives with PROM were 217 (35.17%) compared to 193 (31.28%) normal individuals. There were 400 (64.83%) urban representatives among the PROM subjects compared to 424 (68.72%) in the normal individuals. So majority of subjects recruited were from urban areas and the percentage of PROM was high in urban subjects compared to normal subjects. Chi-square test showed no association between the origin of the subjects and PROM condition (χ^2=2.104; df=1; p=0.1469; Not Sig.) (Table 3.1.1; Fig. 3.1.1).

Table 3.1.1: PROM with respect to origin.

Origin	PROM	Normal	Total
Rural	217	193	410
Urban	400	424	824
Sum	617	617	1234

(χ^2=2.104;df =1; p= 0.1469; Not Sig.)

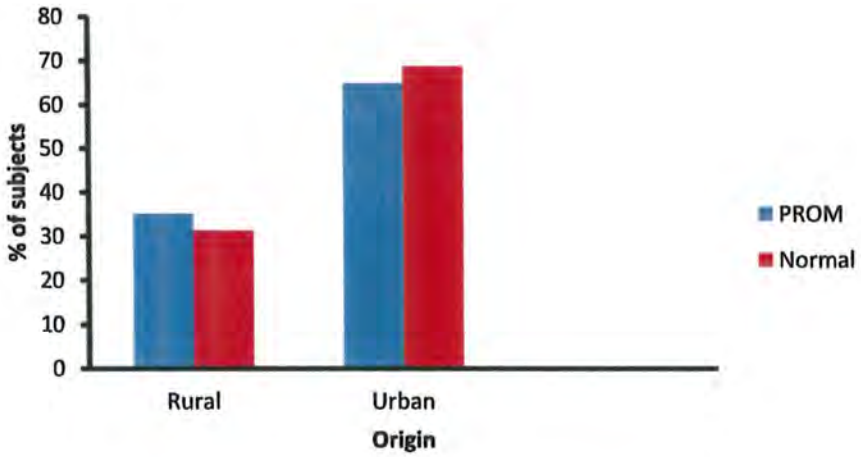


Fig 3.1.1 PROM with respect to origin.

3.1.2 Age group:

The distribution of subjects with PROM and normal was also established in different age intervals. There were 31 (5.02%) representatives with PROM compared to 34 (5.51%) normal individuals ranging 14-19 years old. The individuals ranging 20-24 years old were 194 (31.44%) subjects with PROM compared to 189 (30.63%) normal individuals. Age group 25-29 represented 220 (35.66%) subjects with PROM and 222 (35.98%) normal individuals. 30-34 years old age group represented 111 (17.99%) subjects with PROM compared to 117 (18.96%) normal individuals. 35-39 years old age group represented 61 (9.89%) subjects with PROM compared to 55 (8.91%) normal individuals. The highest number of subjects belonged to the age group of 25-29 years old and PROM cases were greater in this group. Chi square test showed no association between age of the subjects and PROM condition (χ^2=0.6810; df=4; p=0.9536; Not Sig.) (Table 3.1.2; Fig. 3.1.2).

Table 3.1.2: PROM and age group of subjects

Age Group	PROM	Normal	Total
14-19	31	34	65
20-24	194	189	383
25-29	220	222	442
30-34	111	117	228
35-39	61	55	116
Sum	617	617	1234

(χ^2=0.6810; df=4; p=0.9536; Not Sig.)

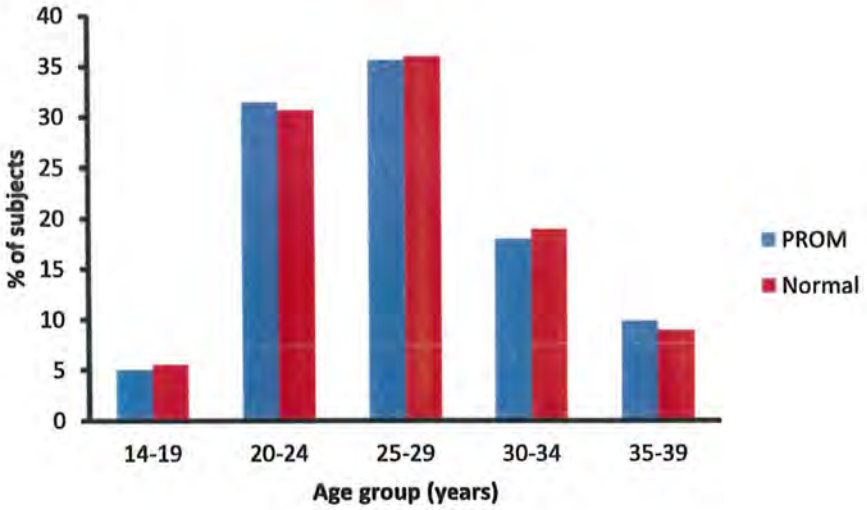


Fig 3.1.2 PROM and age group of subjects

3.1.3 Language:

The distribution of subjects with PROM and normal was also established in different language categories. There were 33 (5.35%) Hindko speaking representatives with PROM compared to 16 (2.59%) normal individuals. The subjects speaking Kashmiri were 48 (7.78%) with PROM compared to 83 (13.45%) normal individuals. The subjects speaking Potohari were 31 (5.02%) with PROM compared to 16 (2.59%) normal individuals. Punjabi speaking representatives were 354 (57.37%) with PROM compared to 362 (58.67%) normal individuals. Pushto speaking representatives were 82 (13.29%) with PROM compared to 78 (12.64%) normal individuals. Urdu speaking representatives were 35 (5.67%) with PROM compared to 34 (5.51%) normal individuals. Subjects with other languages represented 34 (5.51%) with PROM compared to 28 (4.54%) normal individuals. The majority of subjects had Punjabi as their mother tongue and the number of PROM cases was highest in this category. Significant association was obtained between language of the subjects and PROM condition (χ^2=20.80; df=6; p=0.0020; Sig.) (Table 3.1.3; Fig. 3.1.3).

Table 3.1.3: PROM and language.

Language	PROM	Normal	Total
Hindko	33	16	49
Kashmiri	48	83	131
Potohari	31	16	47
Punjabi	354	362	716
Pushto	82	78	160
Urdu	35	34	69
Other	34	28	62
Sum	617	617	1234

(χ^2=20.80; df=6; p=0.0020; Sig.)

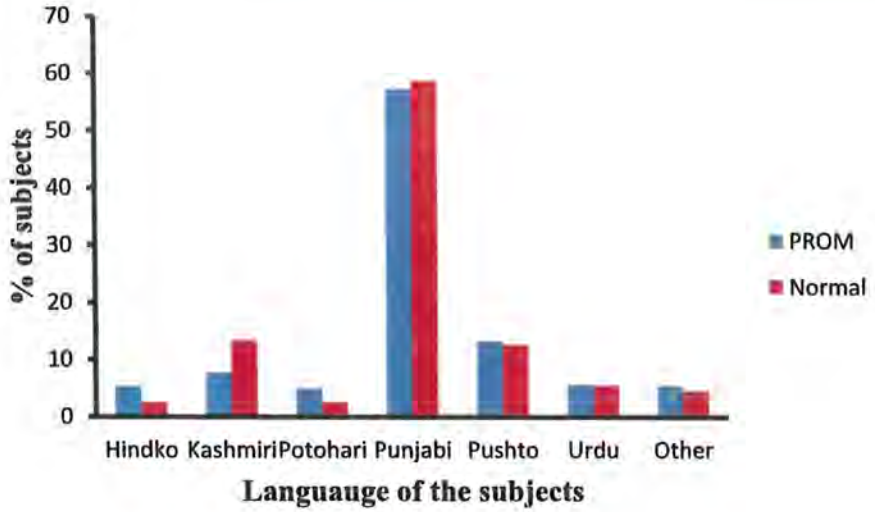


Fig 3.1.3 PROM and language.

3.1.4 Province (residence):

The distribution of subjects with PROM and normal was also established according to residence (province). There were 25 (4.05%) AJK representatives with PROM compared to 27 (4.38%) normal individuals. The subjects having Federal residence were 322 (52.19%) with PROM compared to 303 (49.11%) normal individuals. Those living in KPK were 48 (7.78%) with PROM compared to 31 (5.02%) normal individuals. The subjects having residence in Punjab were 222 (35.98%) with PROM compared to 256 (41.49%) normal individuals.

The highest number of subjects had Federal residence and the percentage of PROM was highest in the subjects of this area. Chi square test showed no association between residence (province) of the subjects and PROM condition (χ^2=6.731; df=3; p=0.0810; Not Sig.) (Table 3.1.4; Fig. 3.1.4).

Table 3.1.4: PROM and Province wise distribution of subjects.

Province	Prom	Normal	Total
AJK	25	27	52
Federal	322	303	625
Kpk	48	31	79
Punjab	222	256	478
Sum	617	617	1234

(χ^2=6.731; df=3; p=0.0810; Not Sig.)

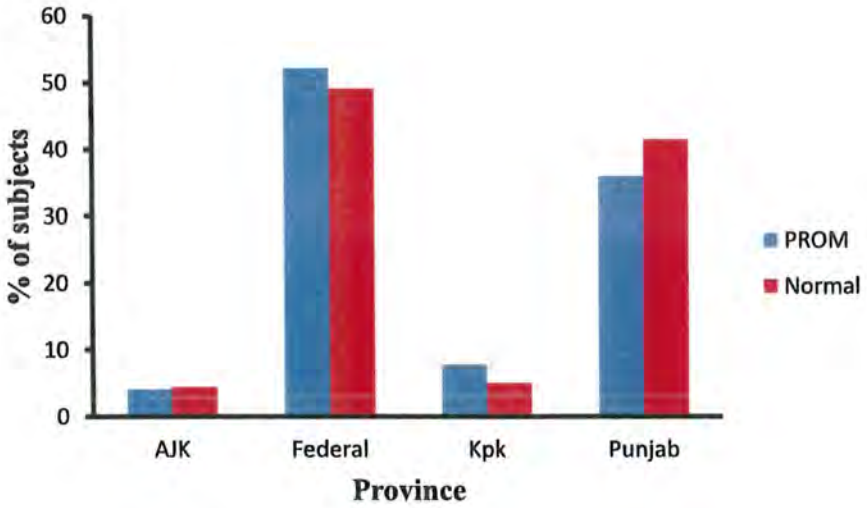


Fig 3.1.4 PROM and Province wise distribution of subjects.

3.1.5 Literacy:

The distribution of subjects with PROM and normal was also established according to literacy rate. There were 480 (77.80%) literate representatives with PROM compared to 487 (78.93%) normal individuals. There were 137 (22.2%) illiterate subjects with PROM compared to 130 (21.07%) without PROM subjects.

The literacy rate was also calculated by different levels of education. The subjects having done their graduation or higher studies were 124 (20.10%) with PROM compared to 116 (18.80%) normal individuals. The subjects with intermediate education were 65 (10.53%) with PROM compared to 74 (11.99%) normal individuals. The percentage of subjects with secondary education was found to be 220 (35.66%) with PROM compared to 219 (35.49%) normal individuals. There were 71 (11.51%) primary education representatives with PROM compared to 78 (12.64%) normal individuals. There were 137 (22.2%) uneducated representatives with PROM compared to 130 (21.7%) normal individuals. The majority of subjects were literate (Table 3.1.5A) and the subjects with secondary education had the highest percentage of PROM among all other categories (Table 3.1.5B). Chi square test showed no association between the literacy rate of the subjects and PROM condition (χ^2=0.2342; df=1; p=0.6284; Not Sig.). Table 3.1.5 A; Fig. 3.1.5A, and (χ^2=1.364; df=4; p=0.8504; Not Sig.) (Table 3.1.5B; Fig. 3.1.5B).

Table 3.1.5(A): PROM and literacy rate of subjects.

Literacy	Prom	Normal	Total
Literate	480	487	967
Illiterate	137	130	267
Sum	617	617	1234

(χ^2=0.2342; df=1; p=0.6284; Not Sig.)

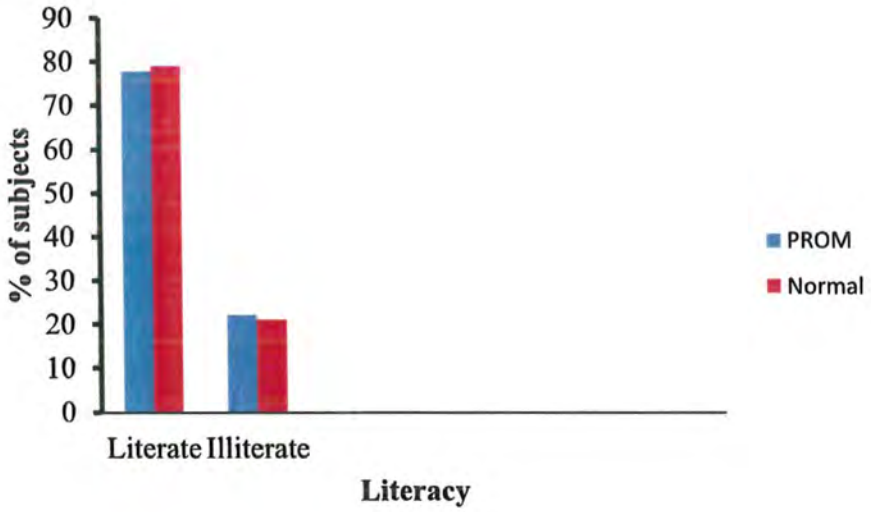


Fig 3.1.5(A) PROM and literacy rate of subjects

Table 3.1.5(B): PROM and literacy rate of subjects.

Literacy	Prom	Normal	Total
Primary	71	78	149
Matric	220	219	439
Intermediate	65	74	139
Graduation and Higher	124	116	240
Uneducated	137	130	267
Sum	617	617	1234

(χ^2=1.364; df=4; p=0.8504; Not Sig.)

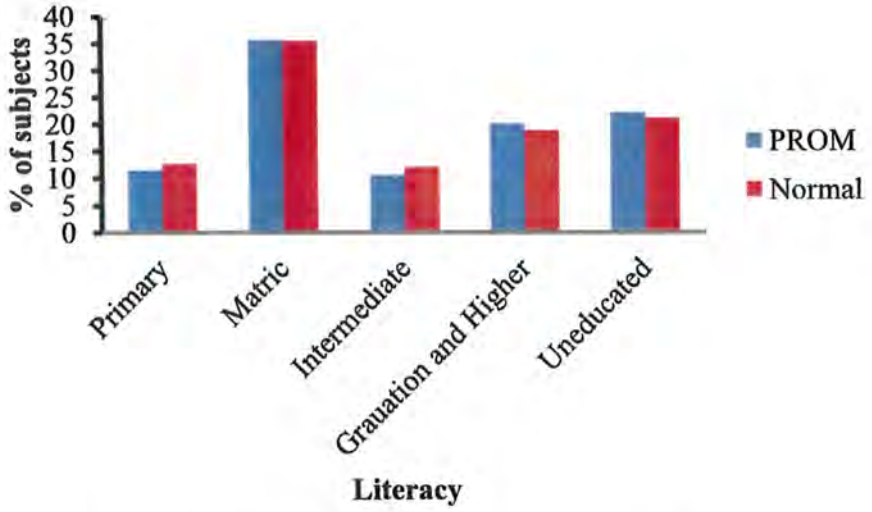


Fig 3.1.5(B) PROM and literacy rate of subjects.

3.1.6 Occupation:

The distribution of subjects with PROM and normal was also established according to occupation. There were 582 (94.33%) representatives being house wives with PROM compared to 595 (96.43%) normal individuals. The subjects with other occupations were 35 (5.67%) with PROM compared to 22 (3.57%) normal subjects. Most of the subjects under study were house wives and the PROM cases were greater in this category as compared to other occupations. No significant association was found between the occupation of subjects and PROM condition. (χ^2=3.108; df=1; p=0.0779; Not Sig.) (Table 3.1.6; Fig. 3.1.6).

Table 3.1.6: PROM and occupation of subjects.

Occupation	PROM	Normal	Total
House wife	582	595	1177
Other occupations	35	22	57
Sum	617	617	1234

(χ^2=3.108; df=1; p=0.0779; Not Sig.)

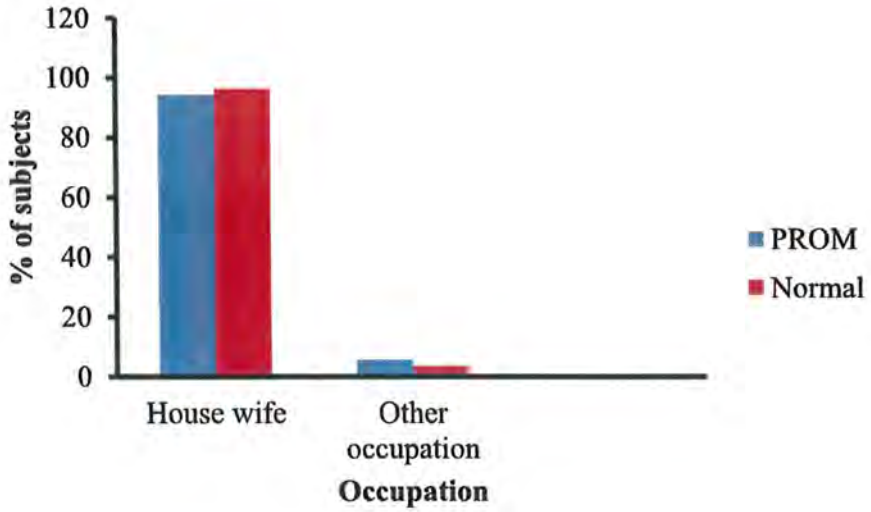


Fig 3.1.6 PROM and occupation of subjects.

3.1.7 Family Type:

The distribution of subjects with PROM and normal was also established according to family type. There were 5 (0.81%) representatives in F1 (single) category with PROM compared to 1 (0.16%) normal individual. The subjects from F2 (nuclear) family type were 134 (21.72%) with PROM compared to 172 (27.88%) normal individuals. There were 51 (8.27%) representatives in F3 (grandparents and one couple) category with PROM compared to 267 (43.27%) normal individuals. The subjects from F4 (more than one couple) family type were 29 (4.70%) with PROM compared to 112 (18.15%) normal individuals. There were 377 (61.10%) representatives in F5 (extended family) with PROM compared to 43 (6.97%) normal individuals. The number of subjects with unknown family type was 21 (3.40%) with PROM compared to 22 (3.57%) normal individuals. The extended family type had the greater number of subjects compared to other family types and the number of PROM was also greater in this group. Chi square test showed significant association between the family types and PROM condition (χ^2=468.6; df=5; p<0.0001; Sig.) (Table 3.1.7; Fig. 3.1.7).

Table 3.1.7: PROM and family type of subjects.

Family Type	Prom	Normal	Total
F1(single)	5	1	6
F2(nuclear)	134	172	306
F3(grandparents and one couple)	51	267	318
F4(more than one couple)	29	112	141
F5(extended)	377	43	420
Unknown	21	22	43
Sum	617	617	1234

(χ^2=468.6; df=5; p<0.0001; Sig.)

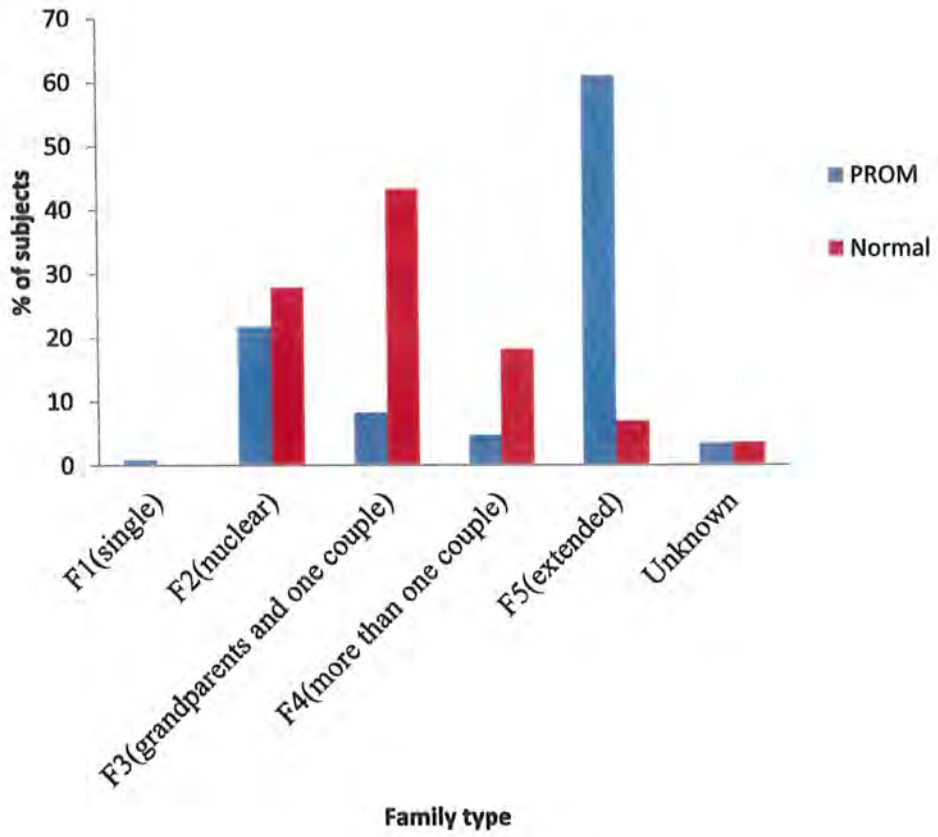


Fig 3.1.7 PROM and family type of subjects.

3.1.8 Caste-system:

The distribution of subjects with and without PROM was also analyzed with respect to their caste. The subjects of Abbasi caste were 64 (10.4%) with PROM compared to 49 (7.94%) normal subjects. The Awan caste had 50 (8.1%) representatives with PROM compared to 71 (11.51%) normal individuals. Subjects belonging to Bhatti/Bhutto caste had 24 (3.9%) representatives with PROM compared to 29 (4.71%) normal subjects. The Choudhary caste had 22 (3.6%) representative with PROM compared to 24 (3.89%) normal individuals. There were 22 (3.6%) Christian representatives with PROM compared to 21 (3.40%) normal individuals. The Kashmiri subjects had 41 (6.6%) representatives with PROM compared to 30 (4.86%) normal subjects. Subjects having Mughal caste had 37 (6%) representatives with PROM compared to 31 (5.02%) normal individuals. The Malik caste had 31 (5%) representatives with PROM compared to 22 (3.57%) normal subjects. The Pathan/ Khan caste had 76 (12.3%) representatives with PROM compared to 75 (12.16%) normal individuals. The Qureshi subjects had 22 (3.4%) representatives with PROM compared to 20 (3.24%) normal individuals. The Rajputs/ Raja had 66 (10.7%) representatives with PROM compared to 67 (10.7%) normal individuals. The Syed subjects had 38 (6.2%) representatives with PROM compared to 58 (9.41%) normal individuals. The subjects with different castes had 125 (20.3%) representatives with PROM compared to 121 (19.16%) normal individuals. No significant association was obtained between the caste of subjects and PROM condition (χ^2=14.24; df=12; p=0.2855; Not Sig.) (Table 3.1.8, Fig. 3.1.8).

Table 3.1.8: PROM and caste of subjects.

Caste	PROM	Normal	Total
Abbasi	64	49	113
Awan	50	71	121
Bhatti/bhutto	24	29	53
Choudhary	22	24	46
Christian	22	21	43
Kashmiri	41	30	71
Mughal	37	31	68
Malik	31	22	53
Pathan/Khan	76	75	151
Qureshi	21	20	41
Rajput/Raja	66	66	132
Syed	38	58	96
Others	125	121	246
Sum	617	617	1234

(χ^2=14.24; df=12;p=0.2855;Not Sig.).

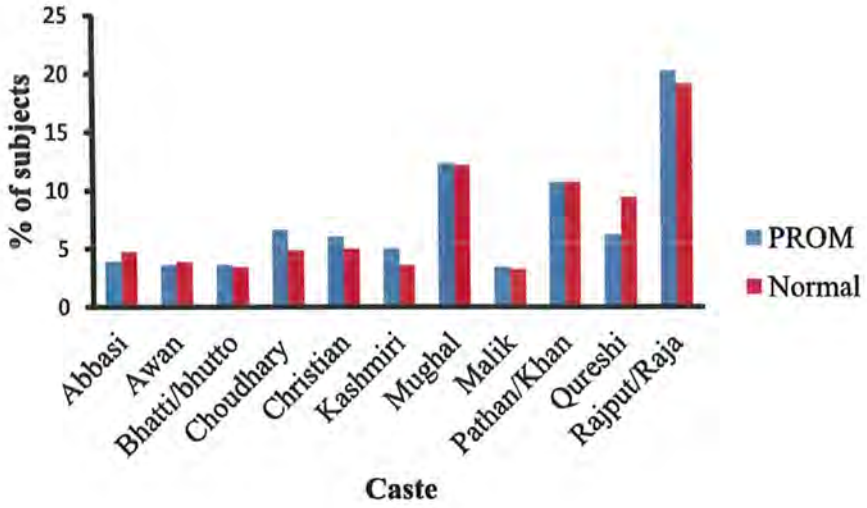


Fig 3.1.8 PROM and caste of subjects.

3.2 Consanguinity:

Normal subjects and those with PROM were analyzed with respect to consanguinity as well. There were 308 (49.92%) representatives with PROM compared to 255 (41.33%) normal individuals under type M1 (first cousins) consanguinity. M6 (double first cousins) had 2 (0.32%) representatives with PROM compared to 4 (0.65%) normal individuals. M7 (first cousin once removed) had 32 (5.19%) subjects with PROM compared to 62 (10.05%) normal individuals. M8 (second cousins) had 26 (4.21%) representatives with PROM compared to 38 (6.16%) normal individuals. M9 (second cousin once removed) had equal representatives from both the groups (with PROM and without PROM) and the consanguinity was found to be 4 (0.65%) for both the groups. M10 (distantly related) had 27 (4.38%) representatives with PROM compared to 48 (7.78%) normal individuals. M11 (not related) had 214 (34.68%) subjects with PROM compared to 187 (30.31%) normal individuals. The subjects with unknown consanguinity were found to be 4 (0.65%) with PROM compared to 19 (3.08%) normal individuals. The majority of the subjects were first cousins of their spouse and the number of PROM cases was high in this category. Chi square test showed a significant association between consanguinity of subjects and PROM condition (χ^2=34.96; df=7; p<0.0001; Sig.) (Table 3.2; Fig. 3.2).

Table 3.2: PROM and Consanguinity.

Consanguinity	PROM	Normal	Total
M1(first cousin)	308	255	563
M6(double first cousins)	2	4	6
M7(first cousin once removed)	32	62	94
M8(second cousin)	26	38	64
M9(second cousin once removed)	4	4	8
M10(distantly related)	27	48	75
M11(not related)	214	187	401
Unknown	4	19	23
Sum	617	617	1234

(χ^2=34.96; df=7; p<0.0001; Sig.)

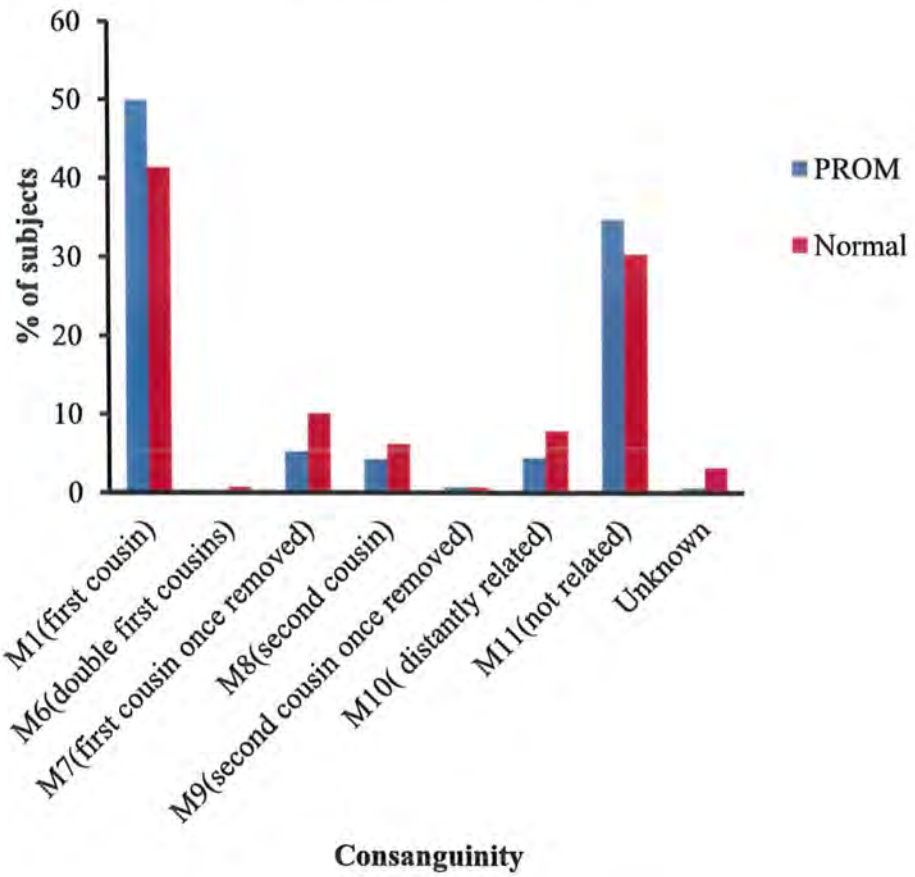


Fig 3.2 PROM and Consanguinity.

3.3 PROM with respect to pregnancy related parameters:

3.3.1 PROM and duration of pregnancy:

The subjects with and without PROM were distributed according to the duration of the pregnancy. The subjects under 1-9 weeks of gestation had no representative with PROM compared to 1 (0.16%) normal individuals. The subjects under 10-18 weeks of gestation had 1 (0.16%) representatives with PROM compared to 4 (0.65%) normal individuals. Those with 19-27 weeks of gestation had equal number of subjects with and without PROM and they were 4 (0.65%) in each group. Subjects with 28-36 weeks pregnancy had 74 (11.99%) representatives with PROM compared to 83 (13.45%) normal individuals. The subjects with 37-45 weeks of gestation had 536 (86.87%) representatives with PROM compared to 490 (79.42%) normal individuals. The subjects not knowing their duration of pregnancy had 2 (0.32%) representatives with PROM compared to 35 (5.67%) normal individuals. the PROM cases were greater under the 37-45 weeks of gestation. Significant association was obtained between the duration of pregnancy of subjects and PROM condition (χ^2=34.81; df=5; p<0.0001; Sig.) (Table 3.3.1; Fig. 3.3.1).

Table 3.3.1: PROM and Duration of pregnancy.

Duration of pregnancy	PROM	Normal	Total
1-9 weeks	0	1	1
10-18weeks	1	4	5
19-27weeks	4	4	8
28-36weeks	74	83	157
37-45weeks	536	490	1026
Unknown	2	35	37
Sum	617	617	1234

(χ^2=34.81; df=5; p<0.0001; Sig.).

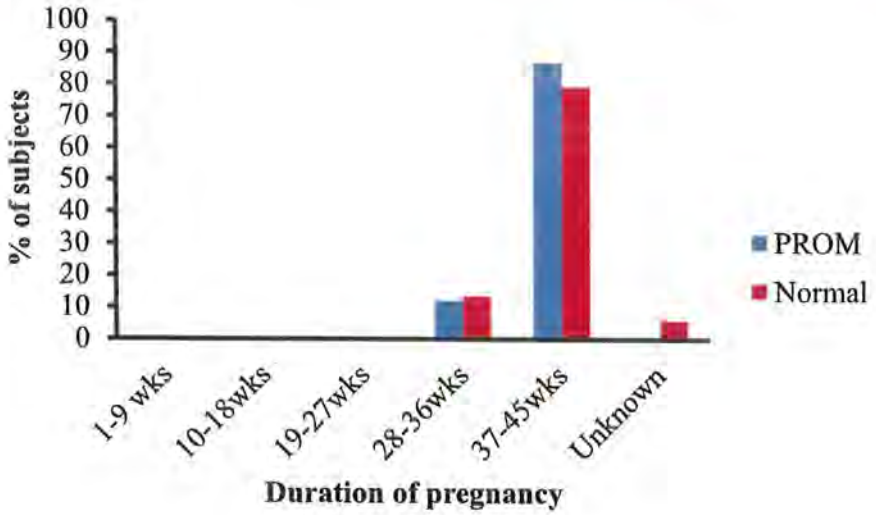


Fig 3.3.1 PROM and Duration of pregnancy.

3.3.2 PROM and mode of delivery:

The subjects with and without PROM were distributed according to the mode of their delivery. There subjects that had undergone abortion had 3 (0.49%) representatives with PROM compared to 7 (1.13%) normal individuals. Those having AVBD mode of delivery had 1 (0.16%) with PROM compared to (0) normal representative. The subjects with Cesarean Section had 271 (43.92%) representatives with PROM compared to 290 (47%) normal individuals. The women who undergone instrumental delivery (SPV n epi) had 136 (22.04%) representatives among PROM compared to 148 (23.99%) normal women. There were 196 (31.77%) subjects with PROM compared to 159 (25.77%) normal subjects who undergone normal delivery. Subjects with OLFD and epi mode of delivery were 4 (0.65%) with PROM compared to 0 normal individuals. Subjects with VBAC mode of delivery were 1 (0.16%) with PROM compared to 0 normal. There was only 1 (0.16%) representative of V epi having PROM compared to 0 normal individual. There were 4 (0.65%) representatives with PROM compared to 13 (2.11%) normal individual, these subjects did not know their mode of delivery. Majority of the PROM subjects had undergone Cesarean section as compared to the other mode of deliveries. Mode of delivery

showed significant association with PROM condition (χ^2=20.55; df=8; p=0.0084; Sig.) (Table 3.3.2; Fig. 3.3.2).

Table 3.3.2: PROM and mode of delivery.

Mode of delivery	PROM	Normal	Total
Abortion	2	7	9
AVBD	2	0	2
Ceserean section	271	290	561
Instrumental delivery (SVDn epi)	136	148	284
Normal delivery (SVD)	196	159	355
OLFD n epi	4	0	4
VBAC	1	0	1
Vepi	1	0	1
Unknown	4	13	17
Total	617	617	1234

(χ^2=20.55;df=8;p=0.0084;Sig.)

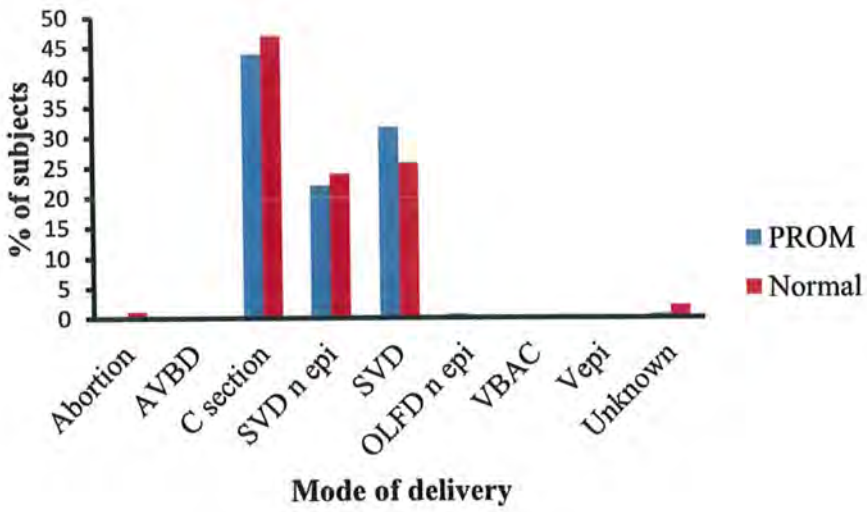


Fig 3.3.2 PROM and mode of delivery.

3.3.3 PROM with respect to Morbidities (General or Congenital) in subjects.

The subjects with and without PROM were also distributed according to their general or congenital morbidities. Out of 617 total representatives of PROM, 121 were reported to have any morbidity whereas in the control group, there were only 29 representatives with any kind of morbidity. The subjects with cardiac problem had 7 (1.13%) subjects with PROM compared to 4 (0.65%) without PROM. The subjects with diabetes had 5 (0.81%) representatives with PROM compared to 7 (1.13%) without PROM. The subjects with depression and anxiety had 5 (0.81%) representatives in each group. The subjects with hepatitis had 12 (1.94%) representative with PROM compared to 6 (0.97%) without PROM. The subjects with hypertension had 16 (2.59%) representatives with PROM compared to 4(0.65%) normal subjects. The subjects with hypertension and diabetes had 7 (1.13%) representatives with PROM compared to 1 (0.16%) subject without PROM. The subjects with PIH, Eclempsia or Pre-eclempsia had 64 (10.37%) representatives with PROM compared to 0 normal individual. The subjects with polio had 5 (0.81%) representatives with PROM compared to 2 (0.32%) normal individual. Chi square test showed a significant association between the general or congenital morbidities among subjects and PROM condition (χ^2=83.99;df=30; p<0.0001;Sig.) (Table 3.3.3).

Table 3.3.3: PROM and morbidities (general or congenital) in subjects.

Morbidities	PROM	Normal	Total
Cardiac problem	7	4	11
Diabetes	5	7	12
Depression and anxiety	5	5	10
Hepatitis	12	6	18
Hypertension	16	4	20
Hypertension+Diabetes	7	1	8
PIH,Pre clempsia,eclempsia	64	0	64
Polio	5	2	7
Sum	121	29	150
Healthy	496	588	1084
Total	617	617	1234

(χ^2=83.99;df=30; p<0.0001;Sig.).

3.4 PROM and pregnancy outcome

3.4.1 PROM and distribution of neonates

The subjects with and without PROM were also distributed with respect to the pregnancy outcome (distribution of neonates). There were 593 (96.11%) alive babies of mothers with PROM compared to 575 (93.19%) of mothers without PROM. Out of 593, 473 (79.76%) neonates were normal (healthy) with PROM subjects compared to 479 (83.30%) among normal mothers. 120 (20.24%) neonates were morbid with PROM mothers compared to 96 (16.70%) without PROM mothers. Of the total 120 morbid neonates with PROM mothers, 56(46.67%) had congenital anomalies, none had reported any infections and the remaining 64 (53.33%) had general morbidities. In the second group, out of 96 morbid neonates among healthy mothers, 43 (44.79%) had congenital anomalies, 4 (4.17%) had infections and 49 (51.04%) had general morbidities. There were 23 (3.73%) dead babies among PROM mothers compared to 37(6%) among healthy mothers. Out of 23 dead babies with PROM mothers, 14 (60.87%) were prenatal dead, 7 (30.43%) were postnatal dead and 2 (8.70%) were abortion cases. Out of 37 dead babies of without PROM mothers, 8 (21.62%) were prenatal dead, 20 (54.05%) were postnatal dead and 9 (24.32%) were abortion cases. There was only 1 (0.16%) representative of unknown pregnancy outcome with PROM mothers compared to 5 (0.81%) without PROM mothers. Pregnancy outcome showed a significant association with PROM (χ^2=28.67;df=10;p=0.0014;Sig.) (Table 3.4.1; Fig. 3.4.1).

Table 3.4.1: PROM and pregnancy outcome.

Distribution of neonates.	PROM	Normal	Total
Alive	**593**	**575**	**1168**
1.Normal	473	479	952
2.Morbid	**120**	**96**	**216**
a-Congenital anomalies	56	43	99
b-Infections	0	4	4
c-general.	64	49	113
Dead	**23**	**37**	**60**
Prenatal (IUD)	14	8	22
Postnatal	7	20	27
Abortion	**2**	9	11
Unknown	**1**	**5**	**6**
Sum	**617**	**617**	**1234**

(χ^2=28.67;df=10;p=0.0014;Sig.)

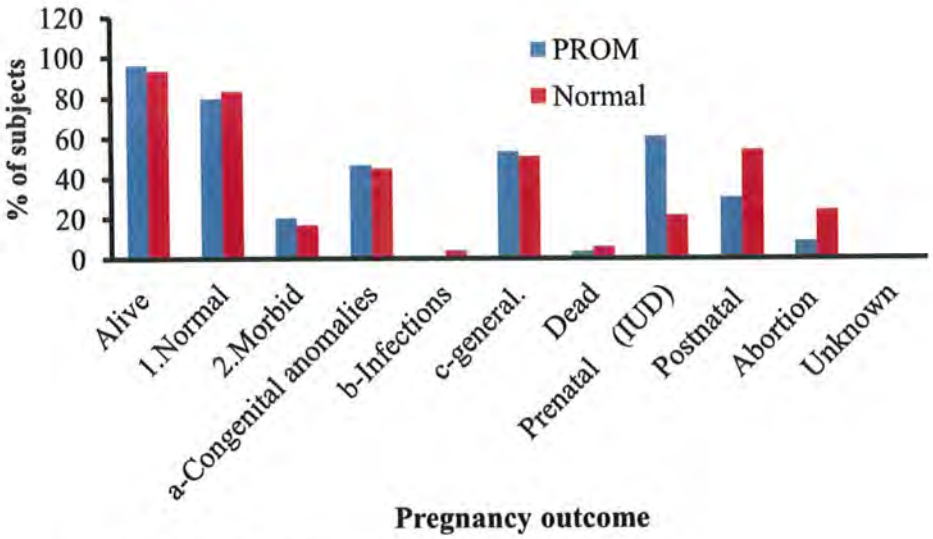


Fig 3.4.1 PROM and pregnancy outcome.

3.4.2 PROM with respect to singleton and multiple gestations:

The distribution of subjects with PROM and normal was established according to the singleton and multiple pregnancies outcome. Subjects with PROM had 604 (97.89%) singleton pregnancies as compared to normal subjects who had 594 (96.27%) singleton pregnancies. The multiple pregnancies category was further divided into twins, triplets and quadruplets. Subjects with PROM had 12 (1.94%) twins pregnancies compared to 20 (3.24%) in normal subjects. There were an equal percentage of representatives from both the groups (with PROM and normal) in triplet pregnancies and it was 1 (0.16%). There was no representative with PROM having quadruplet pregnancies compared to 2 (0.32%) in normal. There was a highest number of singleton pregnancies, so the greater percentage of PROM was seen in this category. No significant association was found between singleton or multiple pregnancies and PROM (χ^2=2.785; df=5; p=0.7332; Not Sig.) (Table 3.4.2; Fig. 3.4.2)

Table 3.4.2 PROM with respect to singleton and multiple gestations.

Pregnancy	PROM	Normal	Total
Singleton	596	589	1185
Multiple			
Twins(in multiple births)	17	20	37
Triplets(in multiple births)	1	1	2
Quadraplets (in multiple births)	0	2	2
Unknown	3	5	8
	617	617	1234

(χ^2=2.785; df=5; p=0.7332; Not Sig.)

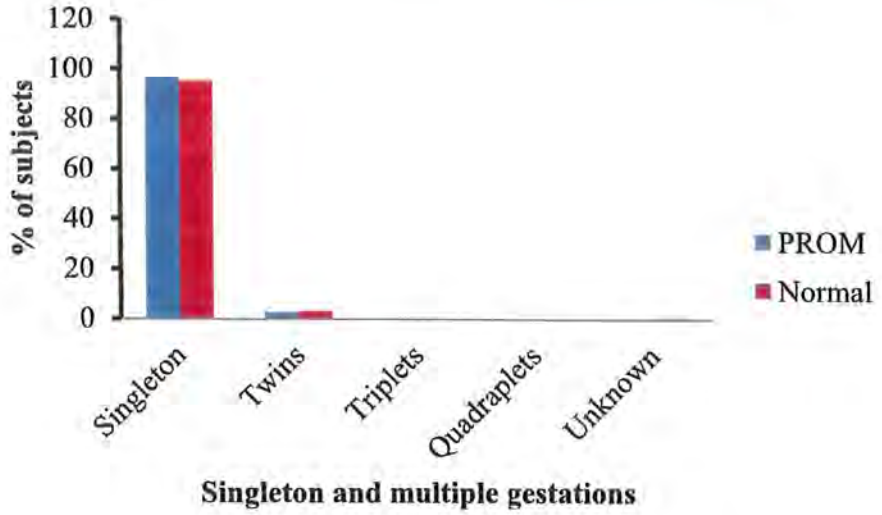


Fig 3.4.2 PROM with respect to singleton and multiple gestations.

3.4.3 PROM and distribution of neonates with respect to gender.

The distribution of neonates with respect to their gender was established in subjects with PROM and normal. There were 317 (51.13%) sons in subjects with PROM compared to 336 (51.45%) in normal. There were 295 (47.58%) representatives of daughters in subjects with PROM compared to 307 (47.51%) in normal. There were 8 (1.29%) representatives of unknown gender in subjects with PROM compared to 10 (1.53%) in normal. The majority of neonates were sons and their mothers had the high percentage of PROM. Gender of neonates was not significantly associated with PROM (χ^2=2.785; df=5; p=0.7332; Not Sig.) (Table 3.4.3; Fig. 3.4.3).

Table 3.4.3 PROM and Gender-wise distribution of neonates.

Gender	PROM	Addition of multiple pregnancy outcome	Normal	Addition of multiple pregnancy outcome	Additions from multiple pregnancies	Total
Son	314	11	318	12	23	655
Daughter	299	9	292	23	23	614
Unknown	4	0	7	1	1	12
	617		617		47	1281

(χ^2=2.785; df=5; p=0.7332; Not Sig.)

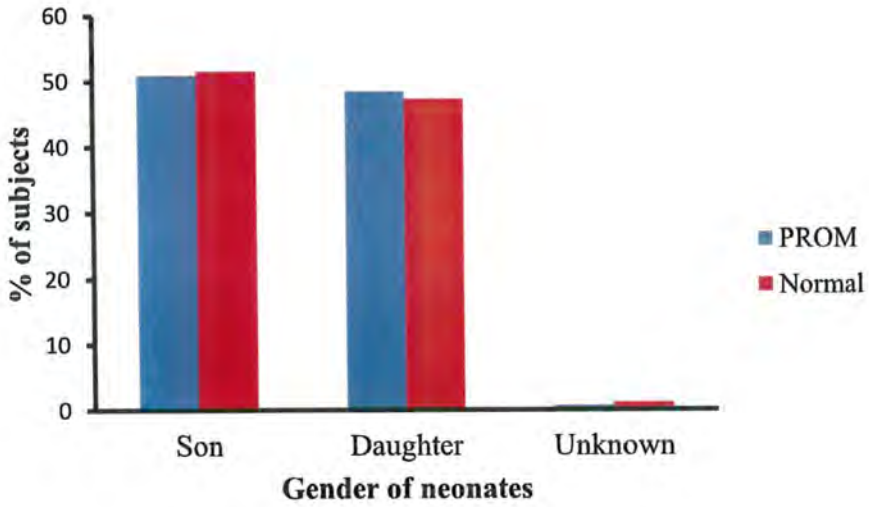


Fig 3.4.3 PROM and Gender-wise distribution of neonates.

3.4.4 PROM and distribution of congenital anomalies in neonates.

The distribution of neonates with respect to different congenital anomalies was established in subjects with PROM and without PROM condition. The PROM subjects had total of 56 neonates with congenital anomalies compared to 43 neonates with congenital anomalies without PROM mothers. The congenital anomalies were categorized into 8 major groups and each group was subdivided into few relevant anomalies. The first category was CNS defects. There was only 1 (1.79%) representative of anencephaly with PROM mothers compared to 0 among normal subjects. The cerebral palsy also had only 1 (1.79%) representative with PROM compared to 0 without PROM. Hydrocephaly had 0 representative with PROM compared to 2 (4.65%) representatives without PROM. Macrocephaly had 1 (1.79%) representative with PROM compared to 0 representatives without PROM. Meningocele had 1 (1.79%) representative with PROM compared to 2 (4.65%) representatives without PROM. Meningitis had 2 (3.57%) representatives with PROM compared to 0 without PROM. Spina bifida had 1 (1.79%) representative with PROM compared to none among normal subjects. Subglial bleed had 3 (5.36%) representatives with PROM compared to 0 among normal individuals. the second category included gastrointestinal defects. Oesophagocele had 0 representative with PROM compared to 1 (2.33%) without PROM. Transesophageal fistula had 1 (1.79%) representative with PROM compared to 1 (2.33%) without PROM. The third category included kidney diseases. Multi cystic dysplastic kidney had 1 (1.79%) representative with PROM compared to 0 without PROM. The fourth category included the musculoskeletal malformations. There was only 1 (1.79%) representative of brachydactyly with PROM compared to 0 without PROM. There was 1 (1.79%) representative of polydactyly with PROM compared to 1 (2.33%) without PROM. There was 1 (1.79%) representative of syndactyly with PROM compared to 0 without PROM. There was 0 representative of talipes with PROM compared to 1 (2.33%) without PROM. The fifth category included orofacial anomalies. There was 1 (1.79%) representative of cleft palate with PROM compared to 1 (2.33%) without PROM. The next category covered respiratory disorders. There were 3 (5.36%) representative of birth asphyxia with PROM compared to 6 (13.95%) without PROM. The lethargic neonates had 0 representative with PROM compared to 1 (2.33%) without PROM.

There were 13 (23.21%) representatives of respiratory distress with PROM compared to 8 (18.60%) without PROM. There were 4 (7.14%) representatives of tachypnea with PROM compared to 5 (11.63%) without PROM. The next category was of multiple anomalies and both the group had equal number of representatives, 8 (14.29%) with PROM and 8 (18.60%) without PROM. The last category included different anomalies. There were 4 (7.14%) representatives of ambiguous genitalia with PROM compared to 2 (4.65%) without PROM. There was only 1 (1.79%) representative having bruice on buttock with PROM compared to 0 without PROM. There was 1 (1.79%) representative of congenital heart problem with PROM compared to 2 (4.65%) without PROM. Only 1 (1.79%) representative without PROM had eczema compared to 0 with PROM. Hypothyroidism had 1 (1.79%) representative with PROM compared to 0 without PROM. There were 4 (7.14%) representatives of IUGR with PROM compared to 1 (2.33%) without PROM. Only 1 (1.79%) representative had low calcium level with PROM compared to 0 without PROM. No significant association was obtained between the congenital anomalies of neonates with PROM. (χ^2=4.475; df=7;p=0.7237; Not Sig.). Table (3.4.4).

Table 3.4.4:PROM and congenital anomalies in neonates.

Anomalies	PROM	Normal	Total
CNS defects	10	4	14
Gastrointestinal defects	1	2	3
Kidney diseases	1	0	1
Musculoskeletal malformations	3	2	5
Orofacial anomalies	1	1	2
Respiratory disorders	20	20	40
Multiple anomalies	8	8	16
Others	12	6	18
Sum	56	43	99

(χ^2=4.475; df=7;p=0.7237; Not Sig.)

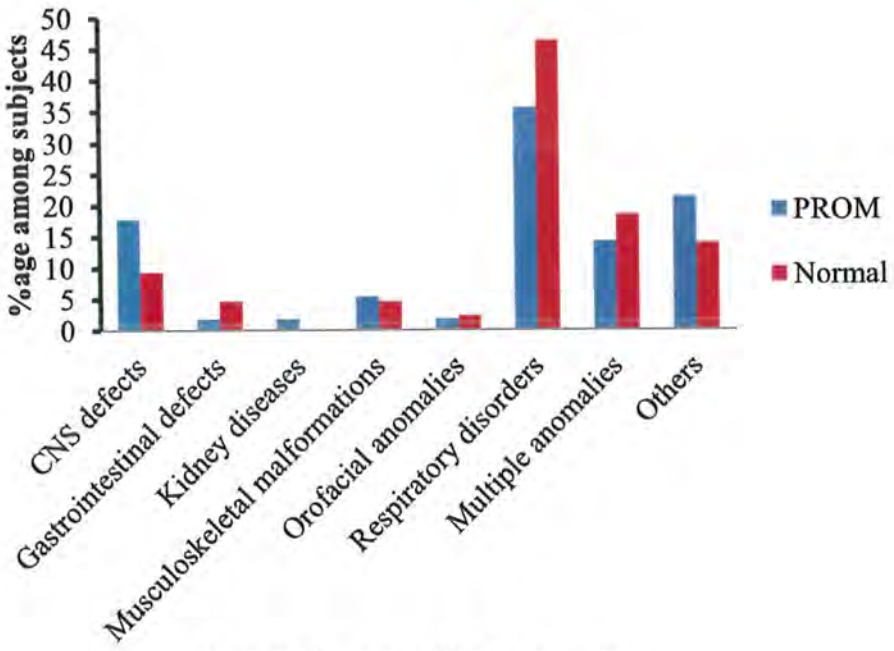


Fig 3.4.4 PROM and congenital anomalies in neonates.

3.4.5 PROM with respect to the weight of neonates.

The distribution of neonates with respect to their birth weight was established among all the subjects (with and without PROM). The number of neonates with less than 1.0 kg weight was 3 (0.49%) among subjects with PROM compared to 5 (0.81%) among normal individuals. There were 46 (7.46%) neonates with 1.0-1.9 kg weight among subjects with PROM compared to 54 (8.75%) among normal individuals. There were 278 (45.06%) neonates with 2.0-2.9 kg weight among subjects with PROM compared to 262 (42.46%) among normal individuals. There were 244 (39.55%) neonates with 3.0-3.9 kg weight among subjects with PROM compared to 241 (39.06%) among normal individuals. There were 16 (2.59%) neonates with 4.0-4.9 kg birth weight among subjects with PROM compared to 14 (2.27%) among normal subjects. The neonates with unknown birth weight were 30 (4.86%) among subjects with PROM compared to 41 (6.65%) among normal individuals. No significant association was obtained between the neonatal weight and PROM. (χ^2=3.470; df=5; p=0.6279; Not Sig.) (Table 3.4.5; Fig. 3.4.5).

Table3.4.5: PROM and neonatal weight at birth.

Weight of neonates (kg)	PROM	Normal	Total
<1.0	3	5	8
1.0-1.9	46	54	100
2.0-2.9	278	262	540
3.0-3.9	244	241	485
4.0-4.9	16	14	30
Unknown	30	41	71
TOTAL	**617**	**617**	**1234**

(χ^2=3.470; df=5; p=0.6279; Not Sig.)

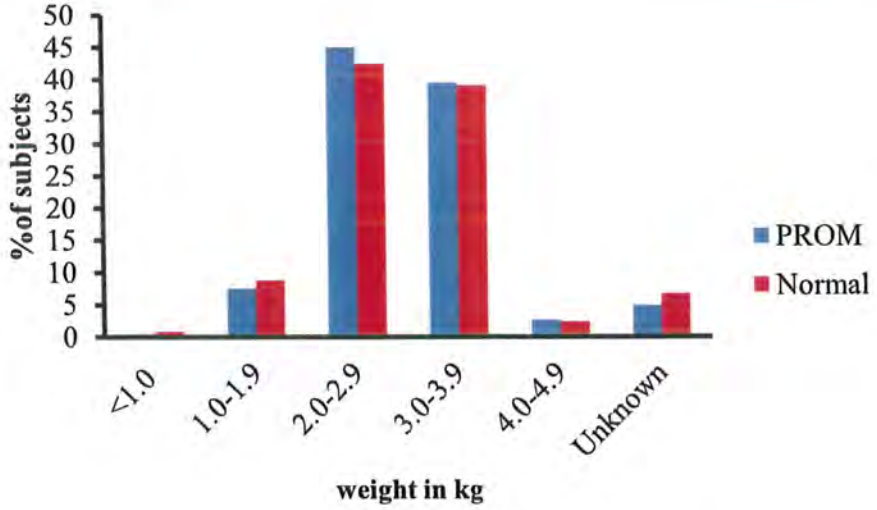


Fig 3.4.5: PROM and neonatal weight at birth.

CHAPTER 4

DISCUSSION

This study was a cross sectional investigation and it was conducted at MCH (Maternal and Child Health Center) of PIMS (Pakistan Institute of Medical Sciences). The data were recruited since 2010 and compiled in 2014. The study included 5363 mothers data, 3127 mothers were morbid. The questionnaire filled by the subjects of different demographic regions revealed information about the various pregnancy related conditions including morbidities (general and congenital), pregnancy related health conditions, neonatal outcome, non-communicable diseases etc. The topic of this study was one of the pregnancy related conditions i.e. premature rupture of membranes. Premature rupture of membranes had the highest percentage among the pregnancy related morbidities i.e. 20%, this percentage was greater than previously reported percentage by Noor et al., (2007) (16%), so it was necessary to analyze the association of different parameters with this pregnancy related condition.

A total of 617 mothers had premature rupture of membranes. An equal number of the control group was selected from the same data for data analysis. Initially the association of PROM was analyzed with different demographic variables including origin, age group, language, province, occupation, literacy rate, family type and caste of the subjects. The relationship of consanguinity with PROM was also checked. Pregnancy parameters were duration of pregnancy (in weeks), mode of delivery (abortion, AVBD, cesarean section, instrumental delivery, normal delivery etc), general or congenital anomalies in the subjects. Premature rupture of membranes was analyzed with respects to these parameters as well.

The association was also analyzed with pregnancy outcome. The association of PROM with distribution of neonates among the subjects was checked. Singleton or multiple pregnancy, gender of the neonates, distribution of congenital anomalies in neonates, neonatal weight at birth were the other pregnancy outcome parameters with which the association of PROM was observed.

With respect to different demographic variables, significant association of PROM was obtained with language and family type of the subjects while no association of PROM was obtained with the origin, age group, province (residence), literacy, occupation and caste of the subjects. PROM was not significantly associated with the origin of the subjects. PROM was observed to be higher in urban subjects (35.17%) compared to the rural ones (31.28%). In comparison, the control group had 64.83% urban representatives and 68.72% rural representatives. This is because the MCH recruits majority of the cases from the twin cities (Islamabad and Rawalpindi) and the nearby small cities and towns. The number of patients coming from far away rural areas is less in such tertiary care hospitals.

With respect to the age group of the subjects, the PROM condition was observed to be higher in subjects having age from 25-29 years old (35.66%). This was followed by 20-24 years old age group (31.44%). The healthy mothers in the control group had 35.98% representatives with age ranging from 25-29 years and 30.63% representatives belonging to age group 20-24 years old. There was no association obtained between the PROM and the age group of the subjects. This finding is supported by another study by Dars et al., (2014) which analyzed that majority of the mothers with PROM had their ages between 20-30 years and it also found no association between the age group of subjects with this pregnancy related condition.

With respect to the native language of the subjects, PROM was reported to be higher in Punjabi speaking subjects (57.37%) followed by Pashto (13.29%) and Kashmiri (7.78%) languages. The controls had highest representatives of Punjabi language (58.67%) followed by Kashmiri (13.45%) and Pashto languages (12.64%). The association of PROM with the language of the subjects was significant.

With respect to the current residence of the subjects, majority of the cases having PROM were Federal residents (52.19%) compared to 49.11% in control

group. Punjab province had the second highest number of representatives with PROM (35.98%) compared to 41.49% in control group. The other provinces had less number of representatives. This might be due to the reason that Sindh and Baluchistan are the farthest provinces from the capital and the subjects cannot travel a long distance during pregnancy. Most of them prefer to visit their nearby health care centers. No significant association was obtained between the residence of the subjects and PROM.

PROM was not significantly associated with the literacy rate of the subjects. Majority of the subjects were literate and PROM was reported to be higher in these subjects (77.80%) compared to 78.93% literacy in control group. The illiterate representatives were only 22.2% with PROM compared to 21.07% subjects without PROM. With respect to literacy levels, PROM was reported to be higher in mothers with Matric education (35.66%). The mothers with less education have little knowledge about the basic health care issues. The control group had 35.49% representatives with Matric level of education. The graduates had 20.10% representatives with PROM compared to 18.80% without PROM.

No significant association was obtained between PROM and the occupation of the subjects. Most of the subjects with PROM were house wives (94.33%) compared to 96.43% normal mothers. Farming, student, teacher and other occupations had very few representatives with PROM.

Significant association was obtained between PROM and the family type of the subjects. The extended family type (F5) had the highest number of representatives with PROM (61.10%) compared to other family types. The percentage of control group representing extended family type was only 6.97%. This was followed by nuclear family type (F2) having 21.72% cases with PROM and F3 (grandparents and one couple) type having 8.27% subjects with PROM. The association of PROM with respect to the caste of subjects was quite variable. PROM was seen more in Pathan/Khan caste (12.3%) followed by Rajput/Raja

(10.7%), Abbasi (10.4%) and Awan (8.1%) castes. No association was obtained between the caste of the subjects and PROM.

With respect to consanguinity, PROM showed significant association. PROM was higher in first cousin category M1 (49.92%). This finding was in parallel with the findings of previous studies by Porter et al. 1997; Winkvist et al., 1998. Familial aggregation of preterm PROM was also observed by Jevon et al., (2008). The fetal and placental membranes growth is mainly controlled by the genes imprinted paternally in fetus Ananth et al., (2001). There is a strong line of evidences showing that maternal genetics factors also influence the preterm PROM (DeFranco et al., 2007; Doody et al., 1997; Lee et al., 2003). It was followed by M11 (not related) category in which there were 34.68% representatives of PROM.

There was a significant association of PROM with duration of pregnancy. The duration of pregnancy was recorded in terms of weeks. 37-45 weeks pregnancy category had the highest percentage of PROM (86.87%) and this was followed by 28-36 weeks pregnancy (11.99%).

Mode of delivery also showed significant association with PROM. PROM was more prevalent in Cesarean sections (43.92%) (n=617) compared to other modes of delivery but this percentage was less than the one reported by Shapla et al., (2015) (69.41%) (n=206); Dana et al., (2008) (50.8%) (n=236). Early gestational age and cesarean section mode of delivery increases the risk for respiratory morbidity Shimokaze et al., (2015). Normal delivery (SVD) had 31.77% and instrumental delivery (SVD and epi) had 22.04% representatives of PROM.

Significant association between PROM and morbidities (general or congenital) in subjects was analyzed. Premature rupture of membranes was more common in mothers with hypertensive disorders (preeclampsia, eclampsia, PIH collectively 10.37% compared to 0% in control group, hypertension 2.59% compared to 0.65% in control group) compared to other morbidities. The

association of PROM with pregnancy outcomes was significant. The live-born neonates were 96.11% with PROM mothers compared to 93.19% normal mothers. This percentage of live-born neonates exposed to PROM is greater than the earlier reported percentage by Patkai et al., (2013) (68%); Everest et al., (2008) (70%). Among the live-born neonates category, the morbid neonates were 20.24% with PROM. The total dead babies were 3.73% with PROM of which the highest percentage was of IUDs i.e. 60.87%.

About 96.60% pregnancies with PROM were singleton compared to 3% multiple pregnancies. The association of PROM with singleton or multiple pregnancies was not significant. The prevalence of PROM in singleton pregnancies is higher than in twin or triplet pregnancies but not statistically significant and this result is also supported by a study of Rujiwetponqston. (2015). Due to other obstetric complications, pre-labor cesarean section may be a reason associated with high prevalence of PROM in singleton pregnancies. The majority of the neonates born were sons 51.13% with PROM compared to 47.58% daughters with PROM. No association was obtained between PROM and gender of the neonates.

With respect to congenital anomalies in neonates, the subjects with PROM had higher percentage of neonates with respiratory disorders (35.71%) followed by central nervous system defects (17.86%). The study also found cases of mental retardation, cerebral palsy, hearing loss etc in neonates whose mothers were exposed to preterm PROM and these long term sequelae of preterm PROM are in concordance with the study of Dana et al. (2008). The percentage of respiratory disorders found in this study was less than earlier reported by Patkai et al., (2013) (CLD 46.7%). The association of PROM with different congenital anomalies was not significant. The neonates have generally more respiratory disorders when their mothers are exposed to preterm premature rupture of membranes (Kilbride et al., 2001). The reason may be that the fetal lungs do not develop properly if the fetal membranes are ruptured prior to the labor onset.

With respect to the birth weight of neonates, no significant association was obtained with PROM. No significant difference of birth weight was found in both the groups. (Dana et al., 2008) also did not find any significant difference of birth weights in both the groups i.e. with and with PROM. The highest percentage was found in 2.0-2.9 kg weight category i.e. 45.06% neonates exposed to PROM, followed by 3.0-3.9 kg birth weight category i.e. 39.06% with PROM. In case of extremely preterm neonates, the birth weight was found to be an independent factor for their morbidity and mortality Mamopoulos et al., (2015).

Conclusion

In this study, significant association of premature rupture of membranes was obtained with language and family types of the subjects whereas no association found with the origin, caste, literacy, occupation, province and age group of the subjects. In relation to consanguinity, a significant association of PROM was observed with consanguinity and the highest percentage of subjects in M1 category had PROM i.e. parents were first cousins. With respect to various pregnancy parameters, PROM was again significantly associated with duration of pregnancy, mode of delivery and morbidities in subjects. Cesarean section deliveries were recorded more with premature rupture of membranes. PROM was more significant in subjects with hypertensive disorders. The association of the neonatal outcome with this pregnancy related condition was also evaluated and it was analyzed to be significantly associated with the distribution of neonates but no significant association was obtained with the gender, birth weight, single or multiple gestation and congenital anomalies in neonates of subjects exposed to PROM.

Recommendations:

The well-being of any society depends directly upon the health of women especially mothers because only a healthy woman can lead a healthy family. In Pakistan where the trend of joint family systems is being rooted since long, the women of any family belonging to this region faces much more health issues compared to the women of developed countries. Despite the progress made in many countries in increasing the availability of maternal healthcare facilities, the majority of women across Pakistan in distant and remote areas remain without full access to this care. Women face a variety of obstacles to improved maternal health. The data if available is rarely highlighted to get the attention of any authoritative agency that can promote health care programs and initiatives to improve maternal health during and after pregnancy. In some cases, the pervasive attitudes about women stop them from accessing the health care facilities and they find themselves in a big trouble where they cannot even share their health related issues with their spouse or in laws. Some families consider such issues to be entirely the business of women and no one bothers the complications which the expecting mother faces during her pregnancy. Following are some of the recommendations regarding pregnancy related morbidities especially the one discussed in my project i.e. PROM that can help improve maternal health.

- Proper checkup of expecting mothers especially in their second and third trimester to evaluate the risk of PROM.
- Implementation of a community based health care project which can educate our women about the very basic maternal health issues.
- Providing any financial aid to the women with low socioeconomic status can improve their health status.
- Families should be taught about the occurrence and high risks of any disorder or medical conditions and they should be guided with evidence about the consequences of consanguinity and close marriages.
- Any morbid women undergoing treatment should be dealt with courage and hope to minimize the drastic effects for both her and her family.

- Regular tutorials must be arranged for the house wives during pregnancy those can counsel them about healthy life style that how to manage their schedule and to cope with the circumstances.

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