AMERICAN UNIVERSITY OF BEIRUT

PATERNAL AGE AND MATERNAL COMPLICATIONS DURING PREGNANCY: IS THERE AN ASSOCIATION?

by
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AN ABSTRACT OF THE THESIS OF

May Al Kassar for Master of Science
Major: Population Health

Title: Paternal Age and Maternal Complications during Pregnancy: Is there an Association?

Introduction:

Although advanced maternal age continues to be associated with higher risks of adverse reproductive outcomes (Kenny et al., 2013), the mean maternal age at first childbirth in developed and developing countries has been increasing over the past three decades (Kenny et al., 2013; Mensch et. al, 2005). Older parenthood and its association with adverse reproductive outcomes are not restricted to females; males are also contributing to the trend of older parenting and its related risks.

Although both partners contribute to pregnancy and fetal outcomes, paternal contribution was not emphasized in the literature as a source of risk until relatively recently. In the last decade, the medical and scientific communities have been shedding more light on adverse reproductive outcomes that are associated with advanced paternal age. The literature, however, is still limited in this respect in comparison to what has been generated on advanced maternal age. Moreover, the literature is still focusing on the association between paternal age and fetal outcomes, rather than on the entire course of pregnancy and its development.

Therefore, this study aims at exploring the effect of paternal age on maternal complications during pregnancy, namely preeclampsia, eclampsia, placenta previa and placenta abruptio.

Methods:

This is a retrospective cross sectional study using data from the National Collaborative Perinatal Neonatal Network (NCPNN). NCPNN is a Lebanese non-governmental hospital-based registry that collects data prospectively on pregnant women and their newborns. This registry covers 30% of the total national births. All women admitted for delivery in one of the NCPNN member hospitals between the years 2002 and 2012 constitute our study sample. Propensity score regression adjustment is used to estimate the effect of advanced paternal age on hypertensive disorders and uteroplacental disorders.

Results:

A consistent statistically significant association kept appearing between paternal age and our four maternal outcomes among young women aged less than 35 years. The odds ratio of developing preeclamsia among this group of women was 1.013 (95%CI= 1.0003-1.025) with each one year increase in father's age, similarly it was 1.016 for

eclampsia (95% CI= 1.004-1.027), 1.049 for placenta previa (95%CI= 1.026-1.071) and 1.043 for placenta abruptio (95%CI=1.021-1.066). No statistically significant results were found between paternal age and obstetric complications among women aged 35 years or more.

Conclusion:

With the increasing proportions of women and men who are delaying marriage and births to an older age in Lebanon and in the region, optimizing obstetric counseling and tailoring it to the need of this group is critical. An approach to collect information on father's age and his health characteristics during prenatal care and prenatal counseling is desirable. This approach would enable healthcare providers to attend to masked risk factors and consequently to contribute towards ameliorating pregnancy outcomes. At the same time, similar data collection needs be adopted by hospitals and birth registries in order to enable researchers to better understand and explore the effect of paternal age and characteristics on pregnancy and neonatal outcomes.

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CHAPTER I

INTRODUCTION

A. Background

Although advanced maternal age continues to be associated with higher risks of adverse reproductive outcomes (Kenny et al. 2013), the mean maternal age at first childbirth in developed countries continues to witness a significant increase over the past three decades (Kenny et al. 2013). At the same time, the mean paternal age at first childbirth shares also a similar pattern of increase over the years, however its association with adverse fetal outcome and maternal complications is very recent. Data from the U.S. Census Bureau (2009) reveal that the median age at first marriage for men was 28.4 years in 2009 whereas it was 26.5 years for women. Similarly, data from the United Nations Economic Commission for Europe (2008) reveal that the mean age at first marriage for men in France was 31.6 years and 33.0 years in Germany in 2008, whereas it was 29.6 years for women in France and 30.0 years for women in Germany.

The same trends are observed for maternal and paternal age at marriage and subsequently age at first birth in developing countries (Mensch, Singh, & Casterline, 2005). Analysis of marriage trends using data from 73 developing countries provided by the United Nations Population Division and data from 52 Demographic and Health Surveys conducted between 1990 and 2001 reveals an increased proportion of both men and women who are first getting married at an older age (Mensch et al., 2005). Table 1 and Table 2 in the Appendix show the percentage of women and men by age, time period and region (Mensch et al., 2005).

Families in the Arab world are following the same pattern of delaying marriage (Rashad, Osman, & Roudi-Fahimi, 2005). Data from eight countries in the Middle East show that the proportion of both men and women married between the of age 20 and 24 years has been falling during the past decade. While the majority of women and men marry by the age of 25 to 29 years, a good percentage from both genders is postponing marriage to an older age (Mensch et al., 2005).

Data on the changing trends of the age at marriage in Lebanon is scarce and outdated. An article that analyzed marriage trends in Lebanon using a large cohort of the Lebanese population, showed an increase in the mean age at first marriage for males and females between 1970 and 1996 (Saxena, Kulczycki, & Jurdi, 2004). However, although the data of this article date to 1996, it still highlights the shift in trends affecting the Lebanese population (Saxena, Kulczycki, & Jurdi, 2004). Another press release from the American University of Beirut echoes this shift in marriage trends. This press release highlights that a survey conducted by the Lebanese Ministry of Social Affairs in 2006 found that the mean age at marriage was 32.8 years for men and 28.8 years for women. No other information about the research design used and sampling is available (Drieskens, 2006).

Older parenthood and its association with adverse reproductive outcomes are not restricted to females; males are also contributing to this trend. Although spermatogenesis is a continuous process throughout lifetime, advanced male age has been shown to have an effect on the reproductive organs and tissues (Wiener-Megnazi, Auslender, & Dirnfeld, 2012). The effect of age develops gradually in men whereas it is an abrupt cease of ovulation in women (Wiener-Megnazi et al., 2012). Older paternal age that is defined as 40 years and above at the time of conception (Toriello & Meck, 2008) is correlated with

higher frequency of point mutations in the sperm DNA, additional breaks, genetic imprinting, loss of apoptosis, anueuploidies and other chromosomal abnormalities (Singh et al., 2003; Sloter et al., 2004; Thacker, 2004). This higher frequency of chromosomal and DNA damage has been attributed to the number of mitotic replications that the male germ cell undergoes before reaching the meiotic prophase (Crow, 1999). Since each replication carries a possibility of DNA error, older paternal age is considered the major cause of new mutations in the population and the source of accumulated mutations in the human gene pool (Crow, 1999; Sartorius & Nieschlag, 2010).

Furthermore, studies show that DNA damage in men aged 36–57 years is three times more than that of men aged less than 35 years (Aitken, Koopman, & Lewis, 2004; Bray et al., 2006). However, it is worth noting that medical literature suggests that most of autosomal trisomies (aneuploidy) originate from maternal origin, whereas no effect is found to be arising from paternal origin (Zaragoza, Jacobs, James, Rogan, & Sherman, 1994). These aneuploidies that arise from non-disjunction during meiosis (MI1MII) account for 30%–50% of all pregnancies, yet most of them, luckily, are lethal and lead to miscarriage (Hassold, Hall, & Hunt, 2007; Suzumori, & Sugiura-Ogasawara, 2010). However, the opposite is shown with regards to sex chromosome aneuploidies, since they are found to be derived from paternal origin in around 55% of cases (Tempest, 2011; Wiener-Megnazi et al., 2012).

CHAPTER II

LITERATURE REVIEW

A. Effects of Advanced Paternal Age

1. *Advanced Paternal Age and Adverse Reproductive Outcomes*

Paternal age is recently gaining rigorous scientific attention. A large number of studies has explored the association between advanced paternal age and reproductive outcomes, and had consistent results. A case–control study of 13 865 women, derived from Jerusalem perinatal database, highlighted that advanced paternal age is significantly associated with spontaneous abortion even after adjusting for maternal age and other factors (Kleinhaus et al., 2006; Wiener-Megnazi et al., 2012). Similarly, Slama et al. (2005) noted that the risk of spontaneous abortion was two times higher in men aged 45 years when compared to those aged 25 years. The concern about miscarriage becomes of high relevance when the woman of those partners reaches the age of 30 years and above (Sartorius & Nieschlag, 2010). Another study by Nybo Andersen et al. examined 23 821 pregnancies from the Danish National Birth Cohort and established an association between paternal age and fetal death; men aged 50 years or more had twice the risk of fetal loss compared to younger men after adjusting for maternal age, reproductive history and lifestyle during pregnancy (Nybo Andersen, Hansen, Andersen, & Davey Smith, 2004; Wiener-Megnazi et al., 2012).

In addition, a population-based retrospective cohort study of 755,334 births in the United States shed light on the relationship between paternal age and the risk of low birth weight (LBW), small size for gestational age (SGA), preterm birth (PTB), and stillbirth.

Results of this study showed that infants born to men aged 40 to 45 years had a 24% increased risk of stillbirth when compared to those born to men aged 25 to 29 years; however they had a reduced risk of SGA (Alio et al., 2012). Infants born to men aged more than 45 years had also a 48% increased risk of late stillbirth, 19% increased risk of LBW, 13% increased risk of PTB and 29% increased risk of very preterm birth (VPTB) (Alio et al., 2012). Yet, at the same time, infants born to men aged 30 to 39 years had a lower risk of LBW, PTB and SGA in contrast to those born to men aged 24 years or younger who had higher probabilities of having the same adverse outcomes (Alio et al., 2012).

Moreover, it was also shown that advanced paternal age is associated with increased risk of neurodevelopment disorders such as autism, schizophrenia, dyslexia, and reduced intelligence (Grether, Anderson, Croen, Smith, & Windham, 2009; Frans et al., 2008; Brown et al., 2002). A study from the US Collaborative Perinatal Project on a sample of 33, 437 children that aimed to assess the neurocognitive performances of children during infancy and childhood (Saha et. al, 2009) found a significant association between advanced paternal age and poor children scores on all neurocognitive measures. The findings were consistent in direction and effect size after adjusting for potential confounding variables (Saha et. al, 2009).

Another Swedish 10- year birth cohort study on 1075, 588 patients demonstrated a significant association between advanced paternal age and the risk of Autism spectrum disorder (ASD). Children of men aged 50 years or older were 2.2 times more likely to have ASD in comparison to children of men younger than 29 years (Hultman, Sandin, Levine, Lichenstein, & Reichenberg, 2011). Furthermore, a meta-analysis of paternal age and the risk of schizophrenia revealed that the relative risk in men aged 50 years was 1.66

compared to younger men years (Miller et al., 2010). The population attributable risk for men aged 30 years was 10% whereas it was 5% for those aged 25 years (Miller et al., 2010). Yang et al. (2007) conducted also a population-based retrospective cohort study of 5, 213, 248 births in the United States from 1999 to 2000 in order to examine the effect of paternal age on birth defects. The researchers looked at 22 categories of birth defects dividing the age of fathers into eight groups with < 20 years being the youngest group and > 50 years being the oldest group. The results showed a progressive elevation of risk for birth defects with a 15% increased risk for babies born to men aged 50 years old in comparison to those born to men aged 25-29 years (Yang et al., 2007). Statistically significant increased risks for heart defects, esophageal atresia, tracheo-oesophageal fistula, musculoskeletal anomalies, Down syndrome and other chromosomal abnormalities were documented with advanced paternal age when compared to risks of babies born to men aged 25-29 years (Yang et al., 2007).

Other conditions were also examined and thought to be associated with paternal age. Yip and colleagues explored the association between paternal age and leukemia in a population of 4.3 million children, his study showed a significant association with incidence rate ratio of 1.31in the oldest age group (Yip, Pawitan, & Czene, 2006; Wiener-Megnazi et al., 2012). Another study demonstrated that the risk of multiple sclerosis increased steadily as the age of the father increases without seeing such effect for maternal age. This risk reached a 2 fold increase for 51-55 year old men when compared to 21-25 year old men (Montgomery, Lambe, Olsson, & Ekbom, 2004; Wiener-Megnazi et al., 2012).

Moreover, some autosomal dominant diseases were proven to be related to pure paternal age effect. Achondroplasia, Apert syndrome, myositis ossificans and Marfan

syndrome are all autosomal dominant diseases caused by mutation of the fibroblast growth factor receptor 3 (FGFR3) (Jones, Smith, Harvey, Hall, & Quan, 1975; Wiener-Megnazi et al., 2012). Others diseases of skeletal dysplasias, including hypochondroplasia and thanatophoric dysplasia are also due to mutations in FGFR3 gene. Also it is interesting to note that the mutations of this gene increases exponentially with paternal age (Dakouane- Giudicelli et al., 2008; Wiener-Megnazi et al., 2012). In addition, mutations of the FGFR2 gene were proved by genetic analysis of the human sperm to be arising from the paternal germ line and were associated with increased paternal age as well. These mutations are responsible for the Crouzon syndrome, Apert syndrome, Pfeiffer syndrome and all craniosynostotic disorders (Tolarova, Harris, Ordway & Vargervik, 1997; Shotelersuk et al., 2003; Wiener-Megnazi et al., 2012).

Many other studies have documented adverse outcomes similar to those detailed above for schizophrenia (Kuhnert & Nieschlag, 2004; Malaspina et al., 2001), birth defects (Kuhnert & Nieschlag, 2004; Savitz, Schwingl, & Keels, 1991; Yang et al., 2007), autism (Reichenberg et al., 2006) low birth weight (Tough, Faber, Svenson, & Johnston, 2003), stillbirth (Nybo Andersen et al., 2004; De la Rochebrochard & Thonneau, 2002), and spontaneous abortion (De la Rochebrochard & Thonneau, 2002; Kleinhaus et al., 2006; Slama et al., 2005).

Furthermore, epigenetic imprinting or the non-genomic pathway of inheritance is gaining more attention recently, and it might be an additional contribution to the explanation of diseases that are characterized by being multifactorial in origin such as neurocognitive, psychiatric and malignant disorders (Perrin, Kleinhaus, Messinger, & Malaspina, 2010; Wiener-Megnazi et al., 2012). Such alteration at the level of gene transcription is thought to add to the susceptibility of children of older men. The possible

explanation to such mechanism is attributed to the exposure to environmental and nutritional toxics for a prolonged period of time (Wiener-Megnazi et al., 2012).

2. ***Advanced Paternal Age and Maternal Complications***

Studies on advanced paternal age have focused on its effect on the health of the fetus and its wellbeing, yet less literature is found exploring the association between older paternal age and maternal obstetric complications that might be encountered during pregnancy.

We have previously highlighted that advanced paternal age was found to be associated with both spontaneous miscarriage and fetal death; yet at the same time it is thought to be associated with the increased rate of Caesarean sections (C/S). Multiple studies shed light on the link between maternal age and Caesarean delivery (Rosenthal and Paterson-Brown, 1998; Ecker et al., 2001; Paulson et al., 2002; Ahmed et al., 2004; Dhillo et al., 2005). However, a recent study suggested an independent additional effect of paternal age. This Taiwanese study evaluated 310 574 singleton deliveries and verified a rise in the C/S rate along with the rise of the paternal age within all maternal ages (Tang et al., 2006; Sartorius & Nieschlag, 2010).

Furthermore, contradictory results have been found regarding the effect of advanced paternal age on pregnancy duration. Whereas retrospective studies from Canada and USA showed no effect (Basso and Wilcox, 2006; Olshan et al., 1995), other Danish & Italian studies reached an opposite conclusion (Astolfi et al., 2005; Astolfi et al., 2006; Zhu et al., 2005a, b). In the analysis of 1 510 823 Italian birth records, significant results of prematurity were shown for preterm births for women aged 20–24 years and men aged 45– 49 years when compared to the reference group of men aged 25–29 years (Astolfi et

al., 2006) . Similarly, in an analysis of 70 347 singleton births, the Danish group reached the same results for preterm birth and very preterm birth (32 weeks of gestation) for women aged 20–24 years and men older than 50 years when compared to 20–24 year old men. These results were all adjusted for maternal age and other confounders. Nevertheless, it is important to note that this associations between paternal age and preterm birth was attenuated when infants with congenital malformations were excluded (Zhu et al., 2005a,b; Sartorius & Nieschlag, 2010).

Moreover, paradoxical outcomes were reached regarding the association between paternal age and gestational trophoblastic diseases (GTD). While some case control studies showed that higher paternal age was not a risk factor for GTD (Yen and MacMahon, 1968; Matsuura et al., 1984; Messerli et al., 1985; Brinton et al., 1989), another case–control study showed a significant relationship after adjusting for maternal age which is an established risk factor (La Vecchia et al., 1984). In that study, the relative risk of women married to men aged 45 years and older was 4.9 when compared to those married to partners younger than 40. Another study showed that women who are married to men aged more than 45 years had higher risk for complete hydatiform mole with no increase for partial hydatiform mole (Parazzini, La Vecchia, & Pampallona, 1986; Sartorius & Nieschlag, 2010).

Finally, the correlation between advanced paternal age and maternal obstetric complications was investigated by a group of researchers who conducted a population-based retrospective cohort study on 755,334 births in the United States (Alio et al., 2012). The findings underlined that females married to partners over 45 years of age were significantly more likely to experience hypertension in pregnancy, placental abruption and placenta previa. A modest but significant dose–response relationship was seen between

the father's age and the mother's complications of placenta previa and hypertension, with rates escalating with increasing paternal age (Alio et al., 2012).

B. Objectives of the Study and its Significance

Although the age and health status of pregnant women is known to contribute heavily to obstetric complications that might arise during pregnancy (Lampinen, Vehviläinen-Julkunen, & Kankkunen, 2009), little attention has been given to the impact of the age dependent alteration of spermatogenesis and its contribution to the fertilized oocyte.

The correlation between advanced paternal age at conception and maternal obstetric complications during pregnancy has not been widely tested. The literature has addressed this issue in a minimal manner that failed to reveal conclusive results (Harlap et al., 2002; Chen et al., 2006). Therefore, the aim of this study is to add to the international, regional and local literature in regards to this inconclusive debate. For instance, epidemiological studies that have shown significant association between advanced paternal age and preeclampsia during pregnancy (Harlap et al., 2002, García-Ortiz et al. 2011) have been countered by another epidemiological study that showed no association between paternal age and new-onset hypertension in late pregnancy (Chen et al., 2006). The latter argues that the association between advanced paternal age and hypertensive disorders that is observed in previous research is due to the colinearity in the model between maternal age and paternal age (Chen et al., 2006). Furthermore, many studies tried to examine the patterns of hypertensive disorders in relation to the site of placental implantation and reached inconsistent conclusions (Ananth et al., 1997; Newton, Barss, & Cetrulo, 1984; Booth, Beard, Wood, & Gibson, 1962).

At the same time, this is one of the first studies in the Middle East and North Africa (MENA) region where the effect of advanced paternal age at conception on the heath of the woman has not been analyzed. Therefore, our main research question focusing on data from Lebanon is: Does advanced paternal age at conception adversely affect the health of the woman leading to obstetric maternal complications during pregnancy?

The scarcity of information regarding this heath issue makes the problem difficult to assess and consequently less visible to the concerned stakeholders. The broad spectrum of complications stemming from older parenthood makes investigating them all together very difficult. We elected to focus on two major problems, namely: 1) hypertensive disorders of pregnancy, specifically gestational hypertension, pre-eclampsia, eclamplsia, and 2) uteroplacental bleeding, specifically placenta previa and placental abruption.

We hypothesize that advanced paternal age contributes to both disorders. This hypothesis is based on two research results. The first is that paternal genes were determined to be crucial in the normal development and normal function of the placenta (Bartolomei & Tilghman, 1997; Lie et al., 1998). The second is that pregnancy hypertensive disorders involve decreased perfusion or a reduction in uteroplacental blood flow (Roberts & Cooper, 2001); similarly, trouble in placentation is a common factor in uteroplacental bleeding disorders.

Therefore, in order to achieve the goal of exploring the effect of paternal age on both disorders, our specific objectives will be:

1. To determine whether advanced paternal age is associated with increased maternal risk of hypertensive disorders of pregnancy, independently of advanced age of the mother, her health characteristics and her lifestyle.

2. To determine whether advanced paternal age is associated with increased maternal risk of placenta previa and placental abruption, independently of advanced age of the mother, her health characteristics and her lifestyle.

C. Hypertensive Disorders of Pregnancy

1. *Definition of Hypertensive disorders of pregnancy*

The National US Working Group on High Blood Pressure in Pregnancy has classified hypertensive disorders of pregnancy into 4 categories:

1. Chronic Hypertension: this category is defined as a measurement of blood pressure of 140/90 mm Hg or more on two separate occasions. These measurements should be before the 20^{th} week of gestation or persistent high measurements after the 12^{th} week postpartum (National Working Group on High Blood Pressure in Pregnancy, 2000).
2. Gestational hypertension: this category is defined as a measurement of high blood pressure without proteinuria after the 20^{th} week of gestation (National Working Group on High Blood Pressure in Pregnancy, 2000). This diagnosis is a provisional one since it includes eventually women with preeclampsia or chronic hypertension and women diagnosed with transient hypertension of pregnancy. It is also noted that 50 % of women with this diagnosis between the 25^{th} and the 35^{th} week of gestation have been found to develop preeclampsia (Barton, O'brien, Bergauer, Jacques, & Sibai, 2001).
3. Preeclampsia: this category is defined as a multi-organ disease with high blood pressure and proteinuria after the 20^{th} week of gestation gestation (National Working Group on High Blood Pressure in Pregnancy, 2000). HELLP Syndrome

is a complication that occurs in 20% of cases of severe preeclampsia (Sibai et al., 1993). It is characterized besides severe preeclampsia by hemolysis, elevated liver enzymes, and low platelet count (Weinstein, 1982).

4. Eclampsia: this category is defined as a condition of hypertension with an eclamptic seizure. Eclampsia might occur in severe preeclampsia or it might be in a woman with minimally elevated blood pressure and no proteinuria. It is noted that 30 to 60 percent of eclamptic women have been found to have mildly elevated blood pressure (National Working Group on High Blood Pressure in Pregnancy, 2000; Sibai, 2005).

2. *Prevalence and Burden of the Disorders*

Hypertensive disorders during pregnancies are the most common complications affecting 6 to 8 percent of pregnancies in the United States (National Working Group on High Blood Pressure in Pregnancy, 2000). In the report of the Global Burden of Disease, pregnancy hypertensive disorders ranked 75th in terms of DALY in 1990, and were found to be responsible for 6% of the burden of all maternal conditions. At the same time, death due to pregnancy hypertensive disorders was estimated to represent 13% of all maternal deaths (World Health Organization, 2003).

Moreover, it is estimated that 50,000 women die yearly from preeclampsia worldwide (Pipkin, 2001). Its incidence rate varies worldwide from two to ten percent depending on the population and the diagnostic criteria (World Health Organization, 1998; Sibai, 2005). In 2000, the incidence rate of pre-eclampsia was estimated to be 2.8% of live births in developing countries whereas it was estimated to be 0.4% of live births in developed countries (World Health Organization, 2003). On the other hand, the incidence

rate of eclampsia was estimated to be 2.3% of pre-eclampsia cases in developing countries whereas it was estimated to be 0.8% of pre-eclampsia in developed countries (World Health Organization, 2003). These rates were estimated with an assumption of having pre-eclampsia/eclampsia account for 50% of all hypertensive disorders (World Health Organization, 2003). In addition, it is important to note that the incidence rates for pre - eclampsia and eclampsia in the EMRO region were estimated to be 2.8 % and 2.3 % respectively in the year 2000 (World Health Organization, 2003) .

Hypertensive disorders are a serious hurdle and one of the major causes of both maternal and neonatal morbidity and mortality. Premature delivery, placental abruption, fetal growth retardation and even fetal death are all consequences of this disorder (Zhang, Zeisler, Hatch, & Berkowitz, 1997). Maternal consequences are no less significant; heterogeneous manifestations of multi organ involvement that may include hemolysis, elevated liver enzymes, low platelet count, seizure, renal damage are all common clinical presentation and problems (Rmnaug et al., 2000).

3. *Risk Factors of the Disorders*

Previous studies suggest that pre-eclampsia/eclampsia has multifactorial etiologies. It is well established that nulliparity is a risk factor (Goldman-Wohl et al., 2000), along with advanced maternal age, obesity, diabetes, insulin resistance, hyperlipidemia, family history of preeclampsia and eclampsia, previous pregnancy that was complicated with pre-eclampsia, multiple gestation, molar pregnancies, hemolytic disease, and partner change between pregnancies (Zhang et al., 1997; Sibai, 1991; Taylor, 1997). At the same time and contrary to expectations, smoking during pregnancy was found to be protective from hypertensive disorders due to its vaso-dilating effect (Zhang

et al., 1997; Sibai, 1991), and regular physical activity was also noted to play a protective role (Saftlas, Logsden-Sackett, Wang, Woolson, & Bracken, 2004).

Furthermore, a meta-analysis of all published studies that were carried out before 2010 highlights that ART-oriented pregnancies especially those that occurred using in-vitro fertilization techniques are associated with increased risk of gestational hypertension and preeclampsia in comparison to non-ART pregnancies even after adjusting for all confounders (Thomopoulos et al.,2013). A Clinical trial that is conducted to explore the association between invasive ART, non-invasive ART and preeclampsia concluded that invasive ART is associated with 2.7-fold increased risk of preeclampsia yet non-invasive ART failed to be a predictor (Shevell et al., 2005).

4. ***Pathophysiology and Causes of Pre-eclampsia/Eclampsia***

The confusion that surrounds the pathophysiology and the causes of pre-eclampsia led to naming it the "disease of theories" (Roberts & Cooper, 2001). Nevertheless, progress has been made during the past decade towards better understanding of the disease. Although the condition is widely recognized to be related to abnormal implantation and abnormal development of the placenta that involves much more than hypertension and renal dysfunction manifested by proteinuria (McInnes & Michaud, 2003), pre-eclampsia is now described as a 2-stage process (Saftlas, Beydoun & Triche, 2005).

It begins by an impaired trophoblastic invasion and a poor remodeling of maternal spiral arteries that consequently leads to a defective placentation (Saftlas et al., 2005; Roberts & Hubel, 1999; Aldrich, Verp, Walker, & Ober, 2000). The result of this run is a poor placental perfusion that creates a hypoxic environment which in turn causes vasoconstriction and increased maternal blood pressure. This poor perfusion is

compromised further by an activation of the coagulation cascade and a complex sequence of events leading to systemic vascular endothelial disruption which represents the second stage of the process (Saftlas et al., 2005; Dekker& Sibai, 1999; Clausen, Djurovic, Brosstad, Berg, Henriksen, 2000).

5. *Theories & Studies on the Paternal Role*

a. Genetic Basis of Pre-eclampsia/Eclampsia

Preeclampsia is considered a disease of pregnancy that is resolved upon delivery. This implies the presence of a role or an interaction between the fetus and/or the placenta with some of the maternal factors (McInnes & Michaud, 2003). It is speculated that the development of the disease may require feto-placental defects from one side and maternal susceptibility to hypertensive and renal disease from the other side (McInnes & Michaud, 2003; Roberts & Lain, 2002; Lachmeijer et al. 2002). Therefore and in follow up to this theory, it is thought that the inherited genes passed from the partner to the baby carry an associated risk besides the risk inherited from the maternal genes (McInnes & Michaud, 2003). Moreover, it has been shown that the change in partner plays a significant risk factor for eclampsia and pre-eclampsia in multiparous women, which points to the importance of the paternal genes role (Roberts & Cooper, 2001; Mills, Klebanoff, Graubard, Carey, & Berendes, 1991; Li & Wi, 2000). In addition, results from a study on twin sisters emphasized the fact that pre-eclampsia is not a disease of maternal basis strictly (Treloar, Cooper, Brennecke, Grehan, &Martin, 2001; McInnes & Michaud, 2003). Other studies that support the theory and the role of fetal contribution in the development of preeclampsia showed that the period of cohabitation (Roberts & Cooper, 2001; Robillard, Dekker, & Hulsey, 1999), the period of maternal exposure to paternal

antigens, the use of barrier contraception, nonpartner donor insemination and oocyte embryo donation, are significant factors that affect the susceptibility to develop preeclampsia (Saftlas et al., 2005; Robillard, Hulsey, Dekker, & Chaouat, 2003; Koelman et al., 2000; Salha et al., 1999). At the same time it was shown that having had a previous abortion contributes to a reduction of the risk of developing preeclampsia in the next pregnancy if it is from the same partner. This reduction of risk is explained by the previous exposure of the mother to the paternal antigen (Harlap et al., 2002; Seidman et al., 1989; Eras et al, 2000).

A study that examined the risk of developing pre-eclampsia in a pregnancy by a man who already fathered a pre-eclamptic pregnancy in a different woman was found to be 1.8 (95% CI 1.2 to 2.6) (Lie et. al, 1998). Therefore, although preeclampsia is believed to have a genetic root (Saftlas et al., 2005; O'Brien, Dausset, Carosella, & Moreau, 2000; Kilpatrick, Liston, Gibson, & Livinstone, 1989), but the exact basis of this genetic interplay remains ambiguous. Gene to gene interactions between the mother and the fetus in addition to a complex genetic maternal susceptibility to pre-eclampsia remain the most credible explanations (Saftlas et al., 2005; Zhang et.al, 1997; Kilpatrick, 1999).

b. Immunogenetic basis of Preeclampsia

Preeclampsia at least in part is also thought to be a consequence of abnormal reaction of the maternal immune system to the antigenic challenge of the fetoplacental allograft (Saftlas et al., 2005; Sibai, 1991).This is the basis of the "immune maladaptation hypothesis" that tends to point out to the immunogenetic basis of preeclamsia (Saftlas et al., 2005; Robillar et al., 2003; Koelman et al., 2000). Normal pregnancy is characterized by having a large number of placental factors that induce immunosuppressive activity in

order to prevent the rejection of the fetus. This phenomenon is seen as a Th2 cell– driven phenomenon (Wegmann, Lin, Guilbert, & Mosmann, 1993; De Groot et al., 2010). Pregnancy complicated with abnormal placentation and spontaneous abortion is demonstrated to have a predominant Th1-type of immunity (Krishnan, Guilbert, Wegmann, Belosevic, & Mosmann, 1996; De Groot et al., 2010). Accordingly it is hypothesized that since preeclamptic pregnancies are characterized by abnormal placentation, preeclampsia might be a result of a disturbed maternal immune tolerance to the fetus (Sargent, Borzychowski, & Redman, 2006; De Groot et al., 2010).

The fetus is considered a semiallograft with 50% of its histocompatibility antigens are coming from the father. This antigenic dissimilarity might trigger a strong maternal alloimmune reaction that may lead to abnormal placentation and consequently to the activation of maternal vascular endothelium (De Groot et al., 2010). It is thought that pregnancies with preeclampsia can be compared to transplant rejection studies by having the fetus matched up with the transplant (De Groot et al., 2010).

Furthermore, it is worth noting that all immune responses are controlled by the genes located in the HLA (Human leukocyte antigens) area which is a strongly linked section of chromosome 6 (Saftlas et al., 2005; Williams et al.1999; Chaouat et al., 1997). The HLA antigens play a major role in recognition, acceptance and rejection of transplanted organs, and similarly it plays a major role in the maternal-fetal immune tolerance (Saftlas et al., 2005; Aldrich et al., 2000; Goldsby, Kindt, & Osborne, 2000; Schmidt & Orr, 1993).

6. ***Advanced Paternal Age & Hypertensive Disorders***

Publications that explore the role of the father's characteristic in pre-eclampsia & eclampsia are rare; those that looked at the effect of paternal age are even scarcer. Harlap et.al (2002) looked at the incidence of preeclamplsia in a large cohort of 81,213 births in Jerusalem between 1964 and 1976 for Jewish and Palestinian residents of the city and its rural county. The potential association of paternal age and preeclampsia was in question after a 21- to 33-year follow-up study on the Jerusalam population. This follow up study revealed that paternal age played a strong risk factor for schizophrenia (Malaspina et al., 2001; Harlap et al., 2002). Hence, since preeclampsia in turn was a known risk factor for schizophrenia, the association with paternal age merited investigation. The authors found that 1.6% (N=1,303) of pregnancies were complicated with pre-eclampsia. Harlap and colleagues went further by exploring the presence of an association between the occurrence of preeclampsia and paternal age. Their results showed that the distribution of preeclamsia cases by paternal age was as follows: less than 0.3% for men aged less or equal to 20 years, 4.4% for men aged 45 years and above, 1.4% for men aged 50 years and above (Harlap et al., 2002). The result of this investigation supported the speculation that paternal age plays a role in developing pre-eclampsia although the effect of maternal age was shown to be stronger. The odds ratios for men aged 35–44 years and for those aged 45 years and above were 1.24 (95% CI =1.05–1.46) and 1.80 (95% CI =1.40 –2.31) respectively when compared to the group aged 25–34 years. The effect of paternal age was consistent within subgroups of many other variables.

Another more recent study that derived data from vital registration in the United States looked into a large cohort of 9,302,675 singleton live births between 1995 and 1998. Chen and colleagues chose to explore the association between new-onset

hypertension (NOH) in late pregnancy that included gestational hypertension, preeclampsia, eclampsia, and the couple's age. It was believed that analyzing maternal age and paternal age in the same multivariate model in the presence of a high significant correlation may lead to colinearity (Chen et al., 2006; De la Rochebrochard & Thonneau, 2002). Therefore, a new variable called couple's age was created out of combining each of the four maternal age groups with all the four paternal age groups.

The incidence rate of NOH in late pregnancy among the study population was found to be 3.80% (Chen et al., 2006).Whereas advanced maternal age was seen to be associated with higher risk of NOH in late pregnancy among nulliparous and multiparous women, advanced paternal age was seen to be associated with higher risk of NOH in late pregnancy among multiparous women (Chen et al., 2006).

In comparison with couples aged 20 to 34 years for both fathers and mothers, older maternal age above 35 years was found to be associated with higher risk of NOH in late pregnancy except for couples with men aged below 20 years. Whereas younger maternal age below 20 years was found to be associated with lower risk of NOH in late pregnancy except for couples with men aged above 45 years (Chen et al., 2006). Furthermore, among nulliparous and multiparous women, the associations between couple age and NOH in late pregnancy were shown to be similar yet the magnitude of this association was more evident among multiparous women. After stratification by maternal age, no significant association between paternal age and NOH in late pregnancy was seen either in nulliparous or multiparous women (Chen et al., 2006).

D. Uteroplacental Bleeding Disorders

1. *Definition & Burden of the Disorders*

Uteroplacental bleeding problems, with placenta previa and placental abruption as the most common disorders under this umbrella, are associated with high rate of morbidity and mortality to the mother and to the fetus (Ananth &Wilcox, 2001). Placental abruption and placenta previa are two serious obstetric complications that are considered among major causes of perinatal deaths, prematurity, intra- uterine fetal growth retardation and stillbirth (Matsuda et al., 2011; Matsuda, Maeda, & Kouno, 2003; Naeye, 1978). Both conditions represent placental abnormalities that may lead to third trimester bleeding, antepartum and postpartum hemorrhage (Matsuda et al., 2011). Although Placental abruption is uncommon, it remains a serious problem that is defined as a premature separation of the placenta from the uterine wall (Matsuda et al., 2011; Jaffe, 1981); whereas placenta previa signifies a serious problem and is defined as having a placenta located at the internal cervical os or the internal orifice of the cervix uteri (Matsuda et al., 2011; Cunningham et al., 2005).

2. *Prevalence of the Disorders*

The prevalence of placenta previa and placental abruption in the United States is estimated to be 3–5 per 1,000 pregnancies and 5–20 per 1,000 pregnancies respectively (Getahun, Ananth, & Vintzileos, 2006; Ananth, Smulian, Demissie, Vintzileos, & Knuppel, 2001; Lowe & Cunningham, 1990). Both abnormal placentations account for 1.7% of all maternal deaths in the US (Atrash et al., 1990). We could not come across other than extrapolated statistics to estimate placenta previa in the Middle East and North Africa. The 2004 International Database of the US Census Bureau projected 277 cases in

Lebanon with an estimated population of 3,777,218 (US Census Bureau, 2004) where 525, 237 women are in the childbearing age of 15 to 49 years (United Nations Population Fund, 2004). Similarly, Jordan was estimated to have 412 cases with an estimated population of 5,611,202(US Census Bureau, 2004) where 1,297,718 women are in the childbearing age of 15 to 49 years (United Nations Statistics Division, 2004). Saudi Arabia was estimated to have 1,896 cases with an estimated population of 25,795,938 (US Census Bureau, 2004) where 4,503,586 women are in the child bearing age of 15 to 49 years (United Nations Statistics Division, 2004).

3. *Risk Factors of the Disorders*

Placental abruption and placenta previa have multifactorial etiologies. risk factors that have been identified previously include advanced maternal age, multiparity, smoking, drug abuse, rapid uterine decompression, short umbilical cord, prolonged premature rupture of membranes, chorioamnionitis, folate deficiency, chronic hypertension, preeclampsia, and previous pregnancy that was complicated with placental abruption or placenta previa (Kramer et al., 1997; Baron & Hill, 1998; Matsuda et al., 2011). Furthermore, in a nationwide population-based study on 845 384 pregnancies in Norway between 1988 and 2002, conducted to explore the influence of ART on the risk of placenta previa, highlighted that singleton pregnancies conceived by ART were at six-fold higher risk of developing placenta previa when compared to naturally conceived pregnancies (Romundstad et al., 2006). Additionally, a retrospective cohort study conducted in England underlines that there is a 1.6% increased risk to placenta previa in a subsequent pregnancy after CS delivery at first birth (Gurol-Urganci et al., 2011). Another retrospective cohort study using the 1989–1997 Missouri longitudinally linked data were

performed underlines that women with a cesarean first birth were more likely to suffer from an abruption in the second pregnancy when compared with women who had a vaginal first birth (Getahun, Oyelese, Salihu, and Ananth, 2006).

4. *The Paternal Role of in Uteroplacental Bleeding Disorders*

The discovery of the vital role that paternal genes play in the normal development and function of the placenta (Getahun et al., 2006; Bartolomei & Tilghman, 1997) led to the speculation that paternal characteristics may have an important role in the genesis of placenta previa and placental abruption (Getahun et al., 2006; Bartolomei & Tilghman, 1997; Lie et al., 1998). A genetic study conducted on healthy infants in Japan demonstrated that inheriting IGF2 CTG haplotype from the paternal allele results in reduction of fetal and placental growth (Nagaya et al., 2009).

An interesting inverse association was described between placenta previa and late development of pregnancy hypertension. This association was observed four decades ago by Bieniarz who exposed his reflection by stating that "There is no eclampsia in placenta previa cases, and on the other hand, in severe toxemia of late pregnancy low implantation of the placenta is met only exceptionally" (Bieniarz, 1958, p. 444; Ananth, Bowes, Savitz, & Luther, 1997). Leibermann, Fraser, Kasis, & Mazor (1991) tried to explain the same observation by noting that in a situation of a low- lying placenta, the isthmic segment of the ascending branch of the uterine artery's has a freer passage and a wider diameter than the distal parts of the blood vessel (Libermann et al., 1991). This situation in turn allows better blood flow and prevents hypoxia of the trophoblast which is the main the reason for pregnancy hypertension (Libermann et al., 1991; Ananth et al., 1997).

Different studies tried to examine the patterns of hypertensive disorders in relation to the site of placental implantation and reached inconsistent conclusions (Ananth et al., 1997; Booth, Beard, Wood, & Gibson, 1962; Newton, Barss, & Cetrulo, 1984). A large population-based Canadian cohort of 121,082 singleton pregnancies examined the risk of pregnancy-induced hypertension among pregnancies complicated by placenta previa between 1980 and 1993 in comparison to pregnancies with fundally implanted placentas. The relative risk of placenta previa was found to be 1.2 (95% CI= 0.4 -3.7) among women with chronic hypertension when compared to normotensive women. Nevertheless, the risk of pregnancy-induced hypertension among women with placenta previa was decreased to half with a relative risk of 0.5 (95% CI= 0.3- 0.7) (Ananth et al., 1997).

A case-cohort design was carried out to explore and compare the risk factors of placental abruption and that of placenta previa. This study was conducted in Japan and examined 242 715 singleton births of both live birth and fetal death from 2001 till 2005. The results revealed that abruption and previa were reported in 1.01 % and 1.32 % respectively among the total births. Whereas pregnancy-induced hypertension was noted as a risk factor for abruption with an adjusted RR of 4.45 (95%CI= 3.68–5.38), it was not observed as a risk factor for previa with an adjusted RR of 0.40 (95%CI= 0.30–0.54) (Matsuda et al., 2011).

Moreover, many studies assessed the relationship between maternal characteristics and the risks of uteroplacental bleeding. Yet less attention was given to the association between paternal characteristics and uteroplacental bleeding disorders (Getahun et al., 2006). It was noticeable that despite shedding light on the role of paternal genes, paternal characteristics continued to be missing from birth certificates. According to the report of the national vital statistics of the United States, for 14% of the birth certificates in the year

2000 paternal age was missing (Getahun et al., 2006; US Department of Health and Human Services, Center for Disease Control and Prevention, 2002). A retrospective cohort study using the U.S. National database for births and infant deaths from 1995 through 2001 looked at the association between missing paternal age and the risk of uteroplacental bleeding disorders among 26,336,549 singleton pregnancies. Interestingly, the relative risk for placental abruption was noted to be 1.30 (95% CI 1.24, 1.37) among pregnancies with missing paternal age; nonetheless no clear pattern of association was found between the missing paternal characteristics and placenta previa (Getahun et al., 2006).

E. Public Health & Policy implications

With increased proportions of women and men who are delaying marriage and births to older age in Lebanon and in the region, optimizing obstetric counseling and tailoring it to the need of this group is critical. Therefore, we aspire that the results of this study draw the attention of health care providers to the needs of this specific population of older parents. An approach to collect information on fathers' age and health characteristics during prenatal care and prenatal counseling is desirable. This approach would enable healthcare providers to attend to masked risk factors and consequently to ameliorate pregnancy outcomes. At the same time, similar data collection needs be adopted by hospitals and birth registries in order to enable researchers to better understand and explore the effect of paternal age and characteristics on pregnancy and neonatal outcomes. Tailoring a comprehensive approach that accounts for biological, social and physical influences contributed by the father, in addition to those of the mother, is the best preparation for a healthy pregnancy outcome. Young healthy pregnant women might be

seen as a low risk group; however accounting for the risks that are arising from an older partner might be a good alert for close prenatal monitoring, and a good clinical tool for an early intervention and management of potential obstetric complications.

This study adds to the body of knowledge in regards to the contribution of fathers' characteristics to reproductive outcomes. Building evidence always requires additional research and replication of results. Once enough evidence is available to support the correlation between paternal characteristics and unfavorable outcomes, alerting policy makers to the needs of this group of older parents, and making recommendations about best management approaches and treatment modalities for those women would be fundamental to avoid, or to at least to minimize, traumatic obstetric experiences and devastating fetal outcomes. Such recommendations would be vital especially for rural health settings in poor developing countries where antenatal care is not advanced and usually provided by other than obstetricians.

Introducing fathers' age to birth certificates and subsequently to vital registration is another important mean for a good surveillance of maternal obstetric complications, fetal congenital malformations, adverse outcomes and deaths. Lebanon lacks complete and comprehensive birth registration that is informative for prioritizing the health agenda and establishing a baseline for reproductive and maternal health problems. It might be ambitious for this study to push for a complete and comprehensive birth registration, yet it will be at least a reminder that minimal and low-cost measures like adequate documentation is a good basis for surveillance system that defines better planning of scarce health resources.

Reproductive choices of couples remain indeed private individual matters, and influenced by interpersonal characteristics of the couples themselves, societal norms and

economic factors. Respecting those choices is essential and at the core of ethical principle of valuing autonomy. However, ensuring that those choices are taking into consideration the drawbacks and the risks associated with postponing birthing to when both parents are at an advanced age is at the core of the efforts made by public health professionals. Spreading awareness and disseminating our research results about the increased relative risk of obstetric complications remain the most ultimate aim of this study so that we ensure that couples' reproductive choices are in fact informed choices, and that research studies are conducted aiming at improving the health of our population.

CHAPTER III

MATERIALS AND METHODS

A. Research Design

This is a retrospective cross sectional study using data from the National Collaborative Perinatal Neonatal Network (NCPNN). Lebanon is a small country that lacks national registries to collect data on births over the years. The only available system that captures all births is the civil registry of the Ministry of Interior. However, this registry is established to document birth and generate legal documents for the newborn, rather than being an ongoing surveillance system for the health status of pregnant women and their newborns. In addition this registry collects basic information that cannot serve as a comprehensive tool for researchers to explore associations between a specific exposure and an outcome. Nevertheless, Lebanon is one of the rare countries of the region where almost all deliveries take place in hospitals. The private sector in Lebanon is the dominant sector in terms of health care deliveries. For instance the number of hospitals that are recognized by the Ministry of Public Health and allowed to be subsidized for rendering services is 138 private hospitals and 25 public hospitals distributed across all Mohafazats, and serve the whole Lebanese population. The fact that 84.66 % of hospitals are owned by the private sector is a reflection by itself of the composition and the nature of the healthcare system in Lebanon.

NCPNN is a non-governmental hospital-based registry that accounts for 30% of the total Lebanese births. The collaborative network grew gradually from 10 hospitals in 2002 to reach 29 member hospitals distributed across Lebanon in 2012. NCPNN is a personal

effort from its director and a group of health care providers who believe in the necessity of creating a birth registry as a way to improve the healthcare of pregnant women and their newborns. This is the only registry in the country that captures information on a sample of deliveries that take place in Lebanon. The member hospitals of the network represent 18.1% of the private hospitals in Lebanon and 16% of the public hospitals. They are distributed across all Lebanon but do not constitute a good representation of all Mohafazats. Beirut and North Lebanon are considered well represented in the NCPNN as Mohafazats, whereas South Lebanon, Nabatieh, Bekaa and Mount Lebanon are still underrepresented in the Network.

The establishment of the NCPNN registry is governed by the Institutional Review Board at the American University of Beirut. The NCPNN registry involves ongoing data collection on pregnant women admitted for delivery and their newborns. The medical charts' review of the records pertaining to mothers and newborns takes place after securing informed consent from the woman. The collected data covers medical history pertaining to antenatal care, intrapartum care, and immediate postpartum care and complications. Similar neonatal chart reviews are carried out to obtain neonatal outcomes. A complementary face -to- face structured interview is conducted before hospital discharge by skilled survey interviewers to collect data on socio-demographic factors.

The NCPNN computerized system represents the data source for this study. It is a reliable source that is characterized by accuracy, comprehensiveness due to the large number of collected variables, and also by being quite complete in some areas of the collected information. The electronic system undergoes several quality checks during the process of data entry to detect inconsistencies and illogical fallacies. In cases of

inconsistencies, the NCPNN staff refers back to the hospital's original data source to validate and correct the collected information.

All women admitted for delivery in one of the 29 member hospitals of the NCPNN between the years 2002 and 2012 constitutes our study sample. This accounts for 182,434 live births and reflects a standard obstetrical population over time.

For the purpose of this study, we relied on the documentation of medical records in the labor-ward for the diagnosis of hypertensive disorders of pregnancy and uteroplacental bleeding. Definition of both disorders in pregnancy is constant and this ensures internal reliability. The NCPNN data distinguishes clearly between the different types of hypertensive disorders including chronic hypertension that might be a pre-existing maternal condition prior to pregnancy.

Our exposure of interest is advanced paternal age. The measure of this concept is the age of the father either in completed years at the time of delivery or the recorded date of birth, or the combination of both. Collection of this variable takes place in its majority during the face- to- face interview with mothers. In rare cases, it is collected from the women's medical chart if it is recorded part of the antenatal history, or if the identity of the father is present as part of the legal documents provided upon hospital admission. On the other hand, our outcomes of interest are maternal hypertensive disorders mainly preeclampsia, eclampsia, and maternal uteroplacental bleeding disorders mainly placental abruption and placenta previa.

Variables on both exposure and outcome were retrieved from the NCPNN database, and originate basically from the medical records. Covariates of previously identified risk factors that might act as potential confounding factors to the relationship

between paternal age and both hypertensive disorders and uteroplacental bleeding disorders were retrieved from the database as well.

The established NCPNN database is a rich source of information that comprise many of the identified risk factors that are divided into socio-demographic information, maternal lifestyle factors, maternal obstetric history, maternal chronic conditions, pregnancy related complications, delivery characteristics, and fetal outcome. Measures of these concepts are all part of the NCPNN questionnaires .The measures are direct variables of "yes" for availability of the condition or "No" for its absence. No proxy measures are used for any of these concepts that are listed above.

B. Data Management

For the sake of this study, I carried out extensive data cleaning to ensure that all potential data entry errors are corrected. I also merged together variables that were collected in different format over years but refer to same conditions or characteristics. Frequency distributions were generated for all variables to check for variability and outliers and to decide on grouping of data. This frequency run showed that we had missing values in almost all of our variables. The percent missing values ranged from 3.1% in some of the variables and reached a maximum of 50.8% in other variables. The table below shows the percent missing records in our exposures of interest:

Table1: Percent missing records in father's age and maternal age

Variable's Name	Missing Records		Valid Records	
	N	%	N	%
Father's age	37505	20.6	144,307	79.4

Maternal age	12012	6.6	170422	93.4

The incidences of hypertensive disorders and uteroplacental bleeding disorders in our study sample inclusive of our missing records were: 0.9 % for preeclampsia representing 1654 cases, 0.1% for eclampsia representing 254, 0.2% for placenta previa representing 427 cases and 0.3% for placental abruption representing 460 cases.

1. Exclusion Criteria

At this stage of exploring our data, we decided to exclude all records of missing father's age and all records of missing maternal age for both hypertensive disorders and uteroplacental disorders. In addition and for the analysis related to hypertensive disorders, we excluded all records of mothers who suffered from chronic hypertension (N= 622 cases) since this condition is a persisting one and our target is to assess the risk of developing hypertension due to paternal age.

2. Imputation Technique

a. Imputation to the Mode

Imputation was carried out to overcome the problem of missing values. Imputation to the mode which is "no", reflecting absence of the condition or the characteristic, was carried out on the following variables:

Consanguinity between the couple, cigarette ever smoking during pregnancy, arguile ever smoking during pregnancy, alcohol consumption during pregnancy, maternal employment status during pregnancy, chronic maternal diabetes, gestational diabetes, chronic maternal renal problems, maternal cardiovascular problems, maternal hemolytic diseases, maternal

chronic hypertension, maternal thyroid problems, maternal respiratory problems, birth defects, use of assisted reproductive Technology, previous neonatal death <28 days, previous premature delivery, placenta previa, placenta abruptio, preclampsia, eclampsia, prolonged rupture of membrane >4 hours, intrapartum fever >38, anterpartum anemia, previous cesarean sections/Myomectomy or surgeries of the uterus, oligohydraminios, polyhydraminios.

The only variable that was imputed to "yes" as the mode was "prenatal care during pregnancy". For paternal and maternal education, the mode was "intermediate level" of schooling; for paternal and maternal religion, the mode was "Muslim"; for the hospital admitted class during delivery, the mode was "3rd class"; and for the type of gestation whether it is a multiple pregnancy or not, the mode was "single gestation". All these variables were imputed to their respective mode accordingly.

b. Imputation to the Mean

Imputation to the mean of 0.96 for the variable of "household crowding index" was performed. Similarly, imputation to the mean for the "maternal pre pregnancy weight", the "weight gain during pregnancy" and the "pre-pregnancy Body Mass Index (BMI)" was done. However, in order to increase the accuracy of the imputation for these three variables, we divided our study sample into subsets according to maternal age. Six subsets of 5-year intervals were created: ≤20 years, 21-25 years, 26-30 years, 31 -35 years, 36-40 years and ≥41. We calculated the mean of each subset separately in regards to the pre-pregnancy weight, weight gain and pre-pregnancy BMI; then we imputed to the mean of each subset independently.

The table below shows the mean of each subset that was used for imputation of missing records:

Table 2: Means of pre-pregnancy weight, BMI and weight gain by subsets of Maternal age

	Means					
Maternal Age in Years	≤20	21-25	26-30	31 -35	36-40	≥41
Pre pregnancy weight (Kg)	59.54	61.29	62.78	64.05	65.34	66
Weight gain during pregnancy (Kg)	12.76	12.94	12.94	12.83	12.65	12.49
Pre pregnancy BMI (kg/m^2)	22.82	23.27	23.69	24.16	24.73	25.12

c. Non-Imputed Records

The variable related to the "year of birth" was a complete record; thus no imputation was done in this regards. Additionally neither the number of "gravida" nor the number of "abortions" was imputed in order to ensure reflecting accurate results and to reduce the margin of errors.

d. Final Study Sample

After imputation and excluding records of missing maternal age, father's age and chronic hypertensive cases, we ended up by having 143,416 deliveries of valid records for analysis related to hypertensive disorders. The incidence rate was 0.9% for preeclampsia (N= 1310) and 0.1% for eclampsia (N=193). As for the analysis related to uterplacental disorders, we ended up by having 143, 949 deliveries of valid records with an incidence

rate of 0.3% for placenta previa (N=372) and an incidence rate of 0.3% for placental abruption (N=365).

C. Data Analysis

The aim of this study is to add to the literature and to help address some of the controversies that were highlighted earlier pertaining to the association between hypertensive disorders and paternal age. We did not plan to replicate one of the studies that were published, thus we had to utilize a sophisticated statistical technique to meet our aim. The statistical approach had to address the problem of high correlation between maternal age and paternal age that is leading to co-linearity when the two variables are to be analyzed together in the same multivariate model. Consequently we elected to utilize Propensity Score Regression Adjustment (PSRA) as an advanced modality for our analysis (Rosenbaum & Rubin, 1983). PSRA is usually used for observational data, and it is a step further from logistic regression because it employs besides logistic regression, the propensity score method to reduce bias when estimating the effect of an exposure on the outcome.

A propensity score is the conditional probability of developing a disease (for example preeclampsia) given certain conditions/characteristics (i.e. observed covariates). It is a summary score for all confounders and is used to adjust for the covariates between cases and control and thus it helps create counterfactual groups. This summary score is usually obtained from logistic regression.

Before embarking on analysis, descriptive statistics were generated for all outcome and independent variables. Some figures were also generated to visualize our data. Then, the first step in our analysis was to create a multivariate unconditional logistic

regression model that includes all covariates. In building our model and deciding on including or excluding a specific covariate, we chose to follow the stricter approach of having a non-parsimonious model.

Parsimonious model is usually the simplest plausible model with the fewest possible number of variables. In this model, only variables that showed significance of p-value ≤ 0.2 at the bivariate level are included in the multivariate analysis. However, this approach might lead to accidental omission of potential predicators that failed to reach statistical significance. On the other hand, the non-parsimonious model that was applied in our analysis allows the inclusion of all potential covariates regardless of their statistical significance. This approach is a robust way of analyzing data, yet its downside comes from the probable loss of the effect of the predictor on the outcome from the excessive adjustments.

The second step after fitting our model, was calculating the probability of the disease for each woman in the study sample given her health conditions and her socio-demographic conditions. These conditional probabilities constituted the propensity scores.

The final step was to run another multivariate logistic regression where the propensity scores were included as a continuous variable along with paternal age which was also included as a continuous variable. Tests of hypothesis were two tailed with a type 1 error rate at 5%. The odds ratio was then calculated to measure the degree of association between the risks of developing one of the two disorders with paternal age. All data was analyzed using SPSS Statistical package, Version 20.

D. Confounders

1. *The Confounders for Preeclampsia/Eclampsia*

The confounders that were included in the first multivariate model for hypertensive disorders were 30 variables: Maternal age, year of birth, maternal pre-pregnancy weight, maternal weight gain, maternal pre-pregnancy BMI, number of gravidas, number of abortions, household crowding index, consanguinity, hospital admitted class during delivery, arguile ever smoking during pregnancy, cigarette ever smoking during pregnancy, alcohol consumption during pregnancy, maternal education, paternal education, mother's religion, father's religion, prenatal care, maternal employment status during pregnancy, type of gestation, gestational diabetes, chronic diabetes, chronic renal problems, cardiovascular problems, use of assisted reproductive technology for the current pregnancy, previous neonatal death <28 days, previous premature delivery, placenta previa, placenta abruptio, and birth defects.

Only maternal age, year of birth, maternal pre-pregnancy weight, maternal weight gain, maternal pre-pregnancy BMI, number of gravidas, number of abortions and household crowding index were used as continuous variables. All other variables were treated as dichotomies or sets of dummies. The ability to accommodate such a large number of confounders is another advantage of PSRA in contrary to logistic regression that can accommodate only 10 confounders for one outcome.

The confounders that were used for the uteroplacental bleeding were almost the same with some minor additions that are specific to placenta previa and placental abruption. 37 variables were included in the multivariate model created for placenta previa, and 39 variables were included in the model created for placental abruption.

2. *The Confounders for Placenta Previa*

We adjusted for all the following variables that were included in the multivariate model used for calculating the propensity scores: maternal age, consanguinity between the couple, cigarette ever smoking during pregnancy, arguile ever smoking during pregnancy, alcohol consumption during pregnancy, maternal education, paternal education, maternal religion, paternal religion, prenatal care, maternal employment during pregnancy, pre-pregnancy weight, weight gain, pre-pregnancy BMI, hospital's admitted class during delivery, household crowding index, year of birth, gestational diabetes, chronic diabetes, chronic hypertension, cardiovascular problems, birth defects, use of assisted reproductive technology for the current pregnancy, previous neonatal death<28 days, previous premature delivery, preclampsia, eclampsia, number of gravida, number of abortions, type of gestation, antepartum anemia, maternal hemolytic diseases, maternal respiratory diseases, maternal thyroid problems, polyhydraminios, oligohydramnios, previous CS or Myomectomy or previous surgery of the uterus.

3. *The Confounders for Placenta Abruptio*

In addition to the above mentioned covariates, we added "Prolonged rupture of membrane >24 hours" and "Intrapartum fever >38°c" as potential confounders for placental abruption.

E. Ethical Considerations

Permission from the National Collaborative Perinatal Neonatal Network was obtained and exemption from the IRB review and oversight for this secondary data analysis was secured prior to study implementation. This study posed less than minimal

risk to subjects. No identified dataset was accessed; it was rather a coded dataset. The coding sheet that linked the original data to the shared one was kept in the custody of the NCPNN. Keeping a coding sheet instead of accessing a complete de-identified dataset was necessary for validation of extreme values and odd data entries. The validation process would be carried out by the NCPNN team if there was a need for it. However, we did not use this safety check during our data cleaning process. Subject autonomy was respected since all recruited women to the NCPNN registry were consented upon enrollment. All recruited subjects were fully aware that their data will be accessed by investigators for different research purposes. Nevertheless all possible efforts was made to maintain confidentiality of data and to respect privacy of individuals.

Potential benefits outweigh the expected risks although no direct benefit is expected to recruited subjects. Benefits to science and contribution to knowledge about our topic of interest especially in Lebanon balances the potential risk of breaching data confidentiality, which is less likely to occur when the safeguarded measures to protect anonymity were followed as described. Access to the dataset which was kept in a password protected computer was restricted to the researcher who underwent ethical training by fulfilling the CITI certification.

Furthermore, dissemination of results to the public will add to the awareness of parents of advanced age regarding the potential risks associated with delayed childbearing and to the possible intervening measures that might contribute to a better obstetric outcome.

Recruitment of subjects was equitable since all women admitted to all NCPNN member hospitals were approached for recruitment with no differentiation among groups. Thus the justice principle is well respected. Moreover the findings of our study will

benefit any parents who are planning to have a family at advanced age regardless of their socio-economic background.

CHAPTER IV

RESULTS

A. Introduction

We will display in this chapter the results of the bivariate and multivariate analyses pertaining to each outcome separately. The results of two multivariate analyses will be presented for each outcome. The first multivariate analysis corresponds to the model built to calculate the propensity scores for the risk of developing the disease. Whereas the second multivariate analysis corresponds to the model used to test and measure the association between paternal age and the outcome of interest.
The distribution of all variables will also be compared between cases and controls.

B. Characteristics of the Study Population and Analysis

1. Preeclampsia

a. Socio-Demographic Characteristics

Socio-Demographic characteristics of women suffered from preeclampsia compared to those who did not have the disease are presented in table 1.1. Statistically significant differences were found between the two groups pertaining to maternal age, paternal age and age difference between the couple (p=0.000). Additionally, statistically significant differences were found between the two groups pertaining to: maternal & paternal education specifically illiterate women (p= 0.001) and college educated (p= 0.039) along with illiterate fathers (p= 0.022); maternal & paternal religions specifically

for Muslim and Christian couples (p= 0.000); and to all hospital admitted classes during delivery whether 1st, 2nd or 3rd class (p= 0.001, 0.000, 0.043).

Women with preeclampsia showed slightly higher mean maternal and paternal ages with higher proportions falling among college educated couples, Christian couples, and among 1st class and 3rd class.

b. Obesity and Life Style Characteristics

Obesity and life style characteristics of women suffered from preeclampsia compared to those who did not have the disease are presented in table 1.2. Statistically significant differences were found between the two groups pertaining to maternal pre-pregnancy weight, maternal pre-pregnancy BMI, weight gain during pregnancy (p=0.000) and for mothers who were employed during pregnancy (p=0.000). No statistical significance was detected between groups in relation to cigarette or arguileh ever-smoking during pregnancy and to alcohol consumption during pregnancy.

Women with preeclampsia showed higher mean pre-pregnancy weight, mean pre-pregnancy BMI, and higher mean weight gain during pregnancy. They also showed lower proportions in regards to cigarette ever-smoking during pregnancy that might be attributed to having more educated women among cases of preeclampsia, yet this explanation does not hold for arghuile ever-smoking during pregnancy.

Moreover, a higher proportion of women who were employed during pregnancy was noted among those who developed preeclampsia compared to those who did not develop the disease (30.1% vs. 22.2%). This is an interesting observation that warrants close examination. To note here, education is not the reason for having higher proportion of women in the category of preeclampsia, since pregnant women living in rural areas

who worked in farming were considered among the labor force and were classified as working mothers.

c. Clinical Characteristics

Clinical characteristics of women who suffered from preeclampsia compared to those who did not have the disease are presented in table 1.3. Clinical profile seemed to play an important role in developing the disease since all variables related to chronic maternal problems, previous obstetric history, and current gestational problems showed statistical significance in comparing the other group. Chronic & gestational diabetes (p=0.000), chronic cardiovascular and renal problems (p=0.000), number of abortions (p=0.015), previous neonatal death less than 28 days of life (0.003), previous premature birth (0.000), number of gravida (p=0.000), having twins or triplets (p=0.000), suffering from uteroplacental disorders during the current pregnancy (placenta previa p= 0.003; planceta abruption p= 0.012), using assisted reproductive technology for this pregnancy (p=0.000), and having a baby with birth defects (p=0.000); all reflected the presence of a potential association with developing preeclampsia.

Preeclampsia cases showed sicker clinical profiles. Higher proportions were noted among cases in terms of obstetrical problems in the current pregnancy, and in terms of past chronic and obstetric history as well.

d. Visual Exploration of Data

Figure 1.1 represents the crude risk of developing preeclampsia by maternal age whereas figure 1.2 represents the crude risk of developing preeclampsia by paternal age.

Both figures show a steady increase in regards to the risk of developing preeclampsia as the fathers or the mothers advance in age. Although the risk reaches 2.1% when the mothers reach the age of 41 or more, yet almost the same level of risk (2.3%) is reached but when fathers reach the age of 51 or more. Similarly, it is noted that the risk starts peaking among the age group of 31- 35 years for mothers, whereas it starts peaking for the age group of 36-40 years for fathers. Although no conclusive remark can be drawn from these figures, yet we can easily note that there is always an age gap of at least 5 years between the effects seen due to maternal age versus those seen due to fathers' age.

Figure 1.3 shows the crude risk of developing preeclampsia by paternal age among different mothers' age groups. Figure 1.4 is plotted for the same purpose yet accounting for the risk of developing either preeclampsia or eclampsia.

Both figures reflect same patterns in terms of the disease behavior. Although the risk of developing preeclampsia /eclampsia increases progressively as the fathers advance in age among mothers of all ages, yet if we stratify by maternal age, we note that the pattern of the relationship between the risk of developing preeclampsia /eclampsia and paternal age remain the same for mothers less than 35 years old. Older mothers show a different pattern in terms of relationship between the disease and paternal age.

Figure 1.5 represents the risk of developing preeclampsia by maternal age and by gravida; and figure 1.6 represents the risk of developing preeclampsia by paternal age and by gravida. These presentations are another way of exploring our data visually.

e. Multivariate Analysis and Propensity Scores

Three models were built to calculate the propensity scores; or the conditional probability of developing preeclampsia for each woman after adjusting for her clinical

profile, socio-demographic characteristics and her obstetric past and present history. All these conditional probabilities constituted the propensity scores variable. The covariates that were included in these models were mentioned earlier under section D of chapter 3. The first model included mothers of all ages. The second model included older mothers of age 35 years or more, whereas the third model included young mothers of age less than 35 years old.

Table 1.4 represents the results of the first multivariate logistic regression model for mothers of all ages. Adjusted odds ratios are displayed as the measures of association. The covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: maternal age (OR=1.058, 95% CI: 1.046-1.069), having a previous neonatal death less than 28 days of life (OR=1.711, 95% CI: 1.183-2.477), having a previous premature birth (OR=1.572, 95% CI: 1.156-2.137), suffering from chronic diabetes (OR=2.568, 95% CI: 1.637-4.031), chronic renal problems (OR=4.258, 95% CI: 2.125-8.533) and from cardiovascular problems (OR=3.539, 95% CI: 2.302-5.442), having gestational diabetes during the current pregnancy (OR=2.399, 95% CI: 1.906-3.020), using assisted reproductive technology for the current pregnancy (OR=2.399, 95% CI: 1.906-3.020), carrying a child with birth defects (OR=2.00, 95% CI: 1.534-2.607), having a twin gestation (OR=1.837, 95% CI: 1.510-2.234), having repeated abortions (OR=1.282, 95% CI: 1.191-1.381), maternal employment status during pregnancy (OR=1.169, 95% CI: 1.016-1.346), pre-pregnancy weight (OR=1.019, 95% CI: 1.009-1.029), pre-pregnancy BMI (OR=1.058, 95% CI: 1.029-1.087) and weight gain during pregnancy (OR=1.061, 95% CI: 1.052-1.070).

However, the covariates that played the role of protective factors and showed statistical significance after adjusting for all characteristics were cigarette ever smoking during

pregnancy (OR=0.763, 95% CI: 0.611-0.952) and the number of gravida (OR=0.793, 95% CI: 0.748-0.841).

Table 1.6 represents the results of the first multivariate logistic regression model for older mothers aged 35 years or more. In this model, the covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: maternal age (OR=1.055, 95% CI: 1.017-1.093), suffering from chronic diabetes (OR=2.126, 95% CI: 1.030-4.386) and from chronic renal problems (OR=4.611, 95% CI: 1.019-20.854), having gestational diabetes during the current pregnancy (OR=2.414, 95% CI: 1.713-3.400), using assisted reproductive technology for the current pregnancy (OR=2.512, 95% CI: 1.737-3.632), having a twin gestation (OR=1.620, 95% CI: 1.159-2.266), pre-pregnancy weight (OR=1.018, 95% CI: 1.000-1.035), pre-pregnancy BMI (OR=1.052, 95% CI: 1.001-1.105) and weight gain during pregnancy (OR=1.050, 95% CI: 1.033-1.067).

On the other hands, the covariates that played the role of protective factors and showed statistical significance after adjusting for all characteristics remained the same: Cigarette ever-smoking during pregnancy (OR=0.682, 95% CI: 0.479-0.970) and number of gravida (OR=0.883, 95% CI: 0.813-0.959).

For young mothers aged less than 35 years, table 1.8 represents the results of the first multivariate logistic regression model for this group. The covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: maternal age (OR=1.047, 95% CI: 1.028-1.067), having a previous neonatal death less than 28 days (OR=2.247, 95% CI: 1.429-3.533), having previous premature birth (OR=1.690, 95% CI: 1.123-2.542), suffering from chronic diabetes (OR=2.784, 95% CI: 1.560-4.970), chronic renal problems (OR=4.077, 95% CI: 1.858-8.945) and from

cardiovascular problems (OR=4.458, 95% CI: 2.715-7.319), having gestational diabetes during the current pregnancy (OR=2.371, 95% CI: 1.737-3.238), using assisted reproductive technology for the current pregnancy (OR=2.182, 95% CI: 1.546-3.080), carrying a child with birth defects (OR=2.426, 95% CI: 1.794-3.280), having a twin gestation (OR=1.996, 95% CI: 1.567-2.543), having repeated abortions (OR=1.443, 95% CI: 1.318-1.581), maternal employment status during pregnancy (OR=1.313, 95% CI: 1.109-1.555), pre-pregnancy weight (OR=1.020, 95% CI: 1.008-1.032), pre-pregnancy BMI (OR=1.060, 95% CI: 1.026-1.096) and weight gain during pregnancy (OR=1.065, 95% CI: 1.054-1.075).

However, the only covariate that played the role of protective factor and showed statistical significance after adjusting for all characteristics was the number of gravida (OR=0.712, 95% CI: 0.654-0.775).

The two models of older and young mothers share most of the risk factors, yet some of the risk factors disappeared from playing a role in the susceptibility of older mothers in developing preeclampsia. These elements are related to previous obstetric history, specifically having previous neonatal death or premature birth, and having repeated abortions. In addition employment of mothers during pregnancy stopped being a risk factor among this group of women, besides carrying a baby with birth defects and suffering from chronic cardiovascular problems.

Furthermore, new risk factors surfaced in the model of young mothers. These factors are: consanguinity (OR=1.212, 95% CI: 1.006-1.459), having placenta previa (OR=2.911, 95% CI: 1.340-6.321), having placenta abruptio (OR=2.423% CI: 1.097-5.351) and carrying triplet gestation (OR=1.801, 95% CI: 1.046-3.101).

Above and beyond that, cigarette ever smoking showed no protective effect among this group of women in contrary to its shielding role among older women.

f. Effect of Paternal Age on Preeclampsia

The effect of paternal age on the risk of developing preeclampsia among all mothers, and among those who are older and younger than 35 years, is presented in table 1.5, 1.7 and 1.9 respectively. Adjusted odds ratios are displayed as the measures of association. ORs are adjusted for propensity scores in these second multivariate logistic regressions that were run to assess the independent effect of paternal age on our outcome of interest: preeclampsia.

Paternal age showed statistical significance as a risk factor in the model that included all mothers (OR=1.025, 95% CI: 1.016-1.034); and in the model of young mothers (OR=1.013, 95% CI: 1.0003-1.025), yet failed to show statistical significance in the model that included older mothers (OR=1.002, 95% CI: 0.983-1.022).
The age of father was added as a continuous variable in all models, thus with each one-year increase during aging of a man, the odds of developing preeclampsia for his partner increases by 1.013 if she is younger than 35 years old. In other words, there is almost a 10% increased risk of developing preeclampsia for a young woman for each 10- year increase in her partner's age.

2. Eclampsia

a. Socio-Demographic Characteristics

Socio-Demographic characteristics of women suffered from eclampsia compared to those who did not have the disease are presented in table 2.1. Women who developed

eclampsia share almost the same socio-demographic profile of those who developed preeclampsia except for the fact that they are mainly with intermediate education in comparison to college education for women with preeclampsia, and with high school education for their husbands in comparison to college education for those with preeclampsia. In addition to that, the majority of women (85.0%) who developed eclampsia along with partners (86.0%) were Muslims and among 2nd class and 3rd class, rather than being either Christians or Muslims and among 1st class and 3rd class for those who developed preeclamsia.

b. Obesity And Life Style Characteristics

Obesity and life style characteristics of women suffered from eclampsia compared to those who did not have the disease are presented in table 2.2. Women who developed eclampsia have similar life style as those who developed preeclampsia except that we noted higher percent of ever-smokers of cigarette among positive cases of eclampsia in comparison to both negative control for eclampsia and positive cases for preeclamsia. In addition, cigarette ever-smoking showed statistical significance among this group of patients, which was not the case for preeclampsia. Nevertheless, maternal employment during pregnancy stopped showing any significant relationship in regards to developing eclampsia.

c. Clinical Characteristics

Clinical characteristics of women suffered from eclampsia compared to those who did not have the disease are presented in table 2.3. Clinical profile of women who developed eclampsia seemed to be different from those who developed preeclampsia.

Past obstetric history had no influence on the susceptibility of the woman to develop eclampsia. Neither repeated abortions, previous neonatal death less than 28 days of life, previous premature birth nor number of gravida showed any statistical difference in comparing between the two groups.

Additionally, suffering from uteroplacental disorders during the current pregnancy, using assisted reproductive technology, and having a baby with birth defects, none reflected the presence of a potential association with developing eclampsia as well.

d. Multivariate Analysis and Propensity Scores

Three models were built also to calculate the propensity scores; or in this case, the conditional probability of developing eclampsia for each woman after adjusting for her clinical profile, socio-demographic characteristics and her obstetric past and present history. The first model included mothers of all ages. The second model included older mothers of age 35 years or more, whereas the third model included young mothers of age less than 35 years old.

Table 2.4 represents the results of the first multivariate logistic regression model for mothers of all ages. Adjusted odds ratios are displayed as the measures of association. The covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: maternal age (OR=1.032, 95% CI: 1.003-1.062), suffering from cardiovascular problems (OR=4.821, 95% CI: 2.072-11.217), having gestational diabetes during the current pregnancy (OR=2.595, 95% CI: 1.396-4.824), having a twin gestation (OR=2.052, 95% CI: 1.205-3.494), pre-pregnancy weight (OR=1.035, 95% CI: 1.012-1.058), and weight gain during pregnancy (OR=1.050, 95% CI: 1.028-1.072).

Eclampsia appears to have fewer factors driving its development than preeclampsia. Obesity leading to gestational diabetes was the only life style factor affecting the disease. Aging, carrying twins and suffering from cardiovascular disease are the only clinical factors that influenced the outcome.

Table 2.6 represents the results of the first multivariate logistic regression model for older mothers aged 35 years or more. In this model, the covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: suffering from cardiovascular problems (OR=4.482, 95% CI: 1.016-19.763), and weight gain during pregnancy (OR=1.048, 95% CI: 1.004-1.094).
Maternal age, pre-pregnancy weight, having gestational diabetes during this pregnancy and having a twin gestation disappeared from being risk factors with statistical significance for developing eclampsia in older mothers. Yet a new risk factor surfaced in this model which is cigarette ever-smoking (OR=2.123 95% CI: 1.089-4.141) and another protective factor surfaced as well which is household crowding index (HCI) (OR=0.593, 95% CI: 0.356-0.998). HCI was calculated as the total number of residents per household excluding the newborn, divided by the total number of rooms excluding kitchen and bathrooms.

Table 2.8 represents the results of the first multivariate logistic regression model for mothers younger than 35 years. The covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: suffering from cardiovascular problems (OR=5.580, 95% CI: 1.989-15.650), having gestational diabetes during the current pregnancy (OR=3.239, 95% CI: 1.543-6.798), having a twin gestation (OR=2.326, 95% CI: 1.260-4.294), pre-pregnancy weight (OR=1.035, 95% CI: 1.008-1.063), and weight gain during pregnancy (OR=1.049, 95% CI: 1.024-1.075).

Maternal age in the model of young mothers did not show any statistical significance in its relationship to eclampsia which is similar to the result of older mothers. The new element that surfaced here is having repeated abortions as a new factor showing an added risk of 1.049 with each time the woman suffer from losing her fetus (OR=1.049, 95% CI: 1.024-1.075). The number of gravida reappeared here again as a protective factor similar to the situation of preeclampsia. The higher the number of gravida, the lesser the risk of eclampsia by 0.804 (OR=0.804, 95% CI: 0.671-0.964).

e. Effect of Paternal Age on eclampsia

The effect of paternal age on the risk of developing eclampsia among all mothers, and among those who are older and younger than 35 years, is presented in table 2.5, 2.7 and 2.9 respectively. Adjusted odds ratios are also displayed as the measures of association here.

Paternal age showed statistical significance as a risk factor for eclampsia in the model that included all mothers (OR=1.036, 95% CI: 1.014-1.059); and in the model of young mothers (OR=1.016, 95% CI: 1.004-1.027), yet failed to show statistical significance in the model that included older mothers (OR=1.001, 95% CI: 0.982-1.019). The age of the father was also used as a continuous variable in all these models, thus with each one-year increase during aging of a man, the odds of developing eclampsia for his partner increases by 1.016 if she is younger than 35 years old. In other words, there is almost a 10% increased risk of developing eclampsia for a young woman for each 10-year increase in her partner's age.

3. Placenta Previa

a. Socio-Demographic Characteristics

Socio-Demographic characteristics of women suffered from placenta previa compared to those who did not have the disease are presented in table 3.1. Statistically significant differences were found between the two groups pertaining to maternal age and paternal age (p=0.000). Additionally, statistically significant differences were found between the two groups pertaining to: Consanguinity (p=0.024), maternal & paternal education specifically for illiteracy (p= 0.000); maternal & paternal religions specifically for Muslim and Christian couples (p= 0.000); and to all hospital admitted classes during delivery whether 1^{st}, 2^{nd} or 3^{rd} class (p= 0.000).

Women with placenta previa showed slightly higher mean maternal and paternal ages with higher proportions falling among college educated women, paternal intermediate education, Christian couples, and among 1^{st} class and 3^{rd} class.

b. Obesity and Life Style Characteristics

Obesity and life style characteristics of women suffered from placenta previa compared to those who did not have the disease are presented in table 3.2. Statistically significant differences were found between the two groups pertaining to maternal pre-pregnancy weight, maternal pre-pregnancy BMI (p=0.008, p=0.001), alcohol consumption during pregnancy (p=0.001) and maternal employment status during pregnancy (p=0.004). No statistical significance was detected between groups in relation to cigarette or arguileh ever-smoking during pregnancy and to maternal weight gain during pregnancy.

Moreover, higher proportion of mothers who were consuming more alcohol (1.9% vs. 0.5%) and who were employed during pregnancy developed placenta previa (28.5% vs. 22.2).

c. Clinical Characteristics

Clinical characteristics of women suffered from placenta previa compared to those who did not have the disease are presented in table 3.3. Clinical profile seemed to play an important role in developing placenta previa as well. Variables that showed statistical significance in comparing the other group are: Gestational diabetes during this pregnancy (p=0.000), maternal hemoglobinopathies and thyroid disorders (p=0.000), number of prior abortions (p=0.000), previous premature birth (0.000), number of gravida (p=0.009), having twins or triplets (p=0.000), suffering from preeclampsia during the current pregnancy (p= 0.000), using assisted reproductive technology for the current pregnancy (p=0.000), and having a baby with birth defects (p=0.000). All reflected the presence of potential association with developing placenta previa.

Higher proportions were also noted among cases of placenta previa in terms of obstetrical problems during the current pregnancy, past ones and chronic medical history.

d. Visual Exploration of Data

Figure 3.1 represents the crude risk of developing placenta previa by maternal age whereas figure 3.2 represents the crude risk of developing placenta previa by paternal age. Both figures show a steady increase in regards to the risk of developing placenta previa as the fathers or the mothers advance in age. However the overall percentages of risk are lower than those showed in preeclampsia's figures. Although the risk reaches 0.6% when

mothers reach the age of 41 or more, yet almost the same level of risk (0.5%) is reached but when fathers reach the age of 46 or more.

Figure 3.3 shows the crude risk of developing placenta previa by paternal age yet among different maternal age groups. This figure reflects the pattern in terms of disease behavior. Although the risk of developing placenta previa increases progressively as the fathers advance in age among mothers of all ages, yet if we stratify by maternal age, we note that the relationship between the risk of developing the disease and paternal age show different patterns.

e. Multivariate Analysis and Propensity Scores

Three models were also built here to calculate the propensity scores; or the conditional probability of developing placenta previa for each woman after adjusting for her clinical profile, socio-demographic characteristics and her obstetric past and present history.

Table 3.4 represents the results of the first multivariate logistic regression model for mothers of all ages. Adjusted odds ratios are displayed here also as the measures of association. The covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: maternal age (OR=1.055, 95% CI: 1.034-1.078), suffering from maternal hemoglobinopathies (OR=2.101, 95% CI: 1.035-4.265), suffering from preeclampsia (OR=2.205, 95% CI: 1.175-4.137), having a previous premature birth (OR=1.883, 95% CI: 1.196-2.966), using assisted reproductive technology for the current pregnancy (OR=2.645, 95% CI: 1.684-4.153), carrying a child with birth defects (OR=3.057, 95% CI: 1.980-4.720), having a triplet gestation

(OR=2.605, 95% CI: 1.267-5.356) and having repeated abortions (OR=1.213, 95% CI: 1.051-1.399).

However, the covariates that played the role of protective factors and showed statistical significance after adjusting for all characteristics were: maternal employment status during pregnancy (OR=0.738, 95% CI: 0.568-0.960), weight gain during pregnancy (OR=0.968, 95% CI: 0.949-0.987) and being admitted to second or third class for delivery (OR=0.673, 95% CI: 0.490-0.924; OR=0.514, 95% CI: 0.374-0.705).

Table 3.6 represents the results of the first multivariate logistic regression model for older mothers aged 35 years or more. In this model, the covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: suffering from maternal hemoglobinopathies (OR=4.365, 95% CI: 1.753-10.868), using assisted reproductive technology for the current pregnancy (OR=3.007, 95% CI: 1.625-5.564), carrying a child with birth defects (OR=3.121, 95% CI: 1.475-6.605) and consanguinity (OR=1.817, 95% CI: 1.021-3.234).

All other variables lost their role of adding risk to the susceptibility of developing placenta previa when the woman is 35 years or older, namely: maternal age, preeclampsia, having a previous premature birth, carrying a triplet gestation and having repeated abortions. One variable appeared as a new risk factor in this model which is consanguinity.

Other interesting remark here is the failure of any protective factor to reach statistical significance at this stage and for older mothers.

Table 3.8 represents the results of the first multivariate logistic regression model for young mothers aged less than 35 years. In this model, the covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics

were: maternal age (OR=1.071, 95% CI: 1.032-1.112), suffering from preeclampsia (OR=2.818, 95% CI: 1.291-6.149), having a previous premature birth (OR=2.365, 95% CI: 1.377-4.063), using assisted reproductive technology for the current pregnancy (OR=2.058, 95% CI: 1.063-3.984), carrying a child with birth defects (OR=3.056, 95% CI: 1.788-5.223), having a triplet gestation (OR=5.086, 95% CI: 2.184-11.843) and having repeated abortions (OR=1.258, 95% CI: 1.038-1.524).

Adding to that, some protective factors resurfaced again in this model and they are: weight gain during pregnancy (OR=0.962, 95% CI: 0.940-0.985) and being admitted to second or third class for delivery (OR=0.669, 95% CI: 0.457-0.979; OR=0.423, 95% CI: 0.286-0.625). Yet, employment of women during pregnancy failed to reach statistical significance.

f. Effect of Paternal Age on Placenta Previa

The effect of paternal age on the risk of developing placenta previa among all mothers, and among those who are older and younger than 35 years, is presented in table 3.5, 3.7 and 3.9 respectively. Adjusted odds ratios are also displayed as the measures of association here.

Paternal age showed statistical significance as a risk factor for placenta previa in the model that included all mothers (OR=1.047, 95% CI: 1.031-1.063); and in the model of young mothers (OR=1.049, 95% CI: 1.026-1.071), yet failed to show statistical significance in the model that included older mothers (OR=1.017, 95% CI: 0.980-1.055). The age of father was also used here as a continuous variable in all these models, thus with each one-year increase during aging of a man, the odds of developing placenta previa for his partner increases by 1.049 if she is younger than 35 years old. In other words, there

is almost a 10% increased risk of developing placenta previa for a young woman for each 10- year increase in her partner's age.

4. Placenta Abruptio

a. Socio-Demographic Characteristics

Socio-Demographic characteristics of women suffered from placenta abruptio compared to those who did not have the disease are presented in table 4.1. Statistically significant differences were found between the two groups pertaining to maternal age and paternal age (p=0.000). Additionally, statistically significant differences were found between the two groups pertaining to: maternal & paternal religions specifically for Muslim, Christian and Druze couples (p= 0.000); and to all hospital admitted classes during delivery whether 1st, 2nd or 3rd class (p= 0.000, 0.000 & 0.049).
Women with placenta abruptio showed slightly higher mean maternal and paternal ages with higher proportions falling among college educated couples, Christian couples, and among 1st class and 3rd class.

b. Obesity and Life Style Characteristics

Obesity and life style characteristics of women suffered from placenta abruptio compared to those who did not have the disease are presented in table 4.2. The only statistically significant difference between the two groups was found in relation to employment of mothers during pregnancy (p=0.000); and of course higher proportion of employed mothers was seen among who developed placenta abruptio (33.4% vs. 22.2%).

No other life style characteristics showed statistical significance; whether this was pertaining to maternal pre-pregnancy weight, pre-pregnancy BMI, weight gain, alcohol consumption during pregnancy, and cigarette or arguile ever-smoking during pregnancy.

c. Clinical Characteristics

Clinical characteristics of women suffered from placenta abruptio compared to those who did not have the disease are presented in table 4.3. Clinical profile seemed to play an important role in developing the disease in placenta abruptio as well. Variables that showed statistical significance in comparing the two groups are: Chronic diabetes (p=0.005), chronic cardiovascular diseases (p=0.001), maternal hemoglobinopathies (p=0.003), number of prior abortions (p=0.003), having a previous neonatal death (0.032), number of gravida (p=0.003), carrying twins or triplets (p=0.000), suffering from preeclampsia during the current pregnancy (p= 0.016), oligohydraminous (p=0.005), using assisted reproductive technology for the current pregnancy (p=0.000), and carrying a baby with birth defects (p=0.000). All reflected the presence of potential association with developing placenta abruptio.

Higher proportions were also noted among cases of placenta abruptio in terms of obstetrical problems during the current pregnancy, past ones and chronic medical history.

d. Visual Exploration of Data

Figure 4.1 represents the crude risk of developing placenta abruptio by maternal age whereas figure 4.2 represents the crude risk of developing placenta abruptio by paternal age.

Both figures show a steady increase in regards to the risk of developing placenta abruptio as the fathers or the mothers advance in age. However the overall percentages of risks are lower than those showed in preeclampsia's figures, yet close to the percentages seen in placenta previa. Although the risk reaches 0.4% when mothers reach the age of 36 years and above, yet the same level of risk (0.4%) is reached but when fathers reach the age of 46 or more.

Figure 4.3 shows the crude risk of developing placenta abruptio by paternal age yet among different maternal age groups. This figure reflects the pattern in terms of the disease behavior. Although the risk of developing placenta abruptio increases progressively as fathers advance in age among mothers of all ages, yet if we stratify by maternal age, we note that the relationship between the risk of developing the disease and paternal age show different patterns. This prototype seen in placenta abruptio is similar to all the three outcomes that were tackled before.

e. Multivariate Analysis and Propensity Scores

Three models were also built here to calculate the propensity scores; or the conditional probability of developing placenta abruptio for each woman after adjusting for her clinical profile, socio-demographic characteristics and her obstetric past and present history.

Table 4.4 represents the results of the first multivariate logistic regression model for mothers of all ages. Adjusted odds ratios are displayed here also as the measures of association. The covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: chronic diabetes (OR=2.535, 95% CI: 1.008-6.375), maternal hemoglobinopathies (OR=3.098, 95% CI: 1.222-7.855),

maternal chronic cardiovascular problems (OR=2.281, 95% CI: 1.036-5.021), oligohydraminous (OR=2.434, 95% CI: 1.563-3.791), using assisted reproductive technology during the current pregnancy (OR=1.884, 95% CI: 1.022-3.476), carrying a child with birth defects (OR=2.231, 95% CI: 1.421-3.502), carrying a twin or a triplet gestation (OR=1.804, 95% CI: 1.206-2.700; OR=3.009, 95% CI: 1.296-6.985) and the number of gravida (OR=1.213, 95% CI: 1.051-1.399).

However, the only covariate that played the role of protective factor and showed statistical significance after adjusting for all characteristics was: admission to hospital under 2nd or 3rd class for delivery (OR=0.214, 95% CI: 0.119-0.386; OR=0.586, 95% CI: 0.390-0.880).

Table 4.6 represents the results of the first multivariate logistic regression model for older mothers aged 35 years or more. In this model, the covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: chronic diabetes (OR=3.849, 95% CI: 1.128-13.132), oligohydraminous (OR=3.291, 95% CI: 1.387-7.812), carrying a child with birth defects (OR=2.258, 95% CI: 1.011-5.039), and carrying a twin or a triplet gestation (OR=3.047, 95% CI: 1.661-5.588; OR=8.030, 95% CI: 2.441-26.418).

At the same time , the same covariate that played the role of protective factor and showed statistical significance after adjusting for all characteristics was: admission to hospital under 2nd or 3rd class for delivery (OR=0.035, 95% CI: 0.004-0.268; OR=0.363, 95% CI: 0.167-0.787).

The new risk factor that emerged in this model of older mothers was developing intrapartum fever of 38°c or more as an indicator of infection or inflammation (OR=4.147, 95% CI: 1.440-11.943). However, having previous cesarean section or a myemectomy or

any uterine surgery emerged surprisingly as a protective factor here (OR=0.449, 95% CI: 0.231-0.872) which is in opposition to the stand of the literature in this regards. Also it is important to note here that previous uterine operations failed to show an association with placenta previa as well.

Table 4.8 represents the results of the first multivariate logistic regression model for young mothers aged less than 35 years. In this model, the covariates that played the role of risk factors and showed statistical significance after adjusting for all characteristics were: maternal hemoglobinopathies (OR=3.970, 95% CI: 1.381-11.412), maternal chronic cardiovascular problems (OR=2.690, 95% CI: 1.063-6.808), oligohydraminous (OR=232, 95% CI: 1.329-3.748), using assisted reproductive technology for the current pregnancy (OR=3.288, 95% CI: 1.506-7.178), and carrying a child with birth defects (OR=2.211, 95% CI: 1.273-3.840).

Additionally, the covariate that played here the role of protective factor and showed statistical significance after adjusting for all characteristics was admission to hospital for delivery under 2nd class (OR=0.314, 95% CI: 0.166-0.596).

The new risk factor that surfaced in this model of young mothers is polihydraminos (OR=2.940, 95% CI: 1.293-6.688) besides oligohydraminos that showed consistent effect along all ages of women. Furthermore, preeclampsia emerged also as a risk factor for placenta abruptio (OR=2.447, 95% CI: 1.129-5.304).

f. Effect of Paternal Age on Placenta Abruptio

The effect of paternal age on the risk of developing placenta abruptio among all mothers, and among those who are older and younger than 35 years, is presented in table

4.5, 4.7 and 4.9 respectively. Adjusted odds ratios are also displayed as the measures of association here.

Paternal age showed statistical significance as a risk factor for placenta abruptio in the model that included all mothers (OR=1.033, 95% CI: 1.017-1.050); and in the model of young mothers (OR=1.043, 95% CI: 1.021-1.066), yet failed to show statistical significance in the model that included older mothers (p= 0.598).

The age of the father was also used here as a continuous variable in all these models, thus with each one-year increase during aging of a man, the odds of developing placenta abruptio for his partner increases by 1.043 if she is younger than 35 years old. In other words, there is almost a 10% increased risk of developing placenta abruptio for a young woman for each 10- year increase in her partner's age.

5. Age Difference between the Couple

We were interested in exploring whether the effect seen so far from paternal age is originating from the age of the father itself or if it is due to the age difference between the couple. Thus we used the 6 models that were built to calculate the propensity scores, and we ran another multivariate logistic regression including age difference, this time, as a continuous variable instead of paternal age along with the propensity scores. These multivariate logistic regressions help us conclude if age difference plays an independent effect toward developing one of the 4 outcomes.

Two models for each outcome, one for young mothers and one for older mothers were employed as basis for our exploration.

a. Effect of Age Difference between the Couple

The effect of age difference on the risk of developing preeclampsia among mothers aged 35 years or more and those who are younger than 35 years, is presented in table 5.1 and 5.2 respectively. Tables 5.3 & 5.4 present the effect on eclampsia among the two groups, tables 5.5 & 5.6 present the effect on placenta previa among the two groups, and tables 5.7 & 5.8 present the effect on placenta abruptio among the two groups. Adjusted odds ratios are also displayed as the measures of association here.

Age difference between the couple failed to achieve statistical significance as a risk factor for preeclampsia in the two models (p=0.571; p=0.114). Similarly, it failed to reach statistical significance for placenta previa (p=0.686; p=0.610) and placenta abruptio (p=0.542; p=0.258).

As for the effect of age difference between the couple on developing eclampsia, the result was statically insignificant for mothers aged 35 years and above (p=0.222); but achieved statistical significance for young mothers (OR=1.038, 95% CI: 1.001-1.076).

CHAPTER V

DISCUSSION

A. Discussion of the Study Results

This study is based on a huge Lebanese cohort that represents a normally distributed obstetric population and 30% of the total birth in Lebanon. It is the first study in the region that addresses the effect of paternal age on maternal complications during pregnancy. It is also an original work that tried to attend to the controversy of the international literature toward this matter.

For many years maternal age and maternal characteristics were observed as the sole risk factors for many fetal complications and unfavorable reproductive outcomes. Many research studies were published highlighting the effects of advanced maternal age on reproduction. This issue added a big burden and more responsibilities on females who chose to postpone childbearing to older age. Aiming for higher education and being in the labor force were seen as reasons driving delaying parenthood to a later stage in females' life. Social criticism to females was further escalated upon introducing the Assisted Reproductive Technology since it was observed as an additional facilitator to postpone maternity.

Paternal contribution was not seen as a source of risk until recently; although both partners contribute to pregnancy and to fetal outcomes. This might be due to the beliefs that childbearing lies heavily on women exclusively, or maybe because spermatogenesis is a continuous process that does not cease at a specific age, or may be because many societies are male- dominated, and the issue of gender equity in rights and duties is a

recent focus. In the recent years, we began to see medical and scientific communities shedding more light on adverse reproductive outcomes that are associated with advanced paternal age. The literature is still little to this effect in comparison to what was generated on maternal age; and it is still focusing on the association between paternal age and fetal outcomes, rather than on the entire course of pregnancy and its development.

Placentation relies on a huge number of genes. However, although redundancy of genes exists in placentation, many maternal and paternal genes are still essential and indispensible for a normal development of the placenta and a normal function. Autosomal genes come in pairs. One is from the maternal side and the other one is from the paternal side. Both copies for the vast majority of our genes are functional; however in a small subset, one copy of these genes is turned off; and is called imprinted gene (Reik & Walter, 2001). Genomic imprinting is the process where a molecule binds to the DNA (epigenetically marked) shifting it to become silent. As a result, expression of this gene is altered and depends upon whether the imprinted genes come from maternal or paternal side (Reik & Walter, 2001). A study by Wang and colleagues demonstrated by RNA sequencing of trophoblast tissues that paternal genome has a major influence on the development of the placenta and that the gene expression related to the process of placentation is paternally predominant (Wanga, Millerc, Harmanc, Antczakc, & Clarka, 2013).

Our findings feed into the same channel of thoughts and theories; the trouble in placentation associated with advanced age of the father seems to play a role in maternal obstetric complications when these complications are linked directly to placental function or placental development and when women are younger. The consistent association that kept appearing between paternal age and our four outcomes among young women is

unlikely to be attributed to chance. Consequently, our findings contribute to the literature regarding the role of paternal genes in developing preeclampsia, eclampsia, placenta previa and placenta abruptio; whether this setback comes from a point mutation or from a prolonged exposure to environmental or nutritional toxicity leading to DNA damage. Nevertheless, this study remains a single study that has its own limitations and we cannot therefore generalize its findings to the population.

Our study results highlighted that the estimated risk of developing one of the four disorders as the father ages, is almost 5% with each 5-year age interval. This projected risk is not to be underestimated since it is coming from one risk factor, namely the paternal age. Evaluation of the cumulative estimated risk of a woman to develop the disease will definitely go far above this level.

Furthermore, although the observed effect of paternal age in our study is modest, it is not less than the observed effect of maternal age. The odds ratios of maternal age, when they were statistically significant, were around the same range of the odds ratios generated for the father's age. The only difference is that maternal age did not show a restricted effect on mothers younger than 35 years.

Adding to that, we think that paternal characteristics did not reach yet the threshold level of capturing the interest of scientific communities. In our perspective, a comprehensive risk assessment entails, besides the age, a full analysis of the medical history, obesity, and life style characteristics of both parents.

Although the aim of our study was to explore the effect of paternal age on maternal complications, we came across another finding that influences clinical care of patients. This study revealed that risk factors are not universal to mothers across all ages. It was noted that some risk factors are restricted to young mothers, and they do not have

any influence on older ones. Similar analogy was found for protective factors. Young women are looked at as the healthiest group, thus less worries and attention are paid to them. The presence of hidden factors that come from fathers is an interesting observation that worth better surveillance. Close monitoring and taking into account that young women are also subject to risks of different levels are very crucial messages to health care providers.

Other secondary findings are related to the role of life style characteristics. Further examination is warranted especially when it comes to the effect of maternal employment during pregnancy. Other features to be investigated are household crowding index, socioeconomic status and weight gain during pregnancy.

B. Further Comments on Each Study Outcome

1. Preeclampsia

It is not surprising to reproduce that clinical characteristics are fundamental key players in developing preeclampsia; yet finding out that obesity and life style characteristics are also vital elements in defining the risk of the disease, is equally important since these factors are altered by the woman herself. Obesity, whether related to pre-pregnancy weight or to weight gain during pregnancy, seems to increase the odds of developing the disease, and besides that, it is associated with gestational diabetes, type II chronic diabetes and cardiovascular problems. The interlink between the life style and the clinical profile and their combo effect on maternal health warrants promotional campaigns to alert women in their reproductive years to the seriousness of their life style choices.

In addition, maternal employment during pregnancy seems to be associated with developing preeclampsia. It is a new risk factor that was never described in the literature

and warrants investigation to closely understand the basis of this association. The probable explanation that might be attributed to such observation is physical stress that burdens the pregnant woman and adds to the trouble of pregnancy.

Cigarette smoking seems to play a protective role in preeclampsia, yet it is a known risk factor that worsens the outcome of pregnancy at other levels; thus it should not be promoted for its protective effect. This protective role is well described in the literature and is due to the vascular dilatation that occurs from smoking and might be a mediator toward protecting from the vasoconstriction that occurs in preeclampsia. Lower percentage of cigarette smoking during pregnancy was also noted among preeclamptic women in comparison to the percentage of arghuile smoking during pregnancy among the same group. These percentages hint that there might be an underestimation of risks associated with arghuile smoking in comparison to risks associated with cigarette smoking during pregnancy. Proper investigation to explore pregnant women's knowledge and practices regarding smoking is warranted in order to tailor public health intervention and awareness campaigns.

Furthermore, our results support the literature in regards to the protective effect of the number of gravida. The literature suggests the longer the exposure to paternal antigen, the less the susceptibility to develop preeclampsia.

The use of assisted reproductive technology and carrying more than one fetus seems to add to the susceptibility of developing preeclampsia. The risks associated with ART use and the choice of transferring multiple fetuses are usually not communicated to infertile couples clearly in order to have informed choices and better assessment of risks upon decision making.

Finally, the figures that present the risk of developing preeclampsia by gravida echo the literature that indicates the odds of developing the disease among primigravida is higher than amomg multigarvida. The new remark that can be added here is that the picture of developing the disease is the same whether the risk of preeclampsia is a function of paternal age or maternal age. The risk of preeclampsia reaches 5.9% for women aged 41 years or more among primigravida whereas it is 1.6% for the same age group among multigravida. Similarly, the risk of preeclampsia reaches 4.2 % when fathers reach the age of 51 years or more among primigravida whereas it is 1.9% for the same age group among multigravida.

2. Eclampsia

Women who developed eclampsia share similar socio-demographic profile with those who developed preeclampsia, but they have different clinical profile. Few clinical risk factors appear to be associated with the disease; however we noted that obesity and life style features play a critical role in eclampsia. Weight gain, living in domestic crowding and smoking, all together were the main factors pushing the course of pregnancy hypertension to a more serious level which is having seizures. In addition, the negative association between eclampsia and HCI as a socioeconomic indicator is a reflection of how low SES, situational stress and its effect on psychological well being can impact developing a disease.

In regards to the effect of paternal age on preeclampsia or eclampsia, the pattern is the same. The impact of father's age appears to be restricted to young mothers rather than to be universal on all women. This trend triggers queries about the patho-physiology that makes paternal antigens have an effect on young women only; despite that one can

assume that this group of women is healthier than older group and less susceptible to systemic diseases.

3. Placenta Previa

Maternal employment and weight gain during pregnancy seem to be consistent factors that are coming into view repeatedly. Yet, we noted a peculiar observation that is related to the opposite effect of these factors in different outcomes. Maternal employment during pregnancy is a risk factor for developing preeclampsia, and weight gain during pregnancy is a risk factor for eclampsia, whereas both factors are playing a protective role in placenta previa. What adds complication to the interpretation of such result is having preeclampsia, itself, a risk factor for placenta previa. This might be simply a protection from nature to facilitate the vast majority of pregnancies.

Furthermore, the protective association between the second/ third class or the less affluent subpopulation and placenta previa is another observation that warrants close investigation since lower SES was always seen as a risk factor rather than a protective one.

Additionally, a common feature was noted between preeeclampsia and placenta previa, this feature is noted in the models that included mothers of all ages where consanguinity did not appear as a risk factor; yet it emerged later on as a risk factor upon stratification. Though, this risk factor was associated with young mothers in preeclampsia but with older ones in placenta previa.

It is clear that risk factors and protective ones are interchangeably materializing in a different way when we are stratifying our analysis by woman's age. This is by itself a remarkable pronouncement since healthcare providers do not manage risk factors according to age.

Finally, this is the third outcome that follows the same trend of noting a paternal age's effect on maternal complication when the woman is young. Assuming that the basis of this effect is the placenta, investigating what is protecting older mothers from this effect is another research question that merits examination and exploration.

4. Placenta Abruptio

We noted here that the socio-demographic profile of women who suffered from placental abruption is almost identical to that of women who suffered from placenta previa, but the life style profile of both groups is very disparate. We also noted that placenta previa and abruptio share a common feature. This feature is the protective effect of lower SES on developing the diseases. This is a pleasant remark especially in our part of the world where a high proportion of our population falls under this category.

Additionally, our study result is consistent with the literature in regards to the duality effect of muligravida. The number of gravida plays a protective role whether in preeclampsia or in eclampsia, but it plays a counter role in placenta abruption; thus, the higher the number of pregnancies, the more the risk of placental abruptions. However and despite classifying multigravida as a known risk factor for placenta previa, our data did not show this association.

Furthermore, the literature highlights that preeclampsia is a risk factor for placenta previa and abruptio, yet some authors indicated that their analysis failed to show an association between preeclampsia and placenta previa and the association was noted to be restricted to placenta abruptio. Our study might explain these controversies in relation to those associations in particular. Our analysis showed that preeclampsia is a risk factor for both disorders, but its impact is limited to young mothers aged less than 35 years old.

Finally, this is the 4th outcome that follows the same trend of noting a paternal age's effect on maternal complication when the woman is young. These consistent results hint toward the existence of a pathway that links obstetric diseases to the aging process of fathers. They also hint that there are multiple factors coming into play to protect older women and makes young ones more susceptible.

5. Age Difference between fathers and mothers

We think that the consistent effect of paternal age on all the four outcomes among young women is due entirely to the age of the man rather than the age gap between him and his partner. Neverthless, the effect of age gap on developing eclampsia among young women is an interesting observation that necessitates closer examination to understand its basis.

C. Study Strengths

We anticipate seeing more research studies in the coming near future that will tackle risk profiling in a broader manner accounting for predictors from both parents. Being one of the first studies in the MENA region that looked at the effect of paternal age on maternal complications is a plus for this study. In addition, being a corner stone for a whole restoration toward a balanced evaluation of pregnancy risks with no over judging for the females' role is another positive asset of our work.

Furthermore and apart from using a large sample size, another advantageous feature of our study is the extensive variables that were collected on each pregnancy permitting us to draw a comprehensive summary for each woman. Adjusting for many socio-demographic characteristics, life style characteristics, past obstetric and medical

histories along with wide range of clinical variables reflecting the course of current pregnancies, led us to believe that what we reached as conclusions are factual rather than probabilities drawn by hazards.

Employing a new statistical technique to analyze data is another strength that allowed us to reach a conclusion about the independent effect of father's age on pregnancy hypertensive disorders and uteroplacental disorders. Propensity score regression adjustment enabled us to eliminate the co-linearity of maternal age and paternal age when both variables are analyzed together in the same multivariate model. This method enhances the potency of our study conclusions and helps enrich the literature with a stimulating approach that tackles limitations of other studies that addressed the same issue.

D. Study Limitations

The downside of our study is the amount of missing values in the data that necessitated us to perform an imputation technique to overcome such problem. However, we were conservative when making some assumptions to carry out these imputations. We preferred to have underestimated results rather than inflated ones that are far from reality.

Caution is also to be applied in generalizing the study results and making inference to the population. This is due to two main limitations. The first one would be attributed to the drawbacks of the cross sectional study design and from using observational dataset. The second issue would be attributed to the selection bias and not using a random selection of hospitals and subsequently a random selection of study subjects. Member hospitals of the NCPNN are not randomly selected from each Mohafaza representing the number of hospitals in this Mohafaza; they are rather personal effort from

the Director of the Network to make the hospital's recruitment happen. Yet, it is noted that these hospitals are distributed across all Mohafazat and not lumped in urban or rural settings. The study sample is not an ideal representation of all Lebanese women, yet the subjects come from different Lebanese areas and from different socio-economic background. Thus, the 30% representation remains a modest representation of the Lebanese population.

Another limitation would be attributed to the lack of any information about fathers' characteristics like occupational hazards, obesity, life style habits and definitely health conditions. Our analysis was restricted to paternal age but it would have been a more comprehensive analysis if we accounted for further information that reflect in a better way the health status of fathers and subsequently his contribution to reproductive outcomes.

Additionally, if our study results have to be interpreted carefully to avoid claiming facts about the universal truth, these results definitely raise a lot of research questions and open up a new era to examine the effect of paternal age on reproduction.

E. Conclusion & Recommendations

This research study is not conducted to call for neglecting the risks of advanced maternal age, or to overemphasize the risks of advanced paternal age, or in order to leave an impression of antagonism against males or to scrutinize the societal views regarding paternal role in reproduction. The main focus of this research study was rather to shed light on the role of fathers as main contributors to pregnancy and fetal outcomes. The aim was also to readdress a skewed risk analysis that accentuated the role of females and ignored the role of her partner.

Additionally, we hope that the study findings will inform health care providers on the needs for a comprehensive approach toward evaluating risks during obstetric counseling and monitoring. Introducing fathers' characteristics in the framework of prenatal care and collecting information on the father's age and his health characteristics during prenatal care and prenatal counseling are also our recommendations as an attempt to improve pregnancy outcomes and care delivery. Although it is too early to claim definitively that fathers' characteristics affect pregnancy and reproductive outcomes, precautions and attention to paternal health status could be warranted, and would not pose onerous demands during the monitoring process of pregnancies. A closer examination to the risk profile of young healthy pregnant women is another recommendation that needs to out reach health care providers. Accounting for hidden risk elements originating from paternal side will definitely allow better care and an early intervention for probable complications.

Furthermore, an approach to incorporate more health information about men in research registries and hospitals' medical charts during antepartum and postpartum care is another recommendation that might be beneficial for future research. A holistic approach will help in a better evaluation and a better understanding of the complete effect of paternal characteristics on the fetus and on maternal obstetric complications. History of paternal smoking, obesity, chronic diseases, occupational exposure to toxicity are all vital information that will inform researchers on adverse reproductive outcomes and on mutations.

Finally, we believe that bridging the gap of knowledge in regards to how fathers' characteristics affect reproductive outcomes is important. Further research studies are necessary to explore a new era related to fathers' contribution. Answering many queries

related to patho-physiology and public health concerns cannot be attended to without additional investigations.

TABLES

A. Preeclampsia

Table 1.1: Percent distribution of all women admitted for delivery by socio-demographic characteristic and preeclampsia

Characteristics	**Preeclampsia** **N= 1310 (0.9%)**	**No-Preeclampsia** **N= 142106**	**P-value**
Mean maternal age	30.8 ± 6.2 Min= 17 Max= 56	28.7 ± 5.8 Min= 10 Max= 56	0.000
Mean paternal age	36.0 ± 6.8 Min= 19 Max= 65	34.3 ± 6.3 Min= 15 Max= 80	0.000
Mean age difference between mother and father	5.2 ± 4.4	5.6 ± 4.3	0.000
Consanguinity	14.6%	15.2%	0.528
Maternal Education			
None	1.2 %	1.8%	0.001
< = Intermediate	35.3 %	39.6%	0.294
High School	28.2 %	28.2%	0.135
College	35.2 %	30.4%	0.039
Paternal education			
None	0.5 %	0.8%	0.022
< = Intermediate	76.2 %	78.3%	0.217
High School	10.1 %	10.1%	0.202

College	13.3 %	10.8%	0.076
Mother's Religion			
Muslim	72.0 %	79.8%	0.000
Druze	3.1 %	2.7%	0.095
Christian	24.9 %	17.5%	0.000
Father's Religion			
Muslim	72.7 %	80.1%	0.000
Druze	3.0 %	2.6%	0.162
Christian	24.4 %	17.3%	0.000
Hospital Admitted Class			
First Class	11.0 %	9.0%	0.001
Second Class	16.7 %	20.1%	0.000
Third Class	72.3 %	70.9%	0.043

Table 1.2: Percent distribution of all women admitted for delivery by obesity and life style characteristics and preeclampsia

Characteristics	**Preeclampsia N= 1310 (0.9%)**	**No-Preeclampsia N= 142106**	**P value**
Mean pre-pregnancy BMI (kg/m2)	25.5 ± 4.5	23.8 ± 3.6	0.000
Mean pre-pregnancy Weight (Kg)	67.8 ± 12.5	62.8 ± 10.4	0.000
Mean weight gain (Kg)	15.1 ± 6.8	12.8 ± 5.4	0.000
Cigarette ever-smokers during pregnancy	6.9%	8.3%	0.070

Arguile ever- smokers during pregnancy	8.0%	7.1%	0.193
Alcohol Consumption during pregnancy	0.9%	0.5%	0.069
Maternal employment status during pregnancy	30.1%	22.2%	0.000

Table 1.3: Percent distribution of all women admitted for delivery by clinical characteristic and preeclampsia

Characteristics	**Preeclampsia N= 1310 (0.9%)**	**No-Preeclampsia N= 142106**	**P Value**
Primigravidae	42.0 %	30.3%	0.000
Prior Abortion	28.8%	25.5%	0.015
Chronic Diabetes	1.8 %	0.4%	0.000
Gestational Diabetes	7.1%	1.7%	0.000
Chronic Cardiovascular Diseases	1.8%	0.5%	0.000
Chronic Renal Diseases	0.7%	0.1%	0.000
Carrying a baby with birth defects	4.8%	1.9%	0.000
Placenta Previa	0.7%	0.3%	0.003
Placenta Abruptio	0.6%	0.2%	0.012
ART use for the current pregnancy	8.4%	1.4%	0.000

Having a previous neonatal death	2.6%	1.6%	0.003
Having a previous premature birth	3.8%	2.1%	0.000
Type of Gestation			
Single	86.6 %	95.9%	0.000
Twins	11.8 %	3.6%	0.000
Triplets	1.5 %	0.4%	0.000
more	0.1 %	0.04%	0.480

Figure 1.1: Risk of developing preeclampsia by maternal age

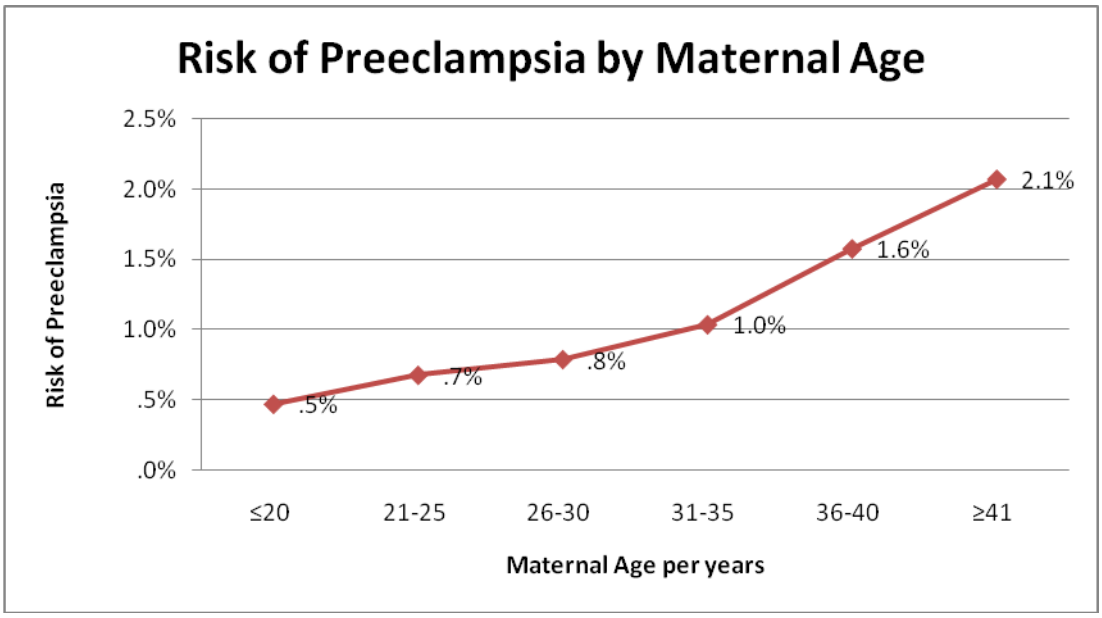


Figure 1.2: Risk of developing preeclampsia by paternal age

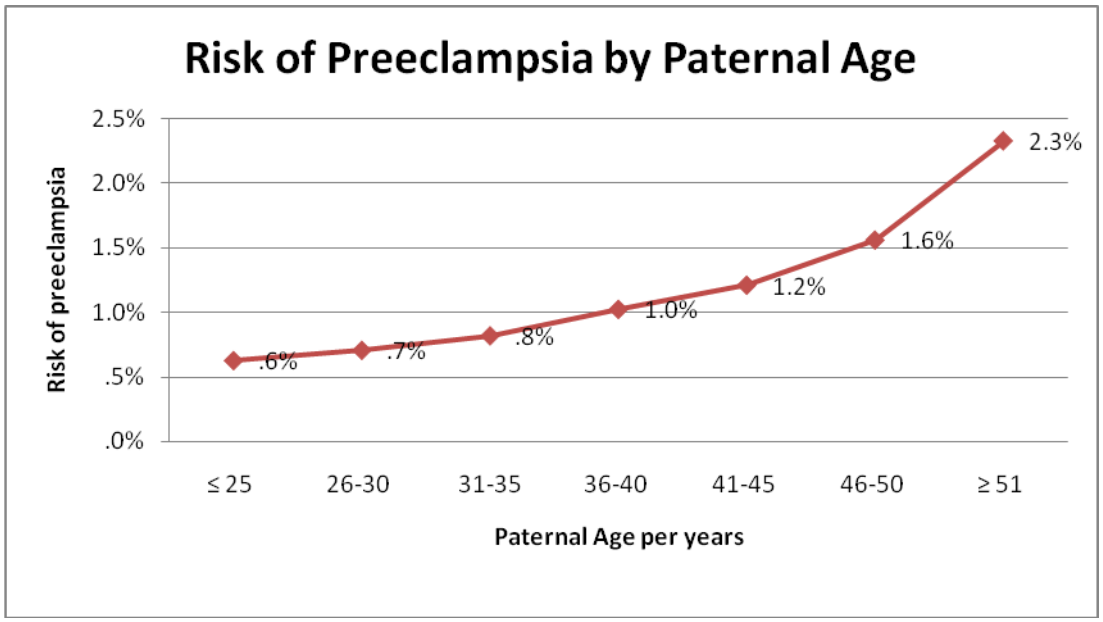


Figure 1.3: Risk of developing preeclampsia by paternal age among different maternal age groups

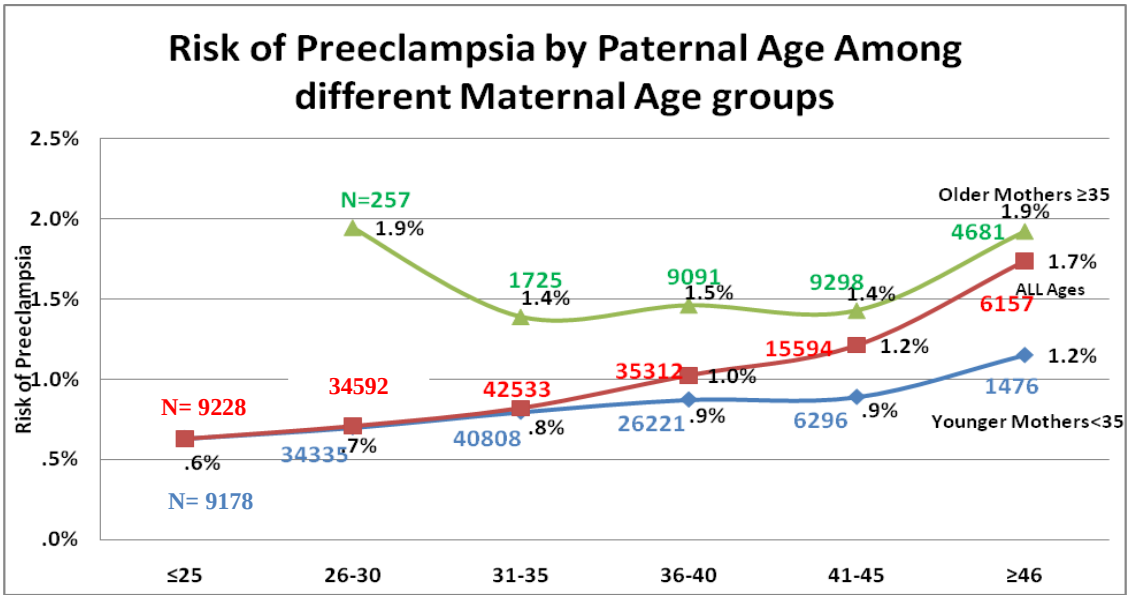


Figure 1.4: Risk of developing preeclampsia or eclampsia by paternal age among different maternal age groups

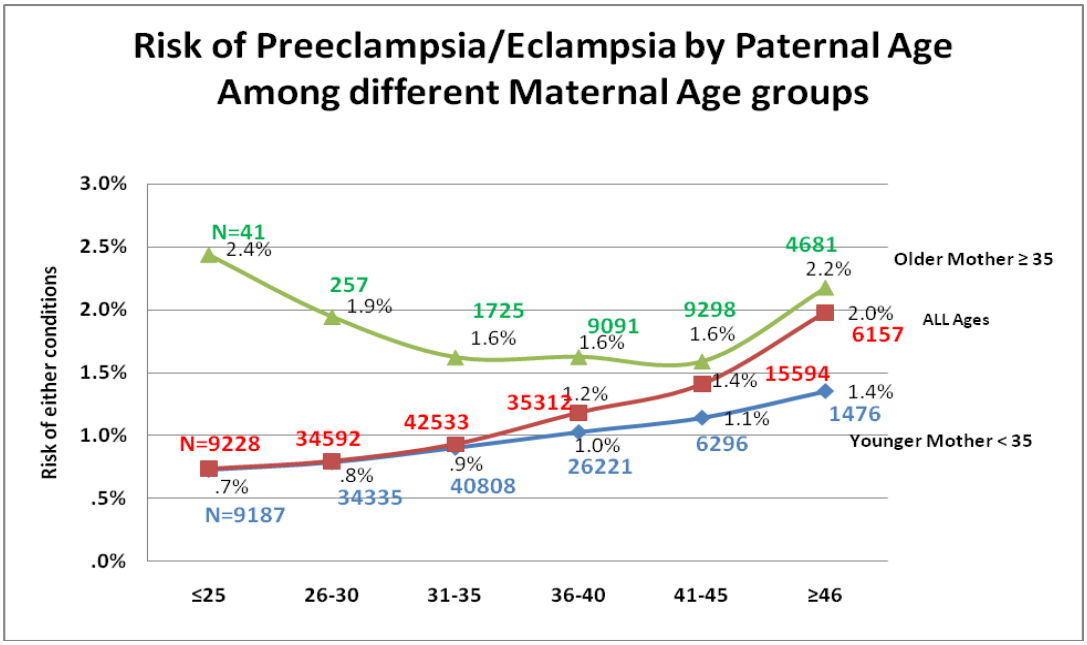


Figure 1.5: Risk of developing preeclampsia by maternal age and gravida

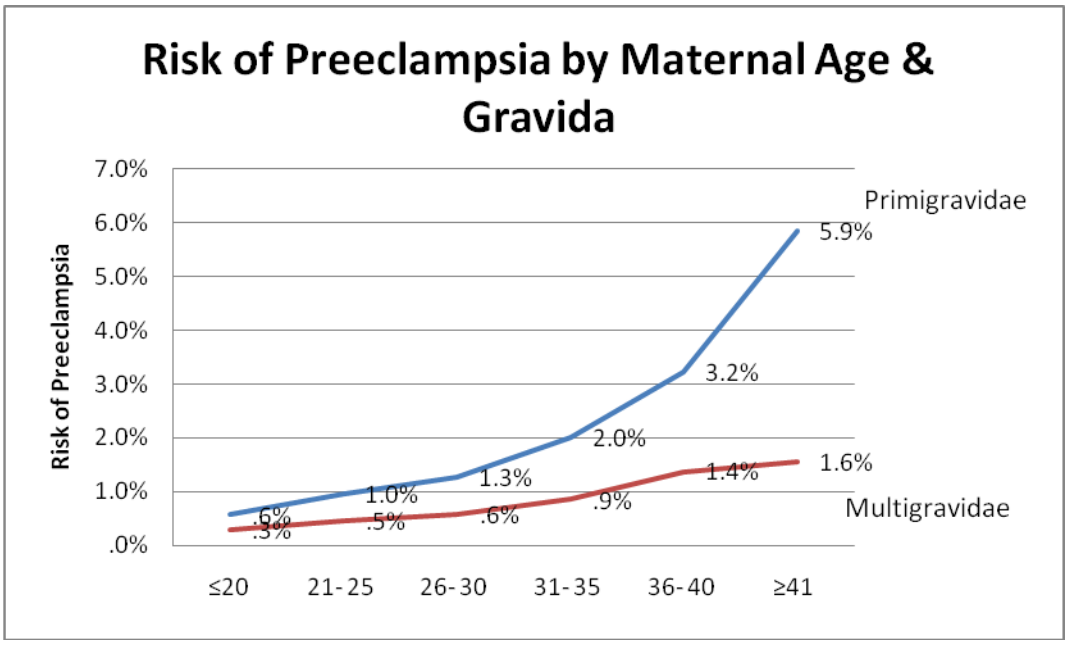
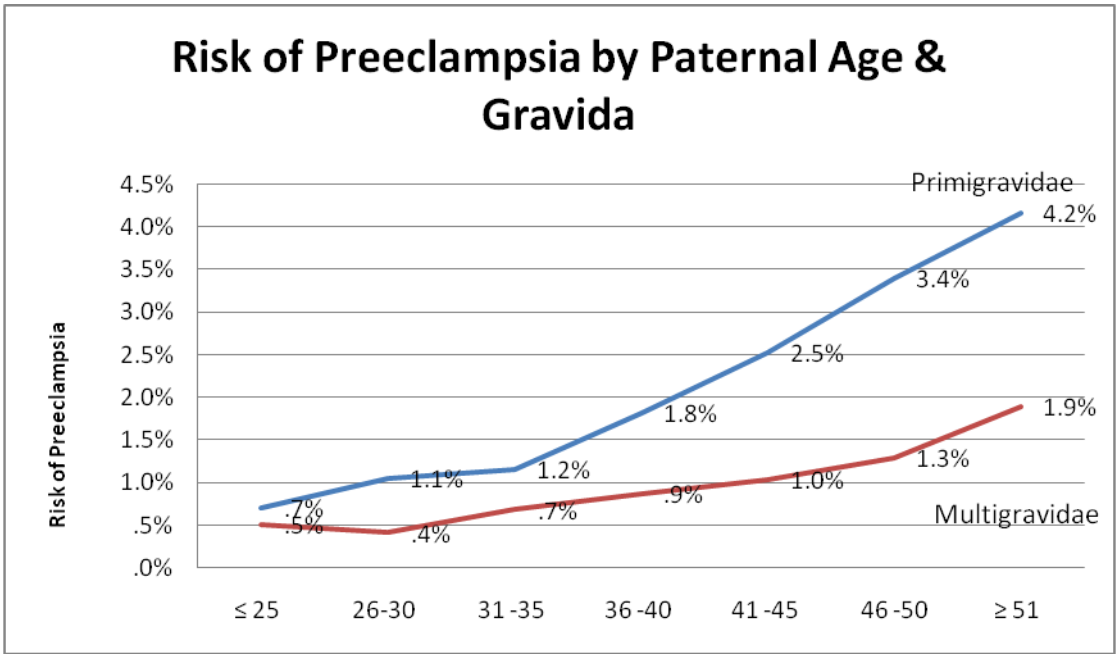


Figure 1.6: Risk of developing preeclampsia by paternal age and gravida



1. Preeclampsia for All Mothers

Table 1.4: 1st Multivariate model built to calculate propensity scores for the risk of developing preeclampsia

Variable	OR	S.E	95% CI	P- value
Year of birth	1.003	0.014	0.975-1.032	0.842
Consanguinity	1.153	0.082	0.981-1.354	0.083
Arguile ever smoking during pregnancy	1.229	0.106	0.999-1.511	0.051
Cigarette ever smoking during pregnancy	0.763	0.113	0.611-0.952	0.017
Alcohol consumption during pregnancy	1.187	0.298	0.661-2.130	0.566
Having a previous neonatal death	1.711	0.189	1.183-2.477	0.004
Having a previous premature birth	1.572	0.157	1.156-2.137	0.004
Chronic diabetes	2.568	0.230	1.637-4.031	0.000
Gestational diabetes	2.399	0.117	1.906-3.020	0.000
Chronic maternal renal problems	4.258	0.335	2.125-8.533	0.000
ART use for this pregnancy	2.274	0.128	1.769-2.922	0.000
Placenta Previa	1.872	0.350	0.942-3.717	0.073

Placenta abruptio	1.781	0.369	0.864-3.672	0.118
Maternal employment status during pregnancy	1.169	0.072	1.016-1.346	0.030
Prenatal care	0.959	0.242	0.597-1.543	0.864
Carrying a baby with birth defects	2.000	0135	1.534-2.607	0.000
Maternal cardiovascular problems	3.539	0.219	2.302-5.442	0.000
# of Gravida	0.793	0.030	0.748-0.841	0.000
# of Abortions	1.282	0.038	1.191-1.381	0.000
Maternal Education				
None	-----	------	-----	0.500 (Ref)
< = Intermediate	0.984	0.264	0.587-1.650	0.952
High School	0.980	0.267	0.580-1.654	0.939
College	0.877	0.271	0.515-1.493	0.629
Paternal education				
None	-----	-----	-----	0.908(Ref)
< = Intermediate	1.260	0.423	0.549-2.888	0.586
High School	1.294	0.431	0.556-3.008	0.550
College	1.325	0.431	0.569-3.085	0.514
Maternal religion				
Muslim	----	-----	----	0.208(Ref)
Druze	1.761	0.576	0.570-5.443	0.326
Christian	1.641	0.319	0.877-3.069	0.121
Paternal religion				

Muslim	----	----	---	0.503 (Ref)
Druze	0.671	0.589	0.212-2.130	0.498
Christian	0.723	0.321	0.385-1.358	0.314
Household crowding index	0.949	0.052	0.857-1.050	0.311
Hospital admitted class				
First Class	----	----	-----	0.017
Second Class	1.004	0.117	0.799-1.262	0.970
Third Class	1.240	0.109	1.002-1.534	0.048
Type of gestation				
Single	---	-----	----	0.000
Twins	1.837	0.100	1.510-2.234	0.000
Triplets	1.367	0.248	0.841-2.223	0.207
more	1.068	1.028	0.143-8.006	0.949
Pre-pregnancy Weight (kg)	1.019	0.005	1.009-1.029	0.000
Weight gain (Kg)	1.061	0.004	1.052-1.070	0.000
Pre-pregnancy BMI (kg/m^2)	1.058	0.014	1.029-1.087	0.000
Maternal Age	1.058	0.006	1.046-1.069	0.000

Table 1.5: 2nd Multivariate model- Effect of paternal age on the risk of developing preeclampsia

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.025	0.004	1.016-1.034	0.000

Propensity Score	----	----	----	0.000

2. Preeclampsia for Older Mothers ≥35 years

Table 1.6: 1st Multivariate model built to calculate propensity scores for the risk of developing preeclampsia for older mothers ≥ 35 years

Variable	OR	S.E	95% CI	P- value
Year of birth	1.002	0.027	0.950-1.057	0.937
Consanguinity	1.017	0.165	0.735-1.405	0.921
Arguile ever smoking during pregnancy	1.401	0.226	0.899-2.183	0.136
Alcohol consumption during pregnancy	0.936	0.594	0.292-2.998	0.912
Cigarette ever smoking during pregnancy	0.682	.180	0.479-0.970	.033
Having a previous neonatal death	1.156	0.329	0.607-2.201	0.660
Having a previous premature birth	1.479	0.239	0.925-2.365	0.102
Chronic diabetes	2.126	0.370	1.030-4.386	0.041
Gestational diabetes	2.414	0.175	1.713-3.400	0.000
Chronic maternal renal problems	4.611	0.770	1.019-20.854	0.047

ART use for the current pregnancy	2.512	0.188	1.737-3.632	0.000
Placenta previa	0.818	.728	0.196-3.410	0.783
Placenta abruptio	0.648	1.014	0.089-4.729	0.669
Maternal employment status during pregnancy	0.889	0.133	0.685-1.154	0.378
Prenatal care	1.156	0.462	0.467-2.861	0.753
Carrying a baby with birth defects	1.206	0.283	0.692-2.101	0.509
Maternal cardiovascular problems	1.922	0.0467	0.770-4.800	0.162
# of Gravida	0.883	0.042	0.813-0.959	.003
# of Abortions	1.075	.071	0.936-1.234	0.305
Maternal Education				
None	---------	-----	-----	0.348
< = Intermediate	1.296	0.438	0.549-3.062	0.554
High School	1.078	0.449	0.447-2.600	0.867
College	0.989	0.459	0.402-2.429	0.980
Paternal education				
None	----	----	-------	0.205
< = Intermediate	0.846	0.614	0.254-2.818	0.786
High School	0.554	0.646	0.156-1.966	0.361
College	0.966	0.631	0.281-3.325	0.956

Maternal religion				
Muslim	--------	------	-------	0.965
Druze	0.895	1.151	0.094-8.542	0.923
Christian	1.161	0.628	0.339-3.972	0.812
Paternal religion				
Muslim	----	-----	-------	0.975
Druze	1.205	1.149	0.127-11.464	0.871
Christian	1.110	0.630	0.323-3.816	0.868
Household crowding index	0.855	0.098	0.706-1.035	0.109
Hospital admitted class				
First Class	-----	--------	----	0.601
Second Class	1.006	0.200	0.679-1.488	0.978
Third Class	1.148	0.188	0.794-1.660	0.462
Type of gestation	-----	----	-------	0.021
Single	1.620	0.171	1.159-2.266	0.005
Twins	0.568	0.607	0.173-1.868	0.352
Triplets	000	000	0.000	000
more				
Pre-pregnancy Weight (kg)	1.018	0.009	1.000-1.035	0.049
Weight gain (Kg)	1.050	0.008	1.033-1.067	0.000
Pre-pregnancy BMI (Kg/m^2)	1.052	0.025	1.001-1.105	0.044

Maternal Age	1.055	.018	1.017-1.093	0.004

Table 1.7: 2nd Multivariate model- Effect of paternal age on the risk of developing preeclampsia among older mothers ≥ 35 years

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.002	0.010	0.983 -1.022	0.812
Propensity Score	----	----	----	0.000

3. Preeclampsia for Young Mother < 35 years

Table 1.8: 1st Multivariate model built to calculate propensity scores for the risk of developing preeclampsia for young mother < 35 years

Variable	OR	S.E	95% CI	P- value
Year of birth	1.001	0.017	0.969-1.035	0.934
Consanguinity	1.212	0.095	1.006-1.459	0.043
Arguile ever smoking during pregnancy	1. 205	0.119	0.954-1.523	0.118
Cigarette ever smoking during pregnancy	0.822	0.145	0.619-1.092	0.176
Alcohol consumption during pregnancy	1.296	0.346	0.657-2.556	0.454

Having a previous neonatal death	2.247	0.231	1.429-3.533	0.000
Having a previous premature birth	1.690	0.208	1.123-2.542	0.012
Chronic diabetes	2.784	0.296	1.560-4.970	0.001
Gestational diabetes	2.371	0.159	1.737-3.238	0.000
Chronic maternal renal problems	4.077	0.401	1.858-8.945	0.000
ART use for the current pregnancy	2.182	0.176	1.546-3.080	0.000
Placenta previa	2.911	0.396	1.340-6.321	0.007
Placenta abruptio	2.423	0.404	1.097-5.351	0.029
Maternal employment status during pregnancy	1.313	0.086	1.109-1.555	0.002
Prenatal care	0.904	0.284	0.518-1.578	0.722
Birth defects	2.426	0.154	1.794-3.280	0.000
Maternal cardiovascular problems	4.458	0.253	2.715-7.319	0.000
# of Gravida	0.712	0.043	0.654-0.775	0.000
# of Abortions	1.443	0.046	1.318-1.581	0.000
Maternal Education **None** **< = Intermediate**	----- 0.891	---- 0.331	---- 0.465-1.706	0.610 0.727

High School	0.948	0.335	0.491-1.828	0.872
College	0.840	0.340	0.432-1.634	0.607
Paternal education				
None	----	----	----	0.501
< = Intermediate	1.719	0.594	0.536-5.510	0.362
High School	0.612	0.600	0.612-6.440	0.253
College	0.544	0.602	0.544-5.769	0.343
Maternal religion				
Muslim	---	----	----	0.111
Druze	2.246	0.624	0.661-7.633	0.195
Christian	1.892	0.364	0.926-3.865	0.080
Paternal religion				
Muslim	----	----	----	0.282
Druze	0.542	0.646	0.153-1.921	0.343
Christian	0.609	0.368	0.296-1.252	0.178
Household crowding index	1.010	0.061	0.897-1.137	0.871
Hospital admitted class				
First Class	---	----	----	0.032
Second Class	1.001	0.144	0.755-1.328	0.994
Third Class	1.266	0.134	0.974-1.646	0.078
Type of gestation				
Single	---	---	---	0.000
Twins	1.996	0.123	1.567-2.543	0.000
Triplets	1.801	0.277	1.046-3.101	0.034
more	1.896	1.038	0.248-14.511	0.538

Pre pregnancy Weight	1.020	0.006	1.008-1.032	0.001
Weight gain	1.065	0.005	1.054-1.075	0.000
Pre pregnancy BMI	1.060	0.017	1.026-1.096	0.001
Maternal Age	1.047	0.009	1.028-1.067	0.000

Table 1.9: 2nd Multivariate model- Effect of paternal age on the risk of developing preeclampsia among young mothers < 35 years

Variable	**OR**	**S.E**	**95% CI**	**P- value**
Paternal Age	1.013	0.006	1.0003-1.025	0.045
Propensity Score	----	----	----	0.000

B. Eclampsia

Table 2.1: Percent distribution of all women admitted for delivery by socio-demographic characteristic and eclampsia

	Eclampsia **N= 193 (0.1%)**	**No-Eclampsia** **N= 143223**	**P Value**
Mean maternal age	30.2 ± 6.1 Min= 17 Max= 45	28.7 ± 5.8 Min= 10 Max= 56	0.001
Mean paternal age	35.9 ± 6.2 Min= 21 Max= 50	34.3 ± 6.3 Min= 15 Max= 80	0.000
Mean age difference Between mother and father	5.8 ± 5.0	5.6 ± 4.3	0.647
Consanguinity	12.4%	15.2%	0.285
Maternal education			
None	1.6 %	1.8%	0.167
< = Intermediate	47.1 %	39.5%	0.594
High School	26.4 %	28.2%	0.903
College	24.9 %	30.5%	0.910
Paternal education			
None	1.0 %	0.8%	0.414
< = Intermediate	76.2 %	78.3%	0.660
High School	13.5 %	10.1%	0.996
College	9.3 %	10.8%	0.558
Mother's Religion			

Muslim	85.0 %	79.7%	0.001
Druze	5.7 %	2.7%	0.025
Christian	9.3 %	17.6%	0.005
Father's Religion			
Muslim	86.0 %	80.0%	0.001
Druze	5.2 %	2.6%	0.060
Christian	8.8 %	17.4%	0.003
Hospital Admitted Class			
First Class	4.1 %	9.0%	0.061
Second Class	22.8 %	20.1%	0.019
Third Class	73.1 %	70.9%	0.026

Table 2.2: Percent distribution of all women admitted for delivery by obesity and life style characteristics and eclampsia

Characteristics	**Eclampsia N= 193 (0.1%)**	**No-Eclampsia N= 143223**	**P Value**
Mean pre-pregnancy BMI (kg/m2)	26.4 ± 5.2	23.8 ± 3.6	0.000
Mean pre-pregnancy Weight (Kg)	70.7 ± 15.3	62.9 ± 10.4	0.000
Mean weight gain (Kg)	14.4 ± 7.5	12.8 ± 5.4	0.000
Cigarette ever-smokers during pregnancy	13.5%	8.2%	0.009
Arguile ever- smokers during pregnancy	9.8%	7.1%	0.139

Alcohol consumption during pregnancy	1.0%	0.5%	0.360
Maternal employment status during pregnancy	20.7%	22.3%	0.609

Table 2.3: Percent distribution of all women admitted for delivery by clinical characteristic and eclampsia

Characteristics	**Eclampsia N= 193 (0.1%)**	**No-Eclampsia N= 143223**	**P Value**
Primigravidae	29.3 %	30.7%	0.095
Prior Abortion	30.2%	25.5%	0.198
Chronic Diabetes	1.6 %	0.4%	0.015
Gestational Diabetes	6.2%	1.8%	0.000
Chronic Cardiovascular Diseases	3.1%	0.5%	0.000
Chronic Renal Diseases	0.0%	0.1%	0.996
Carrying a baby with birth defects	3.6%	1.9%	0.080
Placenta Previa	0.5%	0.3%	0.485
Placenta Abruptio	0.5%	0.3%	0.473
ART use for the current pregnancy	2.6%	1.5%	0.215

Having a previous neonatal death	1.0%	1.6%	0.549
Having a previous premature birth	2.1%	2.2%	0.935
Type of Gestation			
Single	89.6 %	95.9%	0.000
Twins	8.8 %	3.7%	0.000
Triplets	1.6 %	0.4%	0.016
more	0.0 %	0.0%	0.998

1. Eclampsia for All Mothers

Table 2.4: 1st Multivariate model built to calculate propensity scores for the risk of developing eclampsia

Variable	**OR**	**S.E**	**95% CI**	**P- value**
Year of birth	0.767	0.036	0.714-0.823	0.000
Consanguinity	0.715	0.222	0.463-1.106	0.132
Arguile ever smoking during pregnancy	1.396	0.247	0.860-2.264	0.177
Cigarette ever smoking during pregnancy	1.361	0.220	0.885-2.093	0.160
Alcohol consumption during pregnancy	2.145	0.727	0.516-8.923	0.294
Having a previous neonatal death	0.503	0728	0.121-2.098	0.346

Having a previous premature birth	1.258	0.521	0.453-3.495	0.660
Chronic diabetes	1.511	0.613	0.454-5.027	0.501
Gestational diabetes	2.595	0.316	1.396-4.824	0.003
Chronic maternal renal problems	0.000		0.000-0.000	
ART use for the current pregnancy	1.019	0.504	0.380-2.735	0.970
Placenta Previa	2.179	1.018	0.297-16.014	0.444
Placenta abruptio	1.530	1.011	0.211-11.090	0.674
Maternal employment status during pregnancy	1.133	0.206	0.757-1.698	0.544
Prenatal care	1.403	0.718	0.343-5.729	0.637
Carrying a baby with birth defects	1.553	0.396	0.714-3.375	0.267
Maternal cardiovascular problems	4.821	0.431	2.072-11.217	0.000
# of Gravida	0.915	0.066	0.804-1.040	0.175
# of Abortions	1.105	0.082	0.941-1.298	0.224
Maternal Education				
None	-----	---	------	0.855 (Ref)
< = Intermediate	1.116	0.612	0.337-3.701	0.857
High School	0.963	0.627	0.282-3.291	0.952
College	0.958	0.643	0.272-3.376	0.946

Paternal education				
None	-----	----	-----	0.081 (Ref)
< = Intermediate	1.125	0.740	0.264-4.795	0.874
High School	0.844	0.763	0.189-3.770	0.825
College	0.521	0.785	0.112-2.430	0.407
Maternal religion				
Muslim	-----	----	----	0.312
Druze	3.960	0.951	0.614-25.550	0.148
Christian	1.656	0.905	0.281-9.752	0.577
Paternal religion				
Muslim	----	----	----	0.332
Druze	0.476	0.992	0.068-3.327	0.454
Christian	0.296	0.927	0.048-1.821	0.189
Household crowding index	1.016	0.125	0.795-1.298	0.899
Hospital admitted class				
First Class	----	----	-----	0.001
Second Class	2.196	0.404	0.994-4.851	0.052
Third Class	1.038	0.408	0.467-2.308	0.927
Type of gestation				
Single	----	----	----	0.030
Twins	2.052	0.271	1.205-3.494	0.008
Triplets	2.934	0.620	0.871-9.889	0.082
more	0.000	0.000	0.000-0.000	0.998
Pre pregnancy Weight (Kg)	1.035	0.011	1.012-1.058	0.003

Weight gain (Kg)	1.050	0.011	1.028-1.072	0.000
Pre Pregnancy BMI (Kg/m^2)	1.053	0.032	0.988-1.122	0.110
Maternal Age	1.032	0.015	1.003-1.1.062	0.028

Table 2.5: 2nd Multivariate model- Effect of paternal age on the risk of developing eclampsia

Variable	**OR**	**S.E**	**95% CI**	**P- value**
Paternal Age	1.036	0.011	1.014-1.059	0.001
Propensity Score	----	----	----	0.000

2. Eclampsia for Older Mothers ≥35 Years

Table 2.6: 1st Multivariate model built to calculate propensity scores for the risk of developing eclampsia for older mothers ≥35 years

Variable	**OR**	**S.E**	**95% CI**	**P- value**
Year of birth	0.705	0.080	0.603-0.825	0.000
Consanguinity	0.864	0.423	0.377-1.978	0.729
Arguile ever smoking during pregnancy	1.309	0.612	0.394-4.345	0.660
Cigarette ever smoking	2.123	0.341	1.089-4.141	0.027

during pregnancy				
Alcohol consumption during pregnancy	3.882	1.063	0.483-31.182	0.202
Having a Previous neonatal death	0.548	1.040	0.071-4.203	0.563
Having a Previous premature birth	0.623	1.046	0.080-4.838	0.651
Chronic diabetes	2.834	0.826	0.562-14.296	0.207
Gestational diabetes	1.590	0.598	0.493-5.129	0.438
Chronic maternal renal problems	0000	000	000	
ART use for the current pregnancy	1.848	0.661	0.505-6.754	0.353
Placenta previa	5.909	1.069	0.727-48.025	0.097
Placenta abruptio	000	0000	0000	
Maternal employment status during pregnancy	2.049	0.391	0.952-4.414	0.067
Prenatal care	0.825	1.038	0.108-6.319	0.853
Carrying a baby with birth defects	1.853	0.651	0.518-6.635	0.343
Maternal cardiovascular problems	4.482	0.757	1.016-19.763	0.048
# of Gravida	1.098	0.092	0.917-1.315	0.309

# Abortions	0.875	0.172	0.624-1.226	0.437
Maternal Education				-------
None	-----	----	-----	0.448
< = Intermediate	2.325	1.110	0.264-20.457	0.447
High School	1.457	1.157	0.151-14.062	0.745
College	1.252	1.196	0.120-13.042	0.851
Paternal education				
None	----	-----	----	0.134
< = Intermediate	0.570	1.101	0.066-4.935	0.610
High School	0.509	1.157	0.053-4.906	0.559
College	0.049	1.506	0.003-0.944	0.046
Maternal religion				
Muslim	---	----	-----	0.089
Druze	13.975	1.221	1.276-153.088	0.031
Christian	0.465	2.267	0.005-39.552	0.736
Paternal religion				
Muslim	----	---	---	0.153
Druze	0.048	1.565	0.002-1.035	0.053
Christian	0.970	2.266	0.011-82.351	0.989
Household crowding index	0.593	0.261	0.356-0.988	0.045
Hospital admitted class				
First Class	----	----		0.004
Second Class	2.489	0.689	0.645-9.606	0.186
Third Class	0.627	0.740	0.147-2.672	0.528

Type of gestation				
Single	---	---	----	0.106
Twins	1.839	0.532	0.649-5.217	0.252
Triplets	7.752	0.852	1.461-41.141	0.016
more	000	000	0000	---
Pre-pregnancy weight (Kg)	1.037	0.022	0.994-1.082	0.096
Weight gain (Kg)	1.048	0.022	1.004-1.094	0.032
Pre-pregnancy BMI (kg/m^2)	1.030	0.063	0.911-1.165	0.634
Maternal Age	1.049	0.051	0.949-1.159	0.352

Table 2.7: 2nd Multivariate model- Effect of paternal age on the risk of developing eclampsia for older mothers ≥ 35 years

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.001	0.009	0.982-1.019	0.949
Propensity Score	----	----	----	0.000

3. Eclampsia for Young Mothers < 35 years

Table 2.8: 1st Multivariate model built to calculate propensity scores for the risk of developing eclampsia for young mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Year of birth	0.785	0.041	0.724-0.851	0.000
Consanguinity	0.674	0.263	0.402-1.128	0.133
Arguile ever smoking during pregnancy	1.418	0.271	0.833-2.412	0.198
Cigarette ever smoking during pregnancy	1.009	0.308	0.552-1.845	0.977
Alcohol consumption during pregnancy	1.344	1.027	0.179-10.058	0.774
Having a previous neonatal death	0.482	1.020	0.065-3.558	0.474
Having a previous premature birth	1.727	0.600	0.533-5.602	0.362
Chronic diabetes	0.744	1.035	0.098-5.650	0.775
Gestational diabetes	3.239	0.378	1.543-6.798	0.002
Chronic maternal renal Problems	0000	000	000	0000
ART use for the current pregnancy	0.347	1.043	0.045-2.681	0.311
Placenta previa	0000	000	000	000

Placenta abruptio	2.386	1.014	0.327-17.407	0.391
Maternal employment status during pregnancy	0.927	0.247	0.571-1.504	0.758
Prenatal care	1.898	1.009	0.263-13.718	0.525
Carrying a baby with birth defects	1.414	0.511	0.519-3.852	0.498
Maternal cardiovascular problems	5.580	0.526	1.989-15.650	0.001
# of Gravida	0.804	0.093	0.671-0.964	0.019
# of Abortions	1.265	0.099	1.041-1.536	0.018
Maternal Education				
None	-----	----	----	0.988
< = Intermediate	0.868	0.740	0.204-3.697	0.848
High School	0.815	0.754	0.186-3.574	0.786
College	0.833	0.770	0.184-3.768	0.813
Paternal education				
None	----		-----	0.440
< = Intermediate	1.534		0.203-11.587	0.678
High School	1.116		0.141-8.827	0.917
College	0.959		0.118-7.782	0.969
Maternal religion				
Muslim	----	----	----	0.765
Druze	1.285	1.484	0.070-23.559	0.866
Christian	2.039	0.975	0.301-13.790	0.465

Paternal religion				
Muslim	---	----	-----	0.283
Druze	1.832	1.484	0.100-33.595	0.683
Christian	0.229	1.013	0.031-1.665	0145
Household crowding index	1.230	0.138	0.939-1.611	0.132
Hospital admitted class				
First Class	----	----	----	0.061
Second Class	2.044	0.504	0.761-5.489	0.156
Third Class	1.184	0.500	0.444-3.159	0.735
Type of gestation				
Single	----	----	-----	0.060
Twins	2.326	0.313	1.260-4.294	0.007
Triplets	1.725	1.028	0.230-12.937	0.596
more	000	000	000	0.998
Pre pregnancy weight (Kg)	1.035	0.014	1.008-1.063	0.011
Weight gain (Kg)	1.049	0.012	1.024-1.075	0.000
Pre pregnancy BMI (Kg/m^2)	1.059	1.059	0.983-1.141	0.130
Maternal Age	1.043	0.023	0.996-1.091	0.072

Table 2.9: 2nd Multivariate model- Effect of paternal age on the risk of developing eclampsia for young mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.016	0.006	1.004-1.027	0.007
Propensity Score	----	----	----	0.000

C. Placenta Previa

Table 3.1: Percent distribution of all women admitted for delivery by socio-demographic characteristic and placenta previa

Characteristics	Placenta Previa N= 372 (0.3%)	No-Placenta Previa N= 143577	P value
Mean maternal age	31.6 ± 5.8 Min 15- Max 52	28.7 ± 5.8 Min 10- Max 56	0.000
Mean paternal age	36.8 ± 6.4 Min 20- Max 61	34.3 ± 6.3 Min 15- Max 80	0.000
Mean age difference between mother and father	5.3 ± 4.4	5.6 ± 4.3	0.134
Consanguinity	11.0%	15.2%	0.024
Maternal education			
None	1.6 %	1.8%	0.000
< = Intermediate	30.1 %	39.6%	0.685
High School	25.6 %	28.2%	0.990
College	42.7 %	30.4%	0.286
Paternal education			
None	0.0 %	0.8%	0.000
< = Intermediate	91.9 %	78.3%	0.990
High School	3.5 %	10.1%	0.991
College	4.6 %	10.8%	0.990
Mother's Religion			
Muslim	58.3 %	79.8%	0.000
Druze	2.4 %	2.7%	0.517

Christian	39.3 %	17.5%	0.000
Father's Religion			
Muslim	58.6 %	80.1%	0.000
Druze	2.4 %	2.6%	0.484
Christian	39.0 %	17.3%	0.000
Hospital Admitted Class			
First Class	28.8 %	9.0%	0.000
Second Class	24.7 %	20.0%	0.000
Third Class	46.5 %	71.0%	0.000

Table 3.2: Percent distribution of all women admitted for delivery by obesity and life style characteristics and placenta previa

Characteristics	**Placenta Previa N= 372 (0.3%)**	**No-Placenta Previa N= 143577**	**P value**
Mean pre-pregnancy BMI (kg/m2)	23.2 ± 3.5	23.8 ± 3.6	0.001
Mean pre-pregnancy Weight (Kg)	61.5 ± 9.4	62.9 ± 10.4	0.008
Mean weight gain (Kg)	12.4 ± 5.5	12.9 ± 5.4	0.106
Cigarette ever-smokers during pregnancy	9.7%	8.3%	0.321
Arguile ever- smokers during pregnancy	5.4%	7.1%	0.197
Alcohol consumption	1.9%	0.5%	0.001

during pregnancy			
Maternal employment status during pregnancy	28.5%	22.2%	0.004

Table 3.3: Percent distribution of all women admitted for delivery by clinical characteristic and placenta previa

Characteristics	**Placenta Previa N= 372 (0.3%)**	**No-Placenta Previa N= 143577**	**P value**
Multigravidae	72.0 %	68.6%	0.009
Chronic Diabetes	0.5 %	0.4%	0.663
Gestational Diabetes	4.3%	1.8%	0.000
Chronic Cardiovascular Diseases	0.3%	0.5%	0.507
Chronic Hypertensive Disorder	0.5%	0.4%	0.597
Maternal Hemoglobinopathies	2.4%	0.4%	0.000
Maternal Antepartum Anemia	3.0%	1.8%	0.112
Maternal Thyroid disorders	2.4%	0.7%	0.000
Maternal Chronic Respiratory disorders	1.1%	0.9%	0.785
Carrying a baby with	6.2%	1.9%	0.000

birth defects			
Preeclampsia	3.0%	0.9%	0.000
Eclampsia	0.3%	0.1%	0.512
ART use for the current pregnancy	10.8%	1.5%	0.000
Having a previous neonatal death	2.4%	1.6%	0.202
Having a previous premature birth	6.2%	2.2%	0.000
Prior Abortion	35.2%	26.4%	0.000
Previous CS/Myomectemy	16.1%	14.2%	0.299
Polyhydraminous	1.3%	1.2%	0.859
Oligohydraminous	3.5%	3.3%	0.874
Type of Gestation			
Single	89.8 %	95.9%	0.000
Twins	7.2 %	3.7%	0.000
Triplets	3.0 %	0.4%	0.000
more	0.0 %	0.0%	0.998

Figure 3.1: Risk of developing placenta previa by maternal age

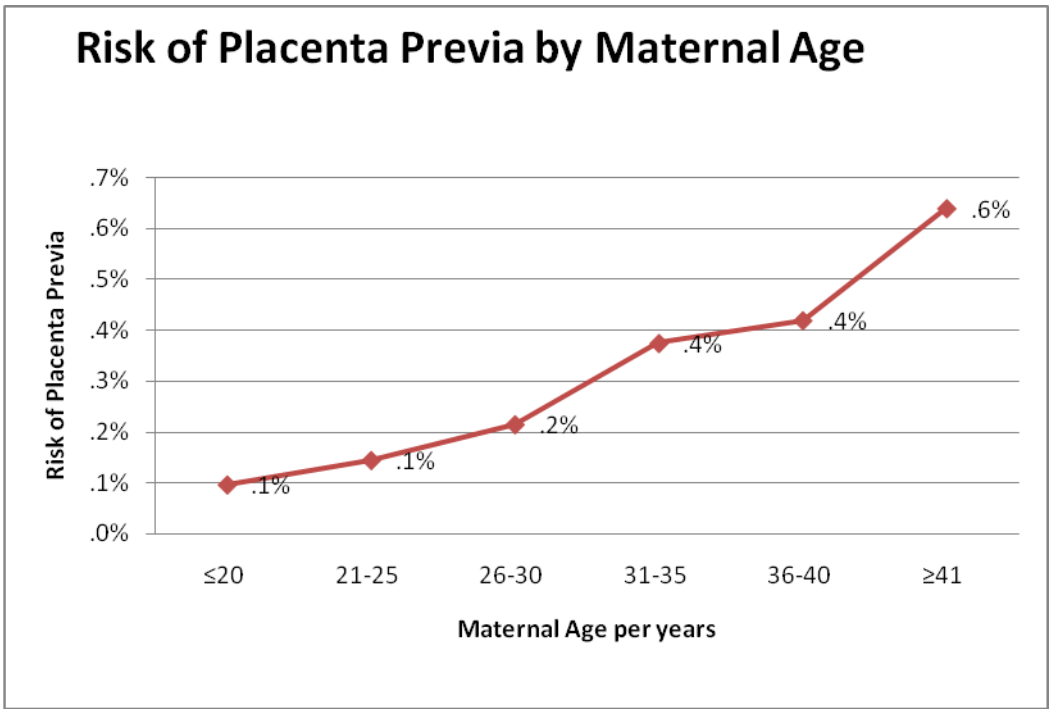


Figure 3.2: Risk of developing placenta previa by paternal age

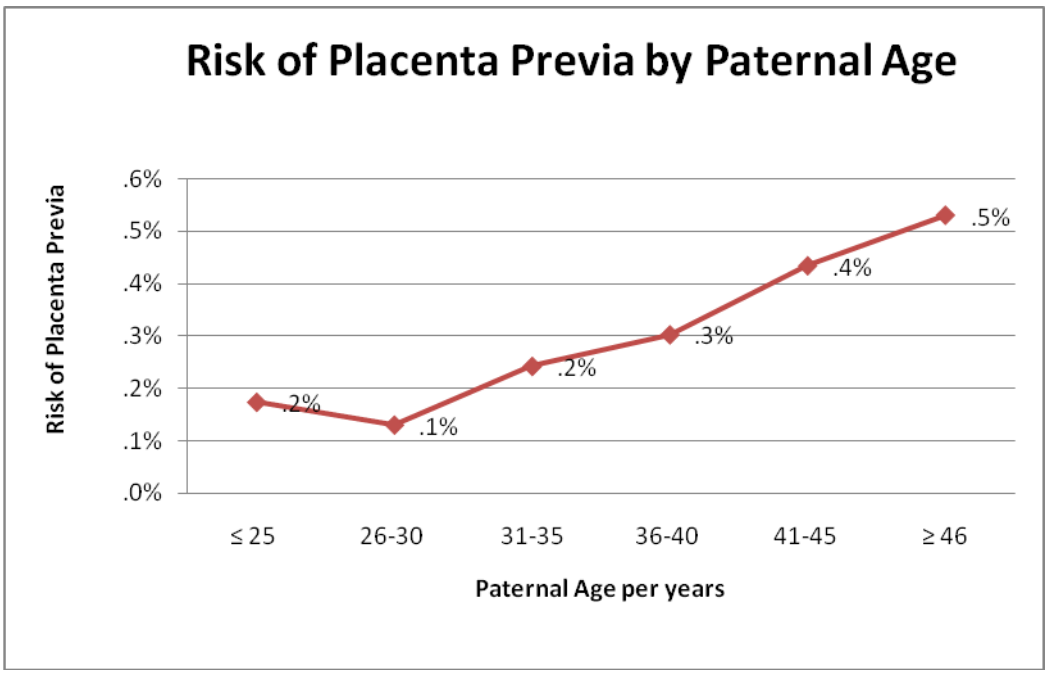
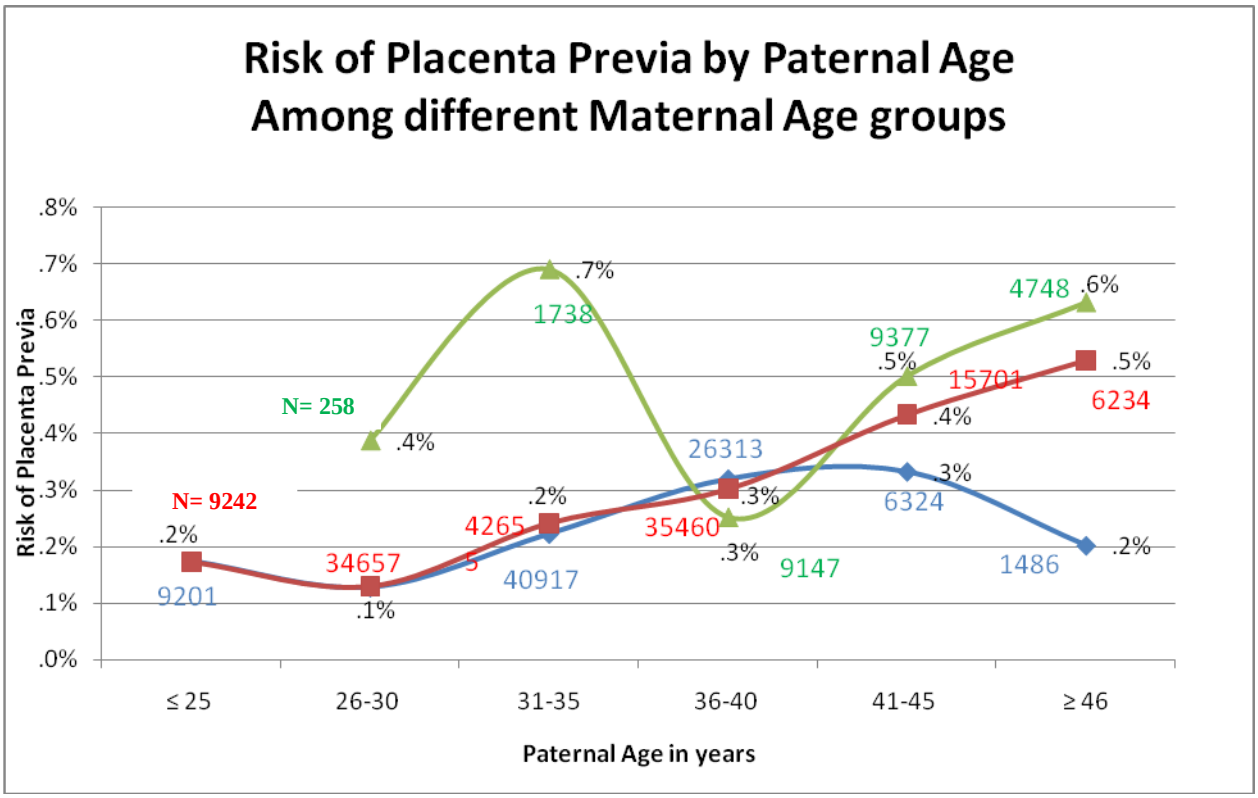


Figure 3.3: Risk of developing placenta previa by paternal age among different maternal age groups



1. Placenta Previa for All Mothers

Table 3.4: 1st Multivariate model built to calculate propensity scores for the risk of developing placenta previa

Variable	OR	S.E	95% CI	P- value
Year of birth	1.105	0.030	1.043-1.171	0.001
Consanguinity	0.925	0.173	0.658-1.299	0.653
Arguile ever smoking during pregnancy	1.006	0.240	0.628-1.611	0.982
Cigarette ever smoking during pregnancy	1.244	0.183	0.869-1.782	0.233
Alcohol consumption during pregnancy	2.105	0.392	0.976-4.539	0.058
Having a Previous neonatal death	1.203	0.359	0.595-2.432	0.606
Having a Previous premature birth	1.883	0.232	1.196-2.966	0.006
Chronic diabetes	1.100	0.724	0.266-4.549	0.895
Gestational diabetes	1.400	0.265	0.833-2.353	0.204
ART use for the current pregnancy	2.645	0.230	1.684-4.153	0.000
Preeclampsia	2.205	0.321	1.175-4.137	0.014
Eclampsia	2.166	1.020	0.293-15.999	0.449

Chronic Hypertension disorder	0.846	0.733	0.201-3.556	0.819
Mother employment status during pregnancy	0.738	0.134	0.568-0.960	0.023
Prenatal care	3.083	0.712	0.764-12.449	0.114
Carrying a baby with birth defects	3.057	0.222	1.980-4.720	0.000
Maternal cardiovascular problems	0.561	1.007	0.078-4.043	0.566
# of Gravida	0.988	0.051	0.893-1.092	0.808
# of Abortions	1.213	0.073	1.051-1.399	0.008
Maternal Education				
None	----	-----	-----	0.632 (Ref)
< = Intermediate	0.707	0.427	0.306-1.632	0.416
High School	0.716	0.437	0.304-1.685	0.444
College	0.820	0.443	0.344-1.955	0.654
Paternal education				
None	---		------	0.185 (Ref)
< = Intermediate			0.000-----	0.990
High School			0.000----	0.991
College			0.000------	0.991
Maternal religion				
Muslim	----	-----	----	0.869 (Ref)
Druze	0.919	1.269	0.076-11.051	0.947
Christian	1.372	0.624	0.404-4.661	0.612

Paternal religion				
Muslim	----	----	-------	0.856
Druze	1.455	1.269	0.121-17.505	0.768
Christian	1.378	0.625	0.405-4.686	0.608
Household crowding index	0.929	0.098	0.767-1.125	0.450
Hospital admitted class				
First Class	----	-----	-----	0.000
Second Class	0.673	0.162	0.490-0.924	0.014
Third Class	0.514	0.161	0.374-0.705	0.000
Type of gestation				
Single	------	----	-----	0.071
Twins	1.057	0.234	0.668-1.674	0.811
Triplets	2.605	0.368	1.267-5.356	0.009
more	0.000	0.0000	0.00-0.00	0.997
Pre pregnancy weight (Kg)	0.992	0.010	0.972-1.013	0.449
Weight gain (Kg)	0.968	0.010	0.949-0.987	0.001
Pre pregnancy BMI (Kg/m^2)	0.951	0.030	0.896-1.010	0.100
Maternal Age	1.055	0.011	1.034-1.078	0.000
Maternal chronic respiratory problems	0.877	0.508	0.324-2.377	0.797
Maternal Thyroid	1.470	0.346	0.747-2.894	0.265

problems				
Maternal ante partum anemia	1.282	0.312	0.696-2.361	0.426
Maternal Hemoglobinopathies	2.101	0.361	1.035-4.265	0.040
Oligohydraminos	1.115	0.287	0.635-1.957	0.706
Polihydraminos	0.937	0.454	0.385-2.281	0.887
Previous CS/Myomectomy/uterine surgery	0.944	0.147	0.708-1.259	0.696

Table 3.5: 2nd Multivariate model- Effect of paternal age on the risk of developing placenta previa

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.047	0.008	1.031-1.063	0.000
Propensity Score	----	----	----	0.000

2. Placenta Previa for Older Mothers ≥ 35 years

Table 3.6: 1st Multivariate model built to calculate propensity scores for the risk of developing placenta previa for older mom ≥35

Variable	OR	S.E	95% CI	P- value
Year of birth	1.146	0.055	1.028-1.278	0.014

Consanguinity	1.817	0.294	1.021-3.234	0.042
Arguile ever smoking during pregnancy	0.633	0.722	0.154-2.604	0.526
Cigarette ever smoking during pregnancy	1.294	0.293	0.729-2.296	0.378
Alcohol consumption during pregnancy	1.858	0.749	0.428-8.069	0.408
Having a previous neonatal death	0.348	1.028	0.046-2.610	0.304
Having a previous premature birth	1.121	0.440	0.473-2.652	0.796
Chronic diabetes	0000	000	0000	
Gestational diabetes	1.079	0.434	0.461-2.528	0.860
Maternal Chronic Hypertensive Disorder	2.242	0.749	0.516-9.738	0.281
ART use for the current pregnancy	3.007	0.314	1.625-5.564	0.000
Preeclampsia	1.592	0.538	0.554-4.574	0.387
Eclampsia	6.084	1.086	0.724-51.133	0.096
Mother employment status during pregnancy	0.657	0.235	0.415-1.042	0.074
Prenatal care	000	000	000	
Carrying a baby with birth defects	3.121	0.382	1.475-6.605	0.003

Maternal cardiovascular problems	000	000	000	
# of Gravida	0.960	0.082	0.817-1.128	0.620
# of Abortions	1.157	0.118	0.917-1.459	0.220
Maternal Education				
None	---	---	---	0.520
< = Intermediate	0.455	0.625	0.134-1.548	0.207
High School	0.545	0.640	0.155-1.912	0.343
College	0.613	0.661	0.168-2.238	0.459
Paternal education				
None	---	---	---	0.054
< = Intermediate	000	000	000	0.995
High School	000	000	000	0.996
College	000	000	000	0.966
Maternal religion				
Muslim	----	----	----	0.999
Druze	0000	0000	0000	0.992
Christian	0.946	1.255	0.081-11.081	0.965
Paternal religion				
Muslim	---	---	----	0.794
Druze	000	000	000	0.992
Christian	2.344	1.255	0.200-27.449	0.497
Household crowding index	0.755	0.195	0.515-1.107	0.150

Hospital admitted class				
First Class	----	----	---	0.321
Second Class	0.636	0.301	0.353-1.146	0.132
Third Class	0.778	0.277	0.452-1.340	0.366
Type of gestation				
Single	---	---	---	0.755
Twins	0.660	0.391	0.306-1.420	0.288
Triplets	0.701	0.785	0.150-3.264	0.650
more	0000	0000	0000	0.999
Weight before pregnancy (Kg)	1.009	0.018	0.974-1.046	0.613
Weight gain (Kg)	0.982	0.018	0.947-1.018	0.312
BMI (Kg/m^2)	0.911	0.054	0.819-1.012	0.081
Maternal Age	1.035	0.035	0.968-1.108	0.315
Maternal chronic respiratory problems	0.438	1.024	0.059-3.258	0.420
Maternal Thyroid problems	2.094	0.475	0.826-5.308	0.119
Maternal ante partum anemia	1.290	0.597	0.400-4.159	0.670
Maternal Hemoglobinopathies	4.365	0.465	1.753-10.868	0.002
Oligohydraminos	0.626	0.723	0.152-2.585	0.518
Polihydraminos	1.196	0.727	0.288-4.972	0.806

Previous CS/Myomectomy/uterine surgery	1.015	0.240	0.634-1.625	0.949

Table 3.7: 2nd Multivariate model- Effect of paternal age on the risk of developing placenta previa for older mothers ≥35 years

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.017	0.019	0.980-1.055	0.377
Propensity Score	----	----	----	0.000

3. Placenta Previa for Younger Mothers < 35 years

Table 3.8: 1st Multivariate model built to calculate propensity scores for the risk of developing placenta previa for young mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Year of birth	1.084	0.035	1.012-1.161	0.021
Consanguinity	0.701	0.218	0.457-1.075	0.103
Arguile ever smoking during pregnancy	1.099	0.256	0.665-1.815	0.714
Cigarette ever smoking during pregnancy	1.233	0.235	0.777-1.956	0.373
Alcohol consumption	2.211	0.465	0.889-5.497	0.088

during pregnancy				
Having a previous neonatal death	1.660	0.390	0.773-3.564	0.193
Having a previous premature birth	2.365	0.276	1.377-4.063	0.002
Chronic diabetes	2.211	0.729	0.530-9.228	0.276
Gestational diabetes	1.717	0.332	0.896-3.288	0.103
Maternal Chronic Hypertensive Disorder	0000	0000	0000	
ART use for the current pregnancy	2.058	0.337	1.063-3.984	0.032
Preeclampsia	2..818	0.398	1.291-6.149	0.009
Eclampsia	0000	000	0000	
Maternal employment status during pregnancy	0.757	0.165	0.548-1.045	0.090
Prenatal care	2.216	0.714	0.547-8.986	0.265
Carrying a baby with birth defects	3.056	0.273	1.788-5.223	0.000
Maternal cardiovascular problems	0.860	1.012	0.118-6.245	0.881
# of Gravida	1.016	0.069	0.887-1.164	0.821
# of Abortions	1.258	0.098	1.038-1.524	0.019

Maternal Education				
None	---	----	----	0.844
< = Intermediate	0.881	0.596	0.274-2.834	0.831
High School	0.863	0.607	0.263-2.837	0.809
College	1.001	0.613	0.301-3.328	0.999
Paternal education				
None	----	----	----	0.833
< = Intermediate	000	000	000	0.992
High School	000	000	000	0.992
College	000	000	000	0.992
Maternal religion				
Muslim	---	---	---	0.861
Druze	1.021	1.370	0.070-14.960	0.988
Christian	1.489	0.735	0.353-6.294	0.588
Paternal religion				
Muslim	---	-----	----	0.887
Druze	1.928	1.370	0.132-28.245	0.632
Christian	1.139	0.737	0.269-4.833	0.859
Household crowding index	0.988	0.114	0.790-1.236	0.916
Hospital admitted class				
First Class	----	---	----	0.000
Second Class	0.669	0.194	0.457-0.979	0.038
Third Class	0.423	0.199	0.286-0.625	0.000

Type of gestation **Single** **Twins** **Triplets** **more**	--- 1.369 5.086 000	---- 0.288 0.431 000	---- 0.779-2.405 2.184-11.843 000	0.003 0.275 0.000 0.998
Pre pregnancy Weight (Kg)	0.982	0.013	0.958-1.008	0.167
Weight gain (Kg)	0.962	0.012	0.940-0.985	0.001
Pre pregnancy BMI (Kg/m^2)	0.975	0.038	0.906-1.049	0.497
Maternal Age	1.071	0.019	1.032-1.112	0.000
Maternal chronic respiratory problems	1.190	0.584	0.379-3.736	0.766
Maternal Thyroid problems	1.177	0.512	0.431-3.212	0.751
Maternal ante partum anemia	1.247	0.367	0.608-2.561	0.547
Maternal Hemoglobinopathies	0.948	0.611	0.286-3.141	0.931
Oligohydraminos	1.389	0.313	0.752-2.566	0.294
Polihydraminos	0.831	0.584	0.264-2.609	0.751
Previous CS/Myomectomy/uterine surgery	0.874	0.187	0.606-1.260	0.470

Table 3.9: 2nd Multivariate model- Effect of paternal age on the risk of developing placenta previa for young mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.049	0.011	1.026-1.071	0.000
Propensity Score	----	----	----	0.000

D. Placenta Abruptio

Table 4.1: Percent distribution of all women admitted for delivery by socio-demographic characteristic and placenta abruptio

Characteristics	Placenta Abruptio N= 365 (0.3%)	No-Placenta Abruptio N= 143584	P value
Mean Maternal Age	30.7 ± 5.7 Min 18- Max 45	28.7 ± 5.8 Min 10- Max 56	0.000
Mean Paternal Age	36.3 ± 5.9 Min 22- Max 59	34.3 ± 6.3 Min 15- Max 80	0.000
Mean age difference between mother and father	5.6 ± 4.4	5.6 ± 4.3	0.823
Consanguinity	12.9%	15.2%	0.210
Maternal education			
None	0.6 %	1.8%	0.000
< = Intermediate	32.6 %	39.6%	0.165
High School	23.8 %	28.2%	0.155
College	43.0 %	30.4%	0.031
Paternal education			
None	0.5 %	0.8%	0.000
< = Intermediate	56.7 %	78.4%	0.967
High School	19.5 %	10.0%	0.157
College	23.3 %	10.8%	0.117
Mother's Religion			
Muslim	65.5 %	79.8%	0.000

Druze	5.5 %	2.7%	0.000
Christian	29.0 %	17.5%	0.000
Father's Religion			
Muslim	65.5 %	80.1%	0.000
Druze	5.7 %	2.6%	0.000
Christian	28.8 %	17.3%	0.000
Hospital Admitted Class			
First Class	14.0 %	9.0%	0.000
Second Class	4.4 %	20.1%	0.000
Third Class	81.6 %	70.9%	0.049

Table 4.2: Percent distribution of all women admitted for delivery by obesity and life style characteristics and placenta abruptio

Characteristics	**Placenta Abruptio N= 365 (0.3%)**	**No-Placenta Abruptio N= 143584**	**P Value**
Mean pre-pregnancy BMI (kg/m2)	23.45 ± 3.6	23.8 ± 3.6	0.062
Mean pre-pregnancy Weight (Kg)	62.41 ± 10.2	62.9 ± 10.4	0.356
Mean weight gain (Kg)	12.9 ± 5.0	12.9 ± 5.4	0.882
Cigarette ever-smokers during pregnancy	10.7%	8.3%	0.093
Arguile ever- smokers during pregnancy	4.7%	7.1%	0.071
Alcohol consumption during pregnancy	0.8%	0.5%	0.470

Maternal employment status during pregnancy	33.4%	22.2%	0.000

Table 4.3: Percent distribution of all women admitted for delivery by clinical characteristic and placenta abruptio

	Placenta Abruptio N= 365 (0.3%)	**No-Placenta Abruptio N= 143584**	**P Value**
Multigravidae	71.8 %	68.6%	0.003
Chronic Diabetes	1.4 %	0.4%	0.005
Gestational Diabetes	3.0%	1.8%	0.085
Chronic Cardiovascular Diseases	1.9%	0.5%	0.001
Chronic Hypertensive Disorder	0.5%	0.4%	0.578
Maternal Hemoglobinopathies	1.4%	0.4%	0.003
Maternal Antepartum Anemia	0.8%	1.8%	0.158
Maternal Thyroid disorders	1.1%	0.7%	0.401
Maternal Chronic Respiratory disorders	1.9%	0.9%	0.058
Carrying a baby with birth Defects	6.3%	1.9%	0.000

Preeclampsia	2.2%	0.9%	0.016
Eclampsia	0.3%	0.1%	0.500
ART use for the current pregnancy	4.9%	1.5%	0.000
Having a previous neonatal death	3.0%	1.6%	0.032
Having a previous premature birth	1.4%	2.2%	0.295
Prior Abortion	33.2%	26.4%	0.003
Previous CS/ Myomectemy	12.3%	14.3%	0.294
Polyhydraminous	1.6%	1.2%	0.489
Oligohydraminous	6.0%	3.3%	0.005
Prolonged Rupture of Membrane > 24	0.8%	0.3	0.111
Intrapartum fever > 38	1.6%	0.9	0.117
Type of Gestation			
Single	89.0 %	95.9%	0.000
Twins	9.1 %	3.7%	0.000
Triplets	1.9 %	0.4%	0.000
more	0.0 %	0.0%	0.998

Figure 4.1: Risk of developing placenta abruptio by maternal age

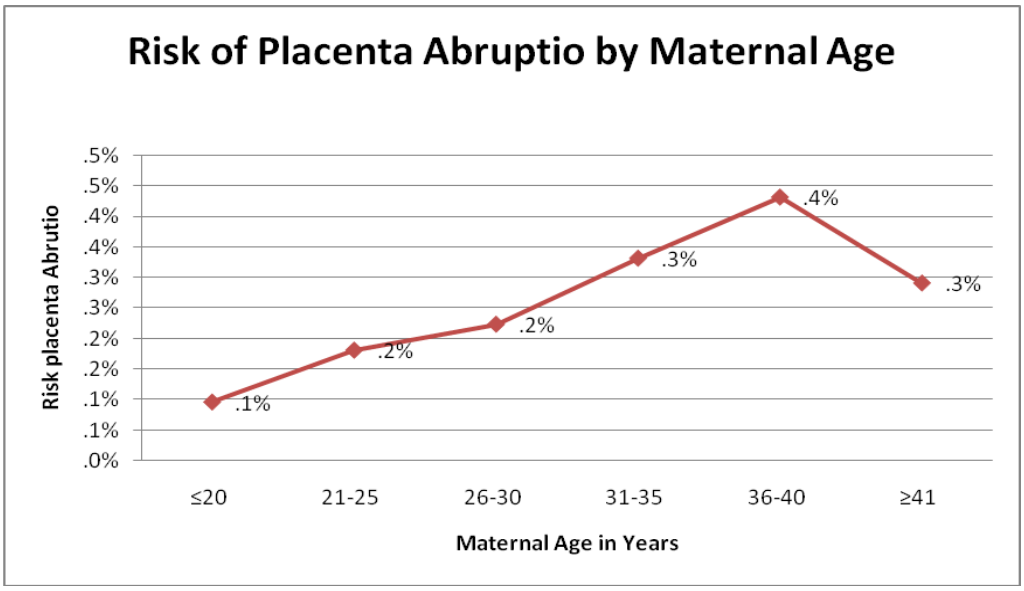


Figure 4.2: Risk of developing placenta abruptio by paternal age

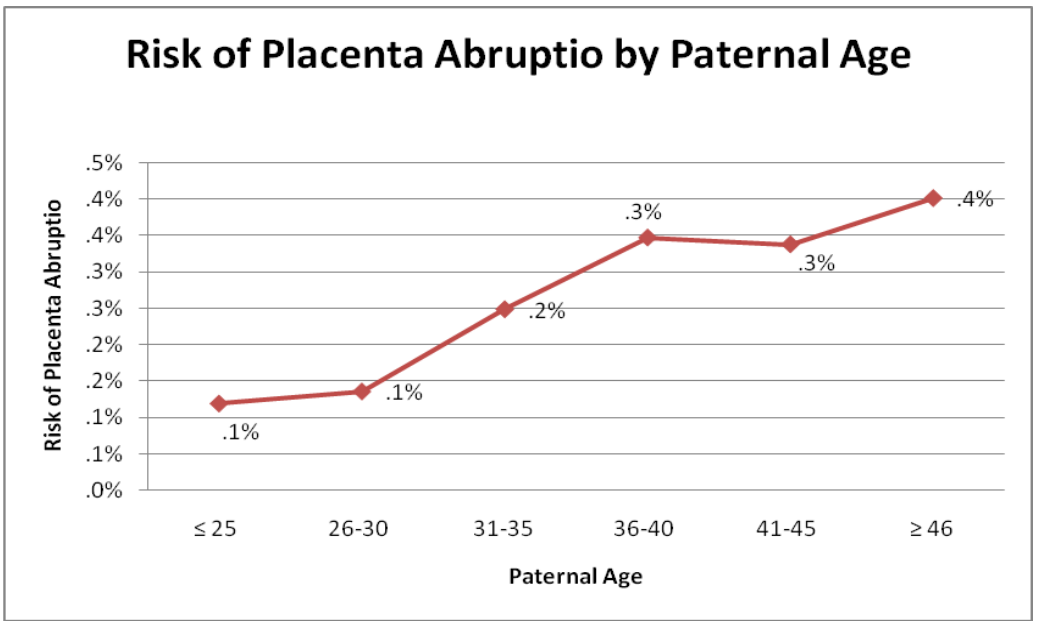
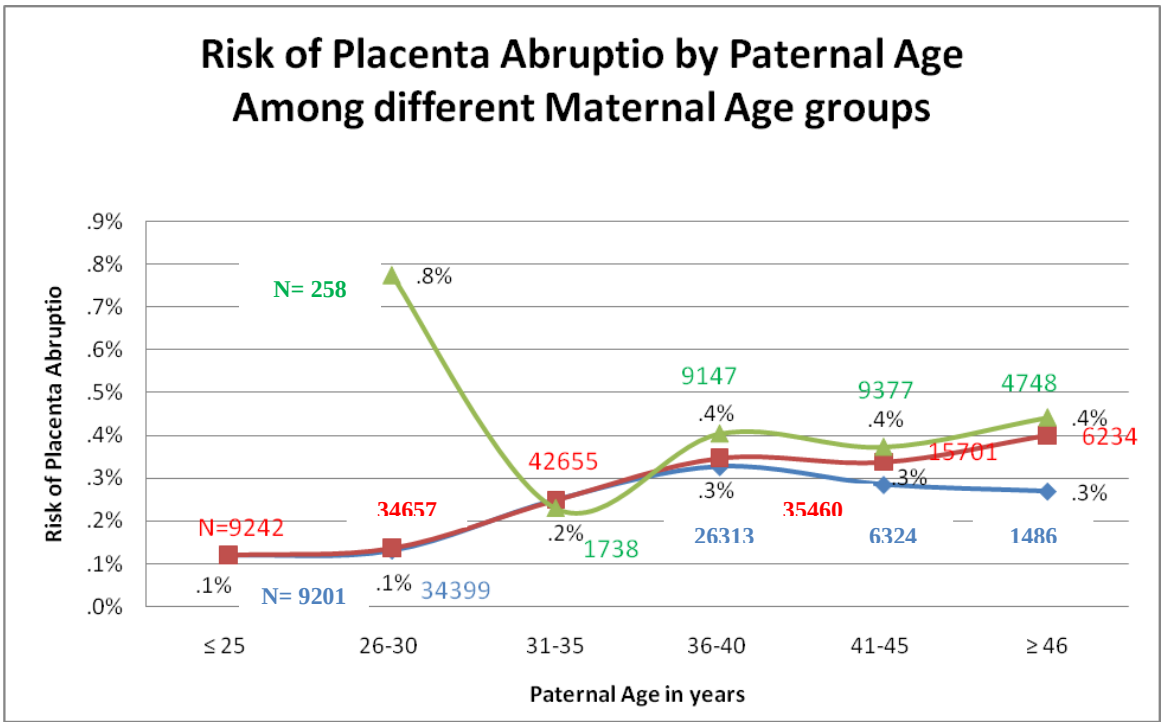


Figure 4.3: Risk of developing placenta abruptio by paternal age among different maternal age groups



1. Placenta Abrubtio for All Mothers

Table 4.4: 1st Multivariate model built to calculate propensity scores for the risk of developing placenta abruptio

Variable	OR	S.E	95% CI	P- value
Year of birth	0.846	0.028	0.800-0.894	0.000
Consanguinity	0.942	0.163	0.684-1.297	0.712
Arguile ever smoking during pregnancy	0.990	0.252	0.604-1.623	0.967
Cigarette ever smoking during pregnancy	1.365	0.180	0.959-1.941	0.084
Alcohol consumption during pregnancy	0.918	0.586	0.291-2.892	0.884
Having a previous neonatal death	1.517	0.339	0.781-2.945	0.218
Having a previous premature birth	0.809	0.465	0.325-2.012	0.648
Chronic diabetes	2.535	0.471	1.008-6.375	0.048
Gestational diabetes	1.331	0.317	0.716-2.477	0.366
ART use for the current pregnancy	1.884	0.312	1.022-3.476	0.042
Preeclampsia	1.675	0.366	0.817-3.435	0.159
Eclampsia	1.624	1.010	0.224-11.760	0.631

Chronic Hypertension disorder	1.095	0.734	0.260-4.613	0.902
Mother employment status during pregnancy	1.262	0.134	0.971-1.639	0.082
Prenatal care	0.00	0.00	0.00	0.
Carrying a baby with birth defects	2.231	0.230	1.421-3.502	0.000
Maternal cardiovascular problems	2.281	0.403	1.036-5.021	0.041
# of Gravida	1.122	0.049	1.020-1.234	0.018
# of Abortions	1.033	0.074	0.895-1.194	0.656
Maternal Education				
None	---	----	---	0.150
< = Intermediate	2.882	0.730	0.689-12.063	0.147
High School	2.640	0.740	0.619-11.266	0.190
College	3.490	0.746	0.809-15.049	0.094
Paternal education				
None	---	---	-----	0.041
< = Intermediate	1.255	0.727	0.302-5.220	0.755
High School	2.021	0.735	0.478-8.545	0.339
College	1.653	0.741	0.387-7.066	0.498
Maternal religion				
Muslim	----	----	-----	0.643
Druze	0.464	0.896	0.080-2.685	0.391
Christian	1.140	0.678	0.302-4.306	0.846

Paternal religion				
Muslim	---	----	----	0.254
Druze	4.270	0.876	0.766-23.793	0.098
Christian	1.288	0.680	0.340-4.887	0.709
Household crowding index	0.918	0.100	0.754-1.117	0.391
Hospital admitted class				
First Class	---	----	----	0.000
Second Class	0.214	0.300	0119-0.386	0.000
Third Class	0.586	0.207	0.390-0.880	0.010
Type of gestation				
Single	---	---	---	0.006
Twins	1.804	0.206	1.206-2.700	0.004
Triplets	3.009	0.430	1.296-6.985	0.010
more	0000	0000	000	0.998
Pre pregnancy weight (Kg)	1.002	0.010	0.982-1.022	0.877
Weight gain (Kg)	0.990	0.010	0.970-1.010	0.307
Pre pregnancy BMI (Kg/m^2)	0.969	0.030	0.913-1.029	0.302
Maternal Age	1.021	0.011	0.998-1.044	0.071
Maternal chronic respiratory problems	1.766	0.387	0.827-3.769	0.142
Maternal Thyroid problems	1.525	0.514	0.557-4.173	0.412

Maternal ante partum anemia	0.792	0.587	0.251-2.502	0.691
Maternal Hemoglobinopathies	3.098	0.475	1.222-7.855	0.017
Oligohydraminos	2.434	0.226	1.563-3.791	0.000
Polihydraminos	2.108	0.417	0.931-4.771	0.074
Previous CS/Myomectomy/uterine surgery	0.805	0.163	0.585-1.109	0.184
Prolonged rupture of membrane > 24h	1.959	0.592	0.615-6.247	0.256
Intra partum fever > 38	1.675	0.417	0.740-3790	0.216

Table 4.5: 2nd Multivariate model- Effect of paternal age on the risk of developing placenta abruptio

Variable	OR	S.E	95% CI	P- value
Paternal Age	1.033	0.008	1.017-1.050	0.000
Propensity Score	----	----	----	0.000

2. Placenta Abruptio for Older Mothers ≥ 35 years

Table 4.6: 1st Multivariate model built to calculate propensity scores for the risk of developing placenta abruptio for old mom ≥35 years

Variable	OR	S.E	95% CI	P- value
Year of birth	0.923	0.058	0.824-1.035	0.169
Consanguinity	0.506	0.405	0.229-1.120	0.093
Arguile ever smoking during pregnancy	1.692	0.472	0.671-4.270	0.265
Cigarette ever smoking during pregnancy	1.342	0.299	0.746-2.414	0.325
Alcohol consumption during pregnancy	000	000	0000	0.995
Having a previous neonatal death	1.026	0.619	0.305-3.451	0.967
Having a previous premature birth	0.993	0.740	0.219-3.983	0.926
Chronic diabetes	3.849	0.626	1.128-13.132	0.031
Gestational diabetes	0.773	0.609	0.235-2.549	0.673
Maternal Chronic Hypertensive Disorder	1.362	1.055	0.172-10.759	0.770
ART use for the current pregnancy	1.038	0.515	0.378-2.846	0.943
Preeclampsia	0.494	1.021	0.067-3.657	0.490

Eclampsia	000	000	000	0.998
Mother employment status during pregnancy	1.098	0.255	0.666-1.809	0.715
Prenatal care	0000	0000	0000	0.993
Carrying a baby with birth defects	2.258	0.410	1.011-5.039	0.047
Maternal cardiovascular problems	2.064	0.748	0.477-8.942	0.333
# of Gravida	1.124	0.072	0.976-1.296	0.105
# of Abortions	1.056	0.108	0.854-1.305	0.616
Maternal Education				
None	----	---	----	0.726
< = Intermediate	1.483	0.783	0.320-6.876	0.615
High School	1.087	0.826	0.215-5.485	0.920
College	1.373	0.845	0.262-7.194	0.708
Paternal education				
None	----	----	---	0.012
< = Intermediate	0.854	1.072	0.104-6.975	0.883
High School	2.452	1.092	0.288-20.845	0.412
College	2.539	1.100	0.294-21.944	0.387
Maternal religion				
Muslim	----	---	----	0.903
Druze	2.163	2.176	0.030-	0.723
Christian	0.697	1.427	153.822	0.800

			0.043-11.428	
Paternal religion **Muslim** **Druze** **Christian**	---- 1.623 1.700	---- 2.174 1.427	---- 0.023-115.012 0.104-27.873	0.916 0.824 0.710
Household crowding index	1.006	0.172	0.717-1.410	0.973
Hospital admitted class **First Class** **Second Class** **Third Class**	--- 0.035 0.363	--- 1.047 0.395	---- 0.004-0.268 0.167-0.787	0.001 0.001 0.010
Type of gestation **Single** **Twins** **Triplets** **more**	---- 3.047 8.030 0000	--- 0.309 0.608 0000	---- 1.661-5.588 2.441-26.418 0000	0.000 0.000 0.001 0.999
Pre pregnancy Weight (Kg)	0.997	0.020	0.960-1.036	0.898
Weight gain (Kg)	0.993	0.020	0.955-1.032	0.728
Pre pregnancy BMI (Kg/m^2)	0.980	0.057	0.877-1.095	0.723
Maternal Age	1.000	0.040	0.925-1.081	0.994
Maternal chronic respiratory problems	0.943	1.016	0.129-6.907	0.954
Maternal Thyroid	2.065	0.747	0.478-8.933	0.332

problems				
Maternal ante partum anemia	2.364	0.742	0.552-10.125	0.246
Maternal Hemoglobinopathies	1.539	1.053	0.196-12.120	0.682
Oligohydraminos	3.291	0.441	1.387-7.812	0.007
Polihydraminos	0000	000	000	0.994
Previous CS/Myomectomy/uterine surgery	0.449	0.339	0.231-0.872	0.018
Prolonged rupture of membrane > 24h	000	0000	000	0.997
Intra partum fever > 38	4.147	0.540	1.440-11.943	0.008

Table 4.7: 2nd Multivariate model- Effect of paternal age on the risk of developing placenta abruptio for older mothers ≥ 35 years

Variable	**OR**	**S.E**	**95% CI**	**P- value**
Paternal Age	0.989	0.021	0.949-1.031	0.598
Propensity Score	----	----	----	0.000

3. Placenta Abruptio for Young Mothers < 35 years

Table 4.8: 1st Multivariate model built to calculate propensity scores for the risk of developing placenta abruptio for young mom < 35

Variable	OR	S.E	95% CI	P- value
Year of birth	0.822	0.033	0.772-0.877	0.000
Consanguinity	1.129	0.180	0.794-1.606	0.499
Arguile ever smoking during pregnancy	0.829	0.299	0.461-1.491	0.531
Cigarette ever smoking during pregnancy	1.422	0.225	0.914-2.212	0.119
Alcohol consumption during pregnancy	1.288	0.591	0.405-4.099	0.668
Having a previous neonatal death	1.852	0.404	0.839-4.085	0.127
Having a previous premature birth	0.791	0.599	0.244-2.559	0.695
Chronic diabetes	1.510	0.743	0.352-6.483	0.580
Gestational diabetes	1.821	0.370	0.882-3.763	0.105
Maternal Chronic Hypertensive Disorder	1.259	1.020	0.171-9.289	0.821
ART use for the current pregnancy	3.288	0.398	1.506-7.178	0.003
Preeclampsia	2.447	0.395	1.129-5.304	0.023

Eclampsia	2.590	1.012	0.356-18.836	0.347
Maternal employment status during pregnancy	1.314	0.158	0.964-1.790	0.084
Prenatal care	000	000	0000	0.986
Carrying a baby with birth defects	2.211	0.282	1.273-3.840	0.005
Maternal cardiovascular problems	2.690	0.474	1.063-6.808	0.037
# of Gravida	1.113	0.069	0.971-1.275	0.124
# of Abortions	1.035	0.106	0.841-1.273	0.744
Maternal Education				
None	----	----	----	0.329
< = Intermediate	000	000	000	0.987
High School	000	000	000	0.987
College	000	000	000	0.987
Paternal education				
None	---	-----	----	0.333
< = Intermediate	1.487	1.010	0.206-10.760	0.694
High School	2.010	1.018	0.273-14.768	0.493
College	1.477	1.024	0198-11.001	0.703
Maternal religion				
Muslim	---	---	----	0.350
Druze	0.282	0.988	0.041-1.953	0.200
Christian	1.298	0.766	0.290-5.822	0.733

Paternal religion				
Muslim	---	----	----	0.228
Druze	5.100	0.951	0.791-32.869	0.087
Christian	1.246	0.769	0.276-5.625	0.775
Household crowding index	0.867	0.123	0.682-1.102	0.243
Hospital admitted class				
First Class	---	----	---	0.002
Second Class	0.314	0.327	0.166-0.596	0.000
Third Class	0.704	0.247	0.434-1.143	0.156
Type of gestation				
Single	----	----	-----	0.920
Twins	1.216	0.288	0.692-2.138	0.497
Triplets	1.229	0.653	0.342-4.416	0.752
more	0000	0000	0000	0.998
Pre pregnancy weight (Kg)	1.002	0.012	0.978-1.026	0.897
Weight gain (Kg)	0.989	0.012	0.965-1.013	0.351
Pre pregnancy BMI (Kg/m^2)	0.969	0.036	0.902-1.041	0.388
Maternal Age	1.019	0.018	0/983-1.057	0.297
Maternal chronic respiratory problems	2.237	0.421	0.980-5.107	0.056
Maternal Thyroid problems	1.268	0.721	0.309-5.211	0.742

Maternal ante partum anemia	0.348	1.008	0.048-2.510	0.295
Maternal Hemoglobinopathies	3.970	0.539	1.381-11.412	0.011
Oligohydraminos	2.232	0.264	1.329-3.748	0.002
Polihydraminos	2.940	0.419	1.293-6.688	0.010
Previous CS/Myomectomy/uterine surgery	1.033	0.188	0.716-1.493	0.861
Prolonged rupture of membrane > 24h	2.840	0.598	0.880-9.161	0.081
Intra partum fever > 38	0.747	0.714	0.184-3.023	0.682

Table 4.9: 2nd Multivariate model- Effect of paternal age on the risk of developing placenta abruptio for young mothers < 35 years

Variable	**OR**	**S.E**	**95% CI**	**P- value**
Paternal Age	1.043	0.011	1.021-1.066	0.000
Propensity Score	----	----	----	0.000

E. Age Difference

1. Age Difference & Preeclampsia for Older Mothers ≥ 35 years

Table 5.1: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing preeclampsia for older mothers ≥ 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	0.994	0.011	0.972-1.016	0.571
Propensity Score	----	----	----	0.000

2. Age Difference & Preeclampsia for Younger Mothers < 35 years

Table 5.2: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing preeclampsia for younger mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	0.987	0.008	0.972-1.003	0.114
Propensity Score	----	----	----	0.000

3. Age Difference & Eclampsia for Older Mothers ≥ 35 years

Table 5.3: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing eclampsia for older mothers ≥ 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	0.962	0.031	0.905-1.024	0.222
Propensity Score	----	----	----	0.000

4. Age Difference & Eclampsia for Younger Mothers < 35 years

Table 5.4: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing Eclampsia for younger mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	1.038	0.018	1.001-1.076	0.043
Propensity Score	----	----	----	0.000

5. Age Difference & Placenta Previa for Older Mothers ≥ 35 years

Table 5.5: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing placenta previa for older mothers ≥ 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	1.009	0.021	0.968-1.051	0.686
Propensity Score	----	----	----	0.000

6. Age Difference & Placenta Previa for Younger Mothers < 35 years

Table 5.6: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing placenta previa for younger mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	0.992	0.015	0.963-1.022	0.610
Propensity Score	----	----	----	0.000

7. Age Difference & Placenta Abruptio for Older Mothers ≥ 35 years

Table 5.7: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing placenta abruptio for older mothers ≥ 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	0.986	0.023	0.942-1.032	0.542
Propensity Score	----	----	----	0.000

8. Age Difference & Placenta Abruptio for Younger Mothers < 35 years

Table 5.8: 2nd Multivariate model- Effect of the age difference between the couple on the risk of developing placenta abruptio for younger mothers < 35 years

Variable	OR	S.E	95% CI	P- value
Age difference between mother and father	1.017	0.014	0.988-1.046	0.258
Propensity Score	----	----	----	0.000

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APPENDIX

Percentage of Women Ever Married

Table 1: Percentage of women ever married, by age, time period, and region[a] (weighted[b] averages)

Region	Percent of region's population represented	Ages 15–19			Ages 20–24			Ages 25–29		
		Time 1[c] 1970–89	Time 2 1990–2000	Annual change	Time 1[c] 1970–89	Time 2 1990–2000	Annual change	Time 1[c] 1970–89	Time 2 1990–2000	Annual change
Africa										
Eastern/Southern Africa	89.8	37.5	24.5	–0.75	77.2	65.6	–0.71	89.2	83.4	–0.38
Western/Middle Africa	30.8	53.0	38.4	–0.89	85.1	78.6	–0.40	93.5	92.3	–0.05
Asia										
Eastern Asia[d]	98.1	4.2	1.3	–0.24	60.1	45.9	–1.19	95.9	91.6	–0.36
South-central/Southeastern Asia	93.3	39.6	32.3	–0.64	80.6	77.4	–0.30	93.7	93.4	–0.02
Former Soviet Asia[e]	37.8	9.4	9.6	0.02	61.2	54.0	–0.70	85.0	80.7	–0.42
Latin America and Caribbean										
Caribbean/Central America	87.5	20.6	18.1	–0.27	59.4	56.1	–0.35	81.0	79.3	–0.20
South America[f]	99.9	14.4	16.3	0.12	51.1	51.3	0.03	75.9	76.0	0.00
Middle East[g]										
Western Asia/Northern Africa	62.8	21.0	14.9	–0.59	64.5	54.6	–0.95	87.7	81.4	–0.58
Total	86.5	26.6	20.8	–0.48	70.8	63.9	–0.56	91.6	89.4	–0.18

[a] Regional groupings are based on *World Population Prospects: The 2002 Revision* (UN, 2003).

Percentage of Men Ever Married

Table 2: Percentage of men ever married, by age, time period, and region (weighted averages)

Region	Percent of region's population represented	Ages 20–24			Ages 25–29		
		Time 1[a] 1970–89	Time 2 1990–2000	Annual change	Time 1[a] 1970–89	Time 2 1990–2000	Annual change
Africa							
Eastern/Southern Africa	89.8	36.0	27.8	–0.56	71.8	66.5	–0.42
Western/Middle Africa	30.8	28.4	26.5	–0.10	61.6	60.5	–0.04
Asia							
Eastern Asia	98.1	39.0	24.9	–1.17	82.7	77.2	–0.46
South-central/Southeastern Asia	93.3	41.6	41.4	–0.03	77.5	77.2	–0.01
Former Soviet Asia	37.8	31.9	23.9	–0.81	78.0	66.0	–1.20
Latin America and Caribbean							
Caribbean/Central America	87.5	38.4	37.5	–0.14	72.0	68.8	–0.36
South America	99.9	28.3	29.3	0.06	65.3	62.8	–0.18
Middle East[b]							
Western Asia/Northern Africa	62.6	24.9	16.8	–0.78	63.0	53.4	–0.91
Total	86.5	37.9	33.0	–0.41	76.0	73.1	–0.24