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The Association of Advanced Maternal Age and Adverse Pregnancy Outcomes

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The Association of Advanced Maternal Age and Adverse Pregnancy Outcomes

By

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THESIS TITLE:

The Association of Advanced Maternal Age and Adverse Pregnancy Outcomes

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ABSTRACT

Introduction: The past decade has seen a significant shift in the demographics of childbearing in the United States. The average age of women at first birth has steadily increased over the last four decades, with the birth rate for women aged 40-44 more than doubling from 1990 to 2012. The aim of this study was to evaluate the risk of adverse pregnancy outcomes with increasing maternal age and paternal age using national health statistics data.

Methods: The study population included 3 495 710 live births among women 15-54+ years of age from the 2012 Natality dataset. Outcomes were modeled for both maternal and paternal 5-year age groups using logistic regression analysis to calculate adjusted and unadjusted odds ratios (AORs, ORs) with 95% confidence intervals. Analysis was performed to examine the association between maternal and paternal age across seven different adverse outcomes, including low birthweight, low Apgar score, early term pregnancies, abnormal newborn conditions and presence of congenital anomalies.

Results: The risks for most outcomes paralleled with advanced maternal age and paternal age. Logistic regression models demonstrated that maternal age groups 40-44, 45-49 and 50-54+ were at highest risk for an adverse pregnancy outcome compared to the 30-34 year old reference group. Abnormal newborn conditions including assisted ventilation, NICU admission and use of antibiotics were significant for all age groups 40 and older. Low Apgar score, low birthweight and early term pregnancies were significantly higher among mothers as well as fathers with advanced age.

Conclusions: These findings suggest that advanced maternal age is a risk factor for a variety of adverse pregnancy outcomes. Women aged 35-39 have a similar risk of an adverse outcome as their younger counterparts. This suggests that perhaps we should begin assessing high-risk pregnancies as starting at an older age versus the de facto standard of 35.

Key Words: advanced maternal age, advanced paternal age, congenital anomalies, low birthweight, gestational age, Apgar score, abnormal newborn conditions

APPROVAL PAGE

The Association of Advanced Maternal Age and Adverse Pregnancy Outcomes

By
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Approved:

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AUTHOR'S STATEMENT

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CHAPTER I

INTRODUCTION

1.1 Background

The past decade has seen a significant shift in the demographics of childbearing in the United States. Though there is no consensus on how to define advanced maternal age, it is implied that age is a continuum of risk (Nilsen, 2014). Waters and Wagen first defined advanced maternal age, in 1950, and their suggested 35-year limit has been the de facto standard commonly used in research (Waters, E.G., & H.P. Wagen. 1950). Delayed childbearing in older women has become a recent trend in the United States and other well-developed countries. Reasons often vary and may include the desire by women to continue their education, invest more time in developing a professional career, or postpone marriage, as well as the increased availability of assisted reproductive techniques (Gravena, A., Sass, A., Marcon, S., & Pelloso, S., 2012). For many women, awareness of their “biological clock,” often as defined by the Waters-Wagen 35-year limit, is a constant reminder of the need to consider family planning options. According to the CDC, the average age of women at first birth has steadily increased over the last four decades, with the birth rate for women aged 40-44 more than doubling from 1990 to 2012 (Mathews T.J. & Hamilton B.E., 2014). Additionally, the rate of first births to women under the age of 30, specifically those younger than 20 years, has declined in the past decade. Despite the decline of total births, first births to older women continue to increase (Mathews T.J. & Hamilton B.E., 2014). The contraceptive revolution, with the introduction of the pill and other effective contraceptives in the 1960’s, made it possible for a woman to choose if and when to have her first child, as well as subsequent children (Nilsen, 2014). But how realistic is it for a younger woman to postpone childbearing into the fifth or sixth decade of her life?

This question has led to an increased surveillance of older women and their offspring in recent decades to carefully examine the effects of delayed motherhood. It is often of interest to researchers and the public to know the average age at which a woman conceives her first child. Birth outcomes are largely influenced by the age of the mother, especially at extremes of both young and old. Increased health risks to older mothers and infants have been well documented over the last decade and have provided insight on the association of advanced maternal age and adverse pregnancy outcomes for both mother and baby. Factors that may negatively influence a pregnancy outcome include declined infertility and an increase in rates of miscarriage, spontaneous abortions, chromosomal abnormalities, hypertensive complications and stillbirths (Heffner, L.J., 2004).

With the steady increase of advanced maternal age, the impact on population structure and healthcare resources are undoubtedly of interest. For example, women of advanced maternal age have a higher rate of delivery complications. The increased risk for cesarean section births, most notably emergency cesarean delivery, has been observed in advanced maternal age (Dulitzki, M., Soriano, D., Schiff, E., Chetrit, A., Mashiach, S., & Sideman, S.D., 1998; Seoud, M., Nassar, A., Usta, I., Melhem, Z., Kazma, A., & Khalil, A., 2002). Cesarean section births require more resources, longer hospital stays and lengthier recovery times. These outcomes alone greatly increase the financial costs of childbearing to both parents and provider. Additionally, the complications undertaken by the mother also increase with age. According to Seoud et al., chronic hypertension, preeclampsia and gestational diabetes were more frequently observed in women of advanced maternal age as compared to their counterparts. Furthermore, the availability of assisted reproductive techniques, which include egg donations, in vitro fertilization and surrogacy available to reproductive-age women, mean that an incredible amount of expenses and

resources are focused on the small sub-group of women who are able to bear the costs of such options.

Less often mentioned is the role that a male undertakes in the reproductive phase. More interestingly, what impact does advanced paternal age or the father's "biological clock", have on pregnancy outcome? According to Rchebrochard, E., & Thonneau, P. (2002) in a study conducted to examine both maternal and paternal ages as risk factors for miscarriages, the investigators found that advanced maternal age greater than 35 and advanced paternal age greater than 40 had a much greater risk for miscarriages than those couples where both partners were younger than 35. Additionally, couples that undergo in vitro fertilization experience difficulty in conception. As noted by a researchers Cohen and Natarjan (2004), pregnancy rates declined as male subjects aged, and paternal age was associated with 11% increased odds of not achieving a pregnancy and 12% increased odds of not having a successful live birth. The associated effect of both paternal and maternal age is of considerable interest to practitioners who discuss family planning options with their patients. As couples begin to age and childbearing is further delayed, provision of educational sessions for this population is of great importance in order to achieve optimal health for both mother and child.

There has been an effort from the American Society of Reproductive Medicine to make the public more aware of the risks of delayed childbearing. As demographics begin to shift in the United States and women delay childbearing, there will be a constant need to monitor and research the affects on pregnancy outcomes. The more aware and educated the public is on the options available to achieve a healthy pregnancy and delivery, the better prepared the mother and/or father will be. Shifting trends towards later childbearing results in a growing need for well-educated and informed practitioners and readily available educational resources to serve the

aging population of first- time mothers and fathers. The topic has been studied intensively and there is unarguably significant evidence that advanced maternal age, greater than 35, lends itself to unfortunate pregnancy outcomes. Yet in many studies, the association of adverse outcomes with increasing age is a continuum rather than a “threshold effect” (Kenny, L., Lavender, T., Mcnamee, R., O’Neill, S., Mills, T., Khashan, A., & Shi, Q., 2013), therefore suggesting that the age of 35 is not the necessarily a specific “cut-off” point for adverse outcomes. Is there reason to believe that significant numbers of adverse outcomes can be equally possible at an even earlier age?

1.2 Purpose of Study

The primary purpose of this study is to examine the association between advanced maternal age, defined as age 35 or greater, and adverse pregnancy outcomes for all births registered in the 50 states of the United States, using the publicly available Natality File for the year 2012 through the Centers for Disease Control and Prevention’s National Center for Health Statistics (NCHS). For purposes of this study, the birth outcomes examined include birthweight, gestational age, Apgar score, abnormal conditions of newborn and congenital anomalies. The scope of the study will examine previous and current literature related to this trending topic, examining the effects of advanced maternal age on childbirth outcomes, as well as the existing factors that can contribute greatly to the birth outcome of an advanced-aged woman compared to her younger counterparts. Finally, recommendations for public health initiatives related to advanced maternal age and family planning will be proposed to direct communication and future goals for those men and women who plan to start families at a later stage in life.

The primary research question is to examine whether there is a significant association between women of advanced maternal age and adverse pregnancy outcomes, using the 2012

Nativity File data. In addition, the second research question proposed for this study aims to see the association of advanced age on childbirth outcomes in relation to paternal age, and what, if any, are the effects on adverse pregnancy outcomes. Lastly, the final research question aims to examine whether significant results are maintained while controlling for possible confounders and/or covariates for advanced maternal age such as ethnicity, marital status, education level, BMI, smoking status, diabetes and hypertension. Furthermore, this study aims to examine objectively what our perception of risk is for advanced maternal age. Has society set the boundaries on what is considered “too old” to become pregnant or is it an arbitrary number contrived from research or society?

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Advanced Maternal Age

Extremes of maternal age adversely affect pregnancy outcomes. Teenage pregnancy, under 19 years of age, has been thoroughly studied because it is a public health concern in both developed and developing countries, especially in the developing world. Previous evidence indicates that that one-third of women become mothers within 19 years of age (Vigas O.A., Wiknsosastro, G., Sahagun, G.H., Chaturachinda, K., & Ratnam, S.S., 1992). On the contrary, advanced maternal age has only more recently become a leading topic for researchers. According to the CDC in the United States mean maternal age increased to 25.8 years in 2012, from 25.6 years in 2011 (Mathews T.J. & Hamilton B.E., 2014). Additionally, first births to women 35 and older has risen steadily from 1 out of 100 births in the 1970s compared to 1 out of 12 births in 2006 (Mathews, T.J., & Hamilton, B.E., 2002; Martin, J., Hamilton, B., Ventura, S., Osterman, M., & Kirmeyer, S., et al 2011). According to Martinez, Daniels and Chandra, the number of

first births to women age 35 to 44 years, rose from 601 in 1995 to 976 in 2006 to 2010 (2012). It has been widely documented that maternal age in pregnancy is increasing around the globe (El-Gilany, A., & Hammad, S., 2012). In defining this rising trend, a commonly accepted definition of advanced maternal age is 35 years or greater, although some researchers arguing that advanced maternal age should be defined as either earlier or later, at 30 or 40 years respectively (Khalil, A., Syngelaki, A., Maiz, N., Zinevich, Y., & Nicolaides, K., 2013). The delay in childbearing may be deemed a cultural phenomenon with more women furthering their education, joining the workforce and placing marriage as a lesser priority while establishing their careers.

Several studies have examined advanced maternal age in relation to adverse pregnancy outcomes, including but not limited to stillbirth, preterm-delivery, gestational diabetes and hypertension, small and large for gestational age, as well as elective or emergency C-sections (Nilsen, 2014; Khalil et al., 2013). Unfortunately, many studies have reported contradictory conclusions about the specific outcomes adversely affected by maternal age as well as the strength of the association (Kenny et al., 2013). The discordance could be due to a variety of factors, including the differences in the populations studied, the definition of adverse outcomes that were examined and the choice of the reference group.

Despite the contradictory findings, overall research suggests that advanced maternal age is linked to various adverse pregnancy outcomes that may affect both mother and neonate. Numerous articles have concluded that advanced maternal age is more likely to be associated with increased obstetric and maternal complications, including adverse labor and birth outcomes (Karabulut, A., Ozkan, S., Bozkurt, A., Karahan, T., & Kayan, S., 2013). A woman's ability to conceive naturally or even with assisted reproductive techniques decreases with age and this is

most pronounced at age 35 or greater (Nilsen, 2014). The ability to conceive naturally could be due to the decreased oocyte quality, which is a probable cause for the increased spontaneous abortions for women of advanced maternal age (Fritz, M.A., & Speroff, L., 2010.; Karabulut et al., 2013).

In addition, women of advanced maternal age are more likely to exhibit various delivery complications. The risk of Caesarean delivery increases with maternal age for both primiparas and multiparas, and an even higher difference for nulliparous women compared to women of younger reproductive years (Luke & Brown 2007; Karabulut, 2013). The Healthy People 2010 target for Caesarean delivery for low-risk women is set at 15% for primiparas and 63% for multiparas with a history of a prior Caesarean; current rates are 80% and 17% higher, respectively, than the national targets (Luke & Brown, 2007). A study conducted by Callaway et al., found that the overall Caesarean section rate in the advanced age group was 49%, as opposed to 23% in the 20-29 year age group (Callaway, L., Lust, K., & McIntyre, H., 2005).). In addition to Caesarean delivery, labor inductions, long postpartum hospitalizations, prolonged and dysfunctional labor, excessive bleeding and breech presentation have been shown to increase with maternal age (Luke & Brown 2007; Klemetti, R., Gissler, M., Sainio, S., & Hemminki, E., 2014). A contributing factor to the increased incidence of Caesarean sections among older women, besides diseases and other obstetrical complications, is that the deterioration of the myometrium caused by aging may account for some of the disorders during delivery that may contribute for the increased cases of Caesarean sections (Gravena et al, 2011). Complications such as these undoubtedly affect birth outcomes of neonates. With older women exhibiting an increase in delivery complications, as compared to their younger counterparts, it is challenging to unravel the effects and to determine if advanced maternal age alone can contribute to such

complications.

Advanced age pregnancies have traditionally been considered high-risk mainly due to the growing incidence of hypertension, increased BMI, obesity and diabetes (Cleary-Goldman, J., Malone, F.D., Vidaver, J., Ball, R.H., Nyberg, D.A., & Comstock, C.H., et al., 2005). In addition, there is a higher percentage of maternal complications in women with pregnancy at an advanced age, such as chronic hypertension, pregestational diabetes, gestational diabetes, fetal death and preeclampsia, which have been also observed in various studies (Hoffman, M., Jeffers, S., Carter, J., Duthely, L., Cotter, A., & Gonzalez-Quintero, V., 2007). Needless to say lifestyle factors such as diet, exercise and smoking habits contribute greatly to the development of these diseases. Obesity and overweight has been associated with preterm births, low Apgar scores, stillbirths (22 weeks of gestation or greater) and neonatal death (Waldenström, U., Aasheim, V., Nilsen, A., Rasmussen, S., Pettersson, H., & Shytt, E., 2014). A systematic review reported that maternal overweight and obesity contributed to approximately 8,000 stillbirths and that advanced maternal age and smoking contributed to 4,200 and 2,800 stillbirths, respectively (Flenady, V., Koopmans, L., Middleton, P., Frøen, J., Smith, G., Gibbons, K., et al., 2011). Smoking as an individual factor has been further explored in regard to pregnancy and the effect on birth outcomes. Smoking increases the risk of preterm births, small-for-gestational-age (SGA) and stillbirth (Waldenstrom et al., 2014). The relative significance of lifestyle factors during pregnancy are less explored but current research suggests that there is a direct casual relationship between factors such as obesity, smoking and being overweight with adverse pregnancy outcomes, which is more pronounced in women of advanced maternal age.

2.2 Birthweight and Gestational Age

Multiple studies focusing on advanced maternal age and pregnancy outcomes have documented that birthweight and gestational age as indeed common factors affected. Kenny et al. (2013) observed that advanced maternal age increases the risks that the fetus will be large for gestational age, very large for gestational age, extremely large for gestational age and Macrosomia. In addition, Kenny et al., found an increased relative risk for pre-term and very pre-term births of 24% in woman over 40 years of age (2013). Khalil et al., however, found that the risk factors for delivering an SGA neonate included maternal age between 35-39.9 years of age (2013). Also, Gravena et al., compared women 35 years of age and older, compared to those less than 35 and found that there was a greater proportion of newborns with low birthweight, Macrosomia, pre-term delivery and post-term delivery (2012). Furthermore, the odds increased for pre-term delivery, low birthweight and very low birthweight increased with advanced maternal age (Hoffman et al., 2007). Advanced maternal age appears to affect neonate birthweight at both ends of the spectrum.

2.3 Congenital Anomalies and Abnormal Newborn Conditions

Women of advanced maternal age often undergo prenatal chromosomal determination evaluations, using amniocentesis to determine whether their offspring may exhibit a chromosomal disorder. Congenital anomalies such anencephaly, spina bifida, cleft palate and Down's syndrome as well as other chromosomal disorders have been documented as outcomes of advanced maternal age. Abnormal clinical findings such as NICU admission, 5-minute Apgar score of less than 7 have also been observed in various studies. In a study conducted by Callaway et al., examining the effects of maternal age on pregnancy outcomes, researchers found that 17% of live born infants required admission to special care nursery for prematurity and respiratory distress syndrome. In addition, Callaway et al. documented in the same study that 6% of the

infants had congenital abnormalities, such as Down's syndrome (2005). Gravena et al., observed infants born to mothers of advanced maternal age to exhibit an Apgar index below seven for the 1st and 5th minutes of life (2011). NICU admission was correlated with advanced maternal age comparing White/Non-Hispanic and Black/Non-Hispanic middle-aged women and teenage maternal population (Jongh, B., Locke, R., Paul, D., & Hoffman, M., 2012). Furthermore, researchers Itzchak, Lahat and Zachor (2011) concluded that advanced parental age is associated with autism spectrum disorder (ASD), a group of neurobehavioral disorders defined by social and communication deficits. Risk was significantly higher in mothers 35 to 44 years of age. ASD was also correlated with low birthweight of offspring for the advanced age group of mothers (Itzchak, Lahat and Zachor, 2011).

2.4 Advanced Paternal Age

Advanced maternal age usually implies advanced paternal age, since men are on average three years older than their partner (Nilsen, 2014). Advanced paternal age, though less studied as a single factor, has been documented to affect birth outcomes of neonates and could be a possible confounder to adverse outcomes exhibited by women of advanced maternal age. Recently, a review of the consequences of the postponement of parenthood, Schmidt et al., concluded “as women in general have partners who are several years older than themselves, it is important to focus more on the combined effect of advanced female and advanced male age on reproductive outcomes in the future” (Schmidt, L., Sobotka, T., Bentzen, J., & Nyboe-Anderson, A., 2012).

Comparable to the literature of advanced maternal age, advanced paternal age has only recently received notice. Although paternal age is not routinely collected, there are a growing number of studies focusing on the effect of paternal age. Older paternal age has been associated with an increase in preterm births, spontaneous abortions, as well as congenital anomalies (Luke

& Brown, 2007). There is also biologic plausibility indicating the possibility that paternal age has an effect on the placenta since it is largely dependent on the expression of genes of paternal origins (Chen, X., Wen, S., Krewski, D., Fleming, N., Yang, Q., & Walker, M., 2008). Furthermore, increasing paternal age has also been linked to miscarriages, fetal death, preeclampsia, caesarean delivery, birth defects, as well as schizophrenia, autism and cancer in offspring (Sartorius & Nieschlag, 2010). However, contradictory findings have been noted. Researchers Chen et al., concluded from their study that paternal age greater than 40 years was not associated with the risk of adverse birth outcomes, but teenage fathers had an increased risk of adverse outcomes, such as preterm births, low birth weight, small-for-gestational-age and low Apgar score (2008). Regardless of these conflicting findings, literature does suggest that advanced paternal age is associated with negative birth outcomes, but the combined effect of advanced maternal age and advanced paternal age should be more closely examined.

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CHAPTER III

MANUSCRIPT

INTRODUCTION

Waters and Wagen first defined advanced maternal age, in 1950, and their suggested 35-year limit has been the de facto standard commonly used in research. Delayed childbearing in older women has become a recent trend in the United States and other well-developed countries. Reasons often vary and may include the desire by women to continue their education, invest more time in developing a professional career, or postpone marriage, as well as the increased availability of assisted reproductive techniques (Gravena, A., Sass, A., Marcon, S., & Pelloso, S., 2012). According to the CDC, the average age of women at first birth has steadily increased over the last four decades, with the birth rate for women aged 40-44 more than doubling from 1990 to 2012 (Mathews T.J. & Hamilton B.E., 2014). Additionally, the rate of first births to women under the age of 30, specifically those younger than 20 years, has declined in the past decade. Despite the decline of total births, first births to older women continue to increase in all states from 2000 to 2012 (Mathews T.J. & Hamilton B.E., 2014).

Women of advanced maternal age have a higher rate of delivery and pregnancy complications. The increased risk for cesarean section births, most notably emergency cesarean delivery, has been observed in advanced maternal age (Dulitzki, M., Soriano, D., Schiff, E., Chetrit, A., Mashiach, S., & Sideman, S.D., 1998; Seoud, M., Nassar, A., Usta, I., Melhem, Z., Kazma, A., & Khalil, A., 2002). Cesarean section births require more resources, longer hospital stays and lengthier recovery times. These outcomes alone greatly increase the financial costs of childbearing to both parents and provider. Additionally, the complications experienced by the mother also increase with age. According to Seoud et al. (2002), chronic hypertension,

preeclampsia and gestational diabetes were more frequently observed in women of advanced maternal age as compared to their counterparts. Also, Gravena et al. (2011) compared women 35 years of age and older to those less than 35 and found that there was a greater proportion of newborns with low birthweight, Macrosomia, pre-term delivery and post-term delivery. Furthermore, the odds for pre-term delivery, low birthweight and very low birthweight increased with advanced maternal age (Hoffman, M., Jeffers, S., Carter, J., Duthely, L., Cotter, A., & Gonzalez-Quintero, V., 2007). Advanced maternal age appears to affect neonate birthweight at both ends of the spectrum.

In a study conducted by Callaway, Lust and McIntyre, examining the effects of maternal age on pregnancy outcomes, researchers found that 17% of live born infants required admission to special care nursery for prematurity and respiratory distress syndrome. In addition, Callaway et. al., documented in the same study that 6% of the infants had congenital abnormalities, such as Down's syndrome. (Callaway, L., Lust, K., & McIntyre, H., 2005). Gravena et al., observed infants born to mothers of advanced maternal age to exhibit an Apgar index below seven for the 1st and 5th minutes of life (2011). NICU admission was correlated with advanced maternal age comparing White/Non-Hispanic and Black/Non-Hispanic middle-aged women and teenage maternal population (Jongh, B., Locke, R., Paul, D., & Hoffman, M., 2012).

Less often mentioned is the role of the male in the reproduction process. More interestingly, what impact does advanced paternal age or the father's "biological clock", have on pregnancy outcome? As noted by a researchers Cohen and Natarjan (2004), pregnancy rates declined as male subjects aged, and paternal age was associated with 11% increased odds of not achieving a pregnancy and 12% increased odds of not having a successful live birth. The

associated effect of both paternal and maternal age is of considerable interest to practitioners who discuss family planning options with patients.

The topic has been studied intensively and there is unarguably significant evidence that advanced maternal age, greater than 35, lends itself to unfortunate pregnancy outcomes. Yet in many studies, the association of adverse outcomes with increasing age is a continuum rather than a “threshold effect” (Kenny, L., Lavender, T., Mcnamee, R., O’Neill, S., Mills, T., Khashan, A., & Shi, Q., 2013), therefore suggesting that the age of 35 is not necessarily a specific “cut-off” point for adverse outcomes. Is there reason to believe that the risk begins much later in life?

The aim of this study is to reexamine the risk of adverse outcomes by age groups and to assess whether the current “cut off” ages for increased risk are still valid. This study will evaluate the association between advanced maternal age, defined as age 35 or greater, and adverse pregnancy outcomes for all births registered in the 50 states of the United States, using the publicly available Natality File for the year 2012 through the Centers for Disease Control and Prevention’s National Center for Health Statistics (NCHS). For purposes of this study, the birth outcomes examined include birthweight, gestational age, Apgar score, abnormal conditions of newborn and congenital anomalies.

METHODS

Data Source

The data for this study were obtained from the 2012 Natality File (NCHS, 2012). The Natality File is a publically available data set representing United States birth data. Currently the birth-registration system of the United States includes all births registered in the 50 states, District of Columbia and the independent registration area of New York City. The Centers for Disease Control and Prevention’s National Center for Health Statistics receives these data

electronically, prepared from individual records processed by each registration area, through the Vital Statistics Cooperative Program (National Center for Health Statistics, 2012). Birth records are limited to births occurring in the United States to U.S. residents and foreign residents. Births occurring to U.S. citizens outside of the country are not included in this file. A total of 3,960,796 were registered in the U.S. in 2012. Data includes items that were collected on the 2003 revision of the U.S. Standard Certificate of Live Birth. Thirty-eight states implemented the revised version as of January 1, 2012. These states were; California, Colorado, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Mexico, New York (including New York City), North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Washington, Wisconsin, and Wyoming. The 38 states with the adopted revised birth certificate and the District of Columbia represent 86.3% of births to U.S. residents (NCHS, 2012).

Study Population

This was a cross-sectional study of women with registered births in the 38 states with the adopted revised birth certificate. The study population includes women ages 15 to 64 years and all live infant births. The Natality file accepts the occurrence of a live birth in accordance with the definition offered by Kowaleski (Kowaleski, J., 1997).

For purposes of this study, the populations of interest are mothers age 35 or greater. Younger mothers ages 30 to 34 years were used as the reference group. The U.S Standard Certificate of Live Birth included a questionnaire related to maternal health and wellbeing as well as pregnancy outcome and newborn health status. Birth outcomes were coded as yes or no and included both abnormal conditions of the newborn and congenital anomalies. Additionally,

birthweight, gestational age and Apgar score were examined. For purposes of this study only the 38 states with the revised 2003 birth certificate were included for analysis.

Predictor Variables

Maternal age

Information for age of mother is available for the entire United States. According to the National Center of Health Statistics, the 1989 U.S. Standard Certificate of Live Birth replaced “Age” with “Date of birth” (2013). For purposes of this study, mother’s age will be treated as a categorical 5-year-age classification, starting with 15 years of age or younger to 50-54 years of age or older.

Paternal age

Age of father is available for the entire U.S. It is derived from the father’s date of birth and is reported by the mother as recommended. Paternal age is based on a 5-year-age classification, starting with 15-19 years of age up to 54+ years of age.

Outcome Variables

Abnormal Newborn Conditions

For purposes of this study abnormal conditions of newborn were recoded as a binary 0 or 1 outcome, with 1 indicating the occurrence of an abnormal condition. Abnormal conditions assessed included: assisted ventilation required immediately following delivery, assisted ventilation required for more than six hours, NICU admission, newborn given surfactant replacement therapy, antibiotics received by newborn for suspected neonatal sepsis, seizure or serious neurological dysfunction and significant birth injury.

Congenital anomalies

For purposes of this study congenital anomalies were grouped as a single variable and recoded as a binary 0 or 1 outcome, with 1 indicating if any of the 12 anomalies were present at birth. Those anomalies with pending outcomes may be undercounted, since final outcome was unknown at birth. Congenital anomalies identified were, anencephaly, spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction defect, cleft lip without cleft palate, cleft palate alone, Down syndrome, suspected chromosomal disorder, and hypospadias.

Birthweight

Birthweight is reported in grams and is consistent with the recommendations from both the ninth and tenth revisions of the *International Statistical Classification of Diseases* (NCHS, 2013). Birthweight was coded as a binary variable. Low birthweight was defined as those less than 2500 grams and normal birthweight as those 2500 grams or more.

Period of gestation

The primary measure used to determine gestational age of the infant is the date of the last menstrual period (LMP). The date of birth of the infant is subtracted from the LMP date to calculate the gestational age of the infant (NCHS, 2013). For purposes of this study gestational age was coded as two variables, one indicating <37 weeks gestation (early term) and one indicating >40 weeks gestation (late term).

5-minute Apgar score

The Apgar score is a measure of the need for resuscitation and a predictor of the infant's chances of surviving the first year of life (NCHS, 2013). It is based on heart rate, respiratory effort, muscle tone, reflex irritability and color. Each of these factors is given a score of 0, 1 or 2. The sum of these 5 values is the Apgar score, which ranges from 0 to 10. Apgar score was coded

as a binary variable. A low Apgar score is defined as less than 7 and a good to excellent Apgar score is defined as 7 or greater.

Statistical Analysis

This study utilized the 9.4 version of the Statistical Analysis System (SAS) to manage the Natality File data that was previously provided in a downloadable zip folder format from the National Health Statistics website. Descriptive statistics were calculated in this study for the distribution of birthweight, gestational age, assisted ventilation required immediately following delivery, assisted ventilation required for more than six hours, NICU admission, newborn given surfactant replacement therapy, antibiotics received by newborn for suspected neonatal sepsis, seizure or serious neurological dysfunction and significant birth injury, presence of any congenital anomaly, and the 5-minute Apgar score.

Maternal and paternal age was studied as a categorical variable. Rates of adverse outcomes were calculated for each maternal and paternal age group. The ORs along with their 95% CIs associated with maternal and paternal age groups, with reference to 30-34 years old, were derived through regression analysis with adjustment for potential confounding variables for each maternal and paternal age group. The ORs for maternal age groups were adjusted for sex of infant, marital status, race (white, black, American Indian and Asian), Hispanic origin, education level (high school or less, some college, bachelors degree, masters degree and doctorate degree). Additionally, it has been well established in literature that associated risk factors increase the likelihood of adverse outcomes in women of advanced maternal age. In this study we controlled for smoking status, hypertension, gestational hypertension, diabetes, gestational diabetes and BMI (underweight, normal, overweight and obese). The ORs for the paternal age groups were adjusted for race (same as maternal), Hispanic origin and level of education.

RESULTS

There were 3 495 710 registered births in the 2012 Natality filed linked to the 38 eight states with the revised birth certificate. As shown in Table 1, the seven abnormal conditions were accounted for in 3 483 667 births, congenital anomalies were accounted for in 3 481 552 births, the 5-minute Apgar score was documented for 3 479 806 births, birthweight was accounted for in 3 491 905 births, and gestational age was accounted for in 3 491 831 births. Risks were highest among NICU admission (7.81%), early term pregnancies (11.45%) and late term pregnancies (14.11%).

The AORs of adverse pregnancy outcomes according to adjusted maternal age groups is described in Table 3. Logistic regression demonstrated that maternal age groups 40-44, 45-49 and 50-54+ were at highest risk for an adverse pregnancy outcome compared to the 30-34 year olds. Particularly so, in the 40-44 age group there was a significant association with maternal age and NICU admission AOR 1.35 [95% CI: 1.32-1.39], assisted ventilation >6hrs AOR 1.24 [95% CI: 1.16-1.33], presence of congenital anomaly AOR 1.80 [95% CI: 1.62-2.01], 5-minute Apgar score <7 AOR 1.27 [95% CI: 1.20-1.34], birthweight <2500 grams AOR 1.46 [95% CI: 1.42-1.50] and gestational age <37 weeks AOR 1.46 [95% CI: 1.43-1.49].

In addition, similar significance among adverse outcomes can be observed among the 45-49 year age group. Notably so, majority of abnormal conditions including assisted ventilation, assisted ventilation >6hrs, NICU admission, use of surfactant and use of antibiotics all proved to have significant results. The AOR for the presence of any congenital anomaly in the 45-49 age was 2.46 [95% CI: 1.76- 3.45]. Whereas, for the same age group the, 5-minute Apgar score <7 AOR was 1.85 [95% CI: 1.58-2.10], birth weight <2500 grams AOR was 2.98 [95% CI: 2.80-3.17] and AOR for gestational age <37 weeks was 2.73 [95% CI: 2.58-2.89].

Furthermore, significant associations were noted among the oldest maternal age group of 50-54+ noted and adverse pregnancy outcomes. Significant results demonstrated a strong association among this age group and multiple abnormal conditions, including NICU admission and assisted ventilation >6hrs. 5-minute Apgar score <7 was significant with a AOR of 2.26 [95% CI: 1.27-4.03], birthweight <2500 grams AOR 4.46 [95% CI: 3.45-5.77] and gestational age <37 weeks AOR 4.40 [3.48-5.57].

Paternal age was available for 3 048 019 live births. For 13% of the study population, paternal age was missing or unreported. The AORs of adverse pregnancy outcomes according to adjusted paternal age groups are reported in Table 5. Using logistic regression, we observed that associations among paternal age groups and adverse pregnancy outcomes were similar to those of advanced maternal age groups. Particularly, 5-min Apgar score <7, birthweight <2500 grams and gestational age <37 weeks were significantly associated among all four advanced paternal age groups. NICU admission was highest among those 55+ with an AOR of 1.54 [95% CI: 1.44-1.64]. Assisted ventilation was highest among the 40-44 age group, with an AOR of 1.35 [95% CI: 1.25-1.45]. Furthermore, presence of congenital anomaly AOR 1.51 [95% CI: 1.10-2.07], birthweight <2500 grams AOR 1.59 [95% CI: 1.48-1.69] and gestational age <37 weeks AOR 1.65 [95% CI: 1.55-1.73] were all highest among the 55 and over age group.

Figures 1 and 2 provide a visual demonstration of the U-shaped curve most often associated with maternal age and adverse pregnancy outcomes. Figure 1 depicts point estimates for advanced maternal age and assisted ventilation. As noted, the point estimates help to create a U-shaped curve, which agrees with well-established literature that younger and older mothers are at highest risk for adverse outcomes. In Figure 1, mothers younger than 15 and those 50 and older are almost twice as likely, to have an infant requiring assisted ventilation. Additionally, in

Figure 2 point estimates are depicted for gestational age less than 37 weeks. The U-shaped curve of this adverse outcome concludes that mothers younger than 15 and mothers 50 and older are almost twice as likely and four times more likely, respectively, to have an early term pregnancy, with women of advanced maternal age having a much higher risk.

DISCUSSION

The purpose of this study was to examine the association of advanced maternal age, and to a lesser extent, advanced paternal age and seven reported adverse pregnancy outcomes using the 2012 Natality File data. The results of this study demonstrate that advanced maternal age, after adjustment for other maternal characteristics and risk factors, is associated with increased risk for a wide range of adverse pregnancy outcomes, including assisted ventilation, NICU admission, use of surfactant and antibiotics, presence of congenital anomaly, low birthweight, low 5-minute Apgar score and early term pregnancies. The rising trend of delayed childbearing secondary to education, career opportunities and assisted reproductive techniques allow these findings to be of particular interest to both the women and their healthcare providers (Khalil, A., Syngelaki, A., Maiz, N., Zinevich, Y., & Nicolaides, K., 2013).

Findings of high AORs are noted in both the youngest and oldest groups, which are to be expected as literature suggests that those at highest risk for adverse outcomes are older and younger mothers. Interestingly so, advanced maternal age was in some instances a protective factor against an adverse outcome. For example, in this study mothers aged 35 and greater had a lesser likelihood of having a late term pregnancy as compared to those 30 years and younger. Notably, the same likelihood was observed in the advanced paternal age groups for gestational age greater than 40 weeks. Although such analysis does not allow accurate estimation of patient-specific risks or causal pathways, it does highlight concerns raised in previous studies about

delayed childbearing in women of advanced maternal age (Nilsen, 2014; Kahlil et al., 2013; Gravena et al., 2011; Hoffman et al., 2007).

In addition, women aged 35-39 had a much lower likelihood of having an adverse outcome compared to their older counterparts and exhibited the same characteristic risk values as those 30 years and younger. This raises the question, of whether age 35 is still the appropriate de facto standard to define advanced maternal age. As Nilsen et al., (2014) suggested, age is a continuum of risk, and an arbitrary “cut-off” point may not be appropriate. The older you are the more likely it is that you may experience a negative pregnancy outcome.

There are both strengths and limitations in this study. The strengths of this study include the large number of women and registered births. The large populations size allows for a more accurate assessment of the adverse outcomes among the maternal age groups and the associated risk factors. In addition, the availability of paternal age--often not collected or reported on birth certificates--allowed for analysis of this factor and adverse outcomes. Moreover, the comprehensive and detailed birth certificate allowed for multiple outcomes to be assessed.

There were many limitations to this study. Due to the cross-sectional design we were only able to assess maternal and paternal age as categorical variables. Ability to assess age as a continuous variable would lend itself to accurately gauging at which specific age the risk begins to shift. Also, paternal age was unknown in 13% of observations, a significant number that could not be included for analysis. The ability to only control for paternal race, Hispanic origin and education level is also a limitation. Other factors such as smoking status, hypertension, diabetes and BMI were not available for assessment. Also, the use of the revised birth certificate questionnaire excluded 12 states from analysis, about 15% of all births for 2012. The exclusion of these states may have altered our results. Furthermore, though this is a relatively large dataset,

overall outcomes were rare and in some instances power was lost in youngest and oldest age groups because sparse data was available.

In conclusion, early identification of women at an increased risk for adverse outcomes would help to facilitate surveillance and intervention. Advanced maternal age is a risk factor for multiple abnormal newborn conditions, possible congenital anomalies, low birthweight, low 5-minute Apgar score and early term pregnancies. Targeted approaches and educational proponents for family planning, particularly for women who plan to delay childbearing, are of crucial importance. In this study, the association of adverse outcomes were noted in women 40 and over. Perhaps we should begin assessing high-risk pregnancies as starting at an older age versus the de facto standard of 35.

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FIGURES AND TABLES

Table 1. Characteristics of Adverse Outcomes

Adverse Outcome	Sum	(N)	Missing	Absolute Risk (%)
Assisted Ventilation	116413	3483667	12043	0.0334 (3.34%)
Assisted Ventilation >6hrs	34683	3483667	12043	0.0100 (1.00%)
NICU Admission	271944	3483667	12043	0.0781 (7.81%)
Use of Surfactant	14497	3483667	12043	0.0042 (0.42%)
Use of Antibiotics	73185	3483667	12043	0.0210 (2.10%)
Seizure	1115	3483667	12043	0.0003 (0.03%)
Birth Injury	2040	3483667	12043	0.0006 (0.06%)
Presence of Congenital Anomaly	11454	3481152	14558	0.0033 (0.33%)
Apgar score at 5 min <7	69379	3479806	15904	0.0199 (1.99%)
Birthweight <2500 g	277305	3491905	3805	0.0794 (7.94%)
Gestational age <37 weeks	399800	3491831	3879	0.1145 (11.45%)
Gestational age >40 weeks	492599	3491831	3879	0.1411 (14.11%)

Table 2. Logistic Regression Model for Maternal Age Unadjusted ORs

Adverse Outcome	Maternal age (years)																	
	Under 15		15-19		20-24		25-29		30-34		35-39		40-44		45-49		50-54	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	ref	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Assisted Ventilation	1.34	(1.13-1.60)	1.16	(1.13-1.18)	1.05	(1.04-1.07)	1.01	(0.99-1.02)	ref	1.08	(1.06-1.10)	1.27	(1.23-1.31)	1.73	(1.55-1.92)	2.40	(1.74-3.32)	
Assisted Ventilation >6hrs	1.48	(1.10-1.99)	1.09	(1.05-1.14)	1.03	(1.00-1.07)	1.00	(0.97-1.03)	ref	1.12	(1.08-1.17)	1.34	(1.26-1.42)	2.42	(2.05-2.85)	4.37	(2.85-6.70)	
NICU Admission	1.45	(1.2901-1.62)	1.07	(1.05-1.08)	0.99	(0.98-1.00)	0.96	(0.95-0.97)	ref	1.15	(1.14-1.17)	1.48	(1.45-1.52)	2.53	(2.37-2.70)	3.74	(3.07-4.56)	
Use of Surfactant	1.60	(1.03-2.48)	1.16	(1.09-1.24)	1.05	(1.00-1.10)	1.03	(0.98-1.08)	ref	1.13	(1.07-1.19)	1.37	(1.25-1.51)	2.36	(1.82-3.05)	3.81	(1.90-7.65)	
Use of Antibiotics	1.75	(1.44-2.13)	1.30	(1.26-1.33)	1.17	(1.14-1.19)	1.07	(1.05-1.09)	ref	1.06	(1.03-1.09)	1.22	(1.16-1.27)	1.67	(1.45-1.92)	1.85	(1.17-2.92)	
Seizure	4.22	(1.57-11.34)	1.14	(0.89-1.44)	1.13	(0.96-1.34)	1.03	(0.87-1.22)	ref	1.15	(0.93-1.40)	1.32	(0.94-1.86)	0.53	(0.07-3.75)	***		
Birth Injury	***		1.31	(1.11-1.55)	1.07	(0.94-1.21)	1.04	(0.92-1.17)	ref	1.11	(0.95-1.29)	0.99	(0.75-1.32)	0.85	(0.27-2.64)	***		
Presence of Congenital Anomaly	0.83	(0.42-1.67)	1.27	(1.18-1.36)	1.13	(1.07-1.20)	0.99	(0.94-1.04)	ref	1.17	(1.10-1.25)	1.89	(1.72-2.07)	2.47	(1.85-3.30)	1.23	(0.31-4.93)	
Apgar score at 5 min <7	2.05	(1.70-2.48)	1.52	(1.48-1.57)	1.25	(1.22-1.28)	1.07	(1.05-1.09)	ref	1.11	(1.08-1.14)	1.34	(1.28-1.40)	1.82	(1.58-2.10)	1.92	(1.20-3.07)	
Birthweight <2500 g	1.78	(1.60-1.97)	1.27	(1.25-1.29)	1.11	(1.10-1.12)	0.97	(0.96-0.98)	ref	1.17	(1.15-1.18)	1.54	(1.51-1.58)	2.98	(2.80-3.17)	4.33	(3.57-5.25)	
Gestational age <37 weeks	2.09	(1.92-2.28)	1.22	(1.21-1.24)	1.05	(1.04-1.06)	0.95	(0.95-0.96)	ref	1.20	(1.18-1.21)	1.56	(1.53-1.59)	2.73	(2.58-2.89)	4.12	(3.45-4.92)	
Gestational age >40 weeks	1.13	(1.021-1.25)	1.28	(1.27-1.30)	1.25	(1.24-1.26)	1.14	(1.13-1.15)	ref	0.82	(0.81-0.83)	0.68	(0.67-0.70)	0.65	(0.60-0.71)	0.54	(0.39-0.74)	

*** Instances of zero events occurring.

Table 3. Logistic Regression Model for Maternal Adjusted ORs

Adverse Outcome	Maternal age (years)								
	Under 15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54
	AOR ^a 95% CI	AOR ^a 95% CI	AOR ^a 95% CI	AOR ^a 95% CI		AOR ^a 95% CI	AOR ^a 95% CI	AOR ^a 95% CI	AOR ^a 95% CI
Assisted Ventilation	1.71 (1.22-2.41)	1.15 (1.11-1.19)	1.01 (0.99-1.03)	0.99 (0.97-1.01)	ref	1.06 (1.03-1.08)	1.19 (1.14-1.23)	1.58 (1.39-1.80)	1.57 (0.96-2.56)
Assisted Ventilation >6hrs	0.96 (0.43-2.15)	1.07 (1.00-1.14)	0.97 (0.93-1.01)	0.97 (0.94-1.01)	ref	1.10 (1.05-1.14)	1.24 (1.16-1.33)	2.20 (1.81-2.67)	3.03 (1.61-5.72)
NICU Admission	1.39 (1.10-1.76)	0.99 (0.97-1.01)	0.92 (0.91-0.94)	0.94 (0.93-0.96)	ref	1.12 (1.10-1.14)	1.35 (1.32-1.39)	2.41 (2.23-2.61)	3.20 (2.44-4.20)
Use of Surfactant	2.60 (1.16-5.83)	1.18 (1.07-1.30)	0.99 (0.93-1.05)	1.01 (0.96-1.07)	ref	1.12 (1.05-1.20)	1.26 (1.13-1.40)	2.40 (1.80-3.21)	1.42 (0.35-5.74)
Use of Antibiotics	2.08 (1.41-3.09)	1.26 (1.21-1.32)	1.15 (1.11-1.18)	1.06 (1.04-1.09)	ref	1.02 (0.99-1.05)	1.12 (1.06-1.18)	1.56 (1.33-1.85)	1.36 (0.70-2.65)
Seizure	7.31 (1.01-52.82)	1.25 (0.86-1.82)	1.17 (0.93-1.48)	0.99 (0.81-1.21)	ref	1.08 (0.84-1.37)	1.27 (0.85-1.89)	0.71 (0.10-5.09)	***
Birth Injury	***	1.35 (1.06-1.72)	1.08 (0.91-1.28)	1.07 (0.93-1.24)	ref	1.03 (0.86-1.23)	0.89 (0.63-1.25)	0.77 (0.19-3.10)	***
Presence of Congenital Anomaly	1.04 (0.26-4.19)	1.30 (1.17-1.44)	1.10 (1.02-1.18)	0.96 (0.90-1.02)	ref	1.16 (1.07-1.24)	1.80 (1.62-2.01)	2.46 (1.76-3.45)	2.00 (0.50-8.04)
Apgar score at 5 min <7	1.94 (1.28-2.94)	1.36 (1.30-1.42)	1.09 (1.06-1.13)	1.03 (1.00-1.05)	ref	1.08 (1.04-1.11)	1.27 (1.20-1.34)	1.74 (1.46-2.06)	2.26 (1.27-4.03)
Birthweight <2500 g	1.04 (0.81-1.33)	0.97 (0.95-0.99)	0.90 (0.88-0.91)	0.91 (0.90-0.92)	ref	1.16 (1.14-1.18)	1.46 (1.42-1.50)	2.74 (2.54-2.96)	4.46 (3.45-5.77)
Gestational age <37 weeks	1.37 (1.13-1.65)	0.93 (0.91-0.95)	0.85 (0.84-0.86)	0.89 (0.88-0.90)	ref	1.18 (1.17-1.20)	1.46 (1.43-1.49)	2.59 (2.42-2.78)	4.40 (3.48-5.57)
Gestational age >40 weeks	1.22 (1.00-1.49)	1.33 (1.31-1.36)	1.30 (1.28-1.31)	1.16 (1.15-1.17)	ref	0.82 (0.81-0.84)	0.69 (0.67-0.71)	0.69 (0.62-0.76)	0.81 (0.56-1.15)

^a Models adjusted for infant sex, marital status, maternal race, maternal Hispanic origin, maternal education, paternal race, paternal Hispanic origin, paternal education, smoking status, hypertension, gestational hypertension, diabetes, gestational diabetes and BMI: women aged 30-34 are the reference group.

*** Instances of zero events occurring.

Table 4. Logistic Regression Model for Paternal Age Unadjusted ORs

Adverse Outcome	Paternal age (years)																		
	Under 15		15-19		20-24		25-29		30-34	35-39		40-44		45-49		50-54		55-98	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Assisted Ventilation	1.36	(0.82-2.24)	1.16	(1.12-1.20)	1.10	(1.08-1.12)	1.04	(1.03-1.06)	ref	1.00	(0.98-1.02)	1.13	(1.10-1.15)	1.13	(1.14-1.23)	1.23	(1.14-1.31)	1.36	(1.23-1.50)
Assisted Ventilation >6hrs	1.15	(0.43-3.09)	1.13	(1.05-1.21)	1.09	(1.05-1.13)	1.06	(1.02-1.09)	ref	1.02	(0.99-1.06)	1.18	(1.13-1.24)	1.33	(1.24-1.42)	1.38	(1.22-1.55)	1.24	(1.03-1.50)
NICU Admission	1.50	(1.08-2.09)	1.15	(1.12-1.18)	1.04	(1.03-1.06)	0.99	(0.99-1.01)	ref	1.06	(1.05-1.08)	1.22	(1.20-1.24)	1.37	(1.34-1.41)	1.45	(1.39-1.51)	1.65	(1.55-1.76)
Use of Surfactant	0.70	(0.10-4.94)	1.18	(1.06-1.31)	1.07	(1.01-1.13)	1.05	(1.00-1.11)	ref	1.02	(0.97-1.08)	1.18	(1.10-1.27)	1.24	(1.11-1.39)	1.28	(1.06-1.54)	1.38	(1.04-1.82)
Use of Antibiotics	1.94	(1.14-3.31)	1.29	(1.23-1.35)	1.16	(1.13-1.91)	1.07	(1.05-1.10)	ref	0.99	(0.96-1.01)	1.05	(1.02-1.09)	1.17	(1.11-1.23)	1.16	(1.06-1.27)	1.17	(1.02-1.34)
Seizure	***		1.15	(0.77-1.70)	1.16	(0.94-1.43)	1.08	(0.90-1.30)	ref	1.04	(0.85-1.29)	1.12	(0.86-1.47)	1.17	(0.76-1.79)	1.45	(0.75-2.83)	1.50	(0.56-4.04)
Birth Injury	***		1.24	(0.94-1.63)	1.31	(1.13-1.51)	1.19	(1.04-1.36)	ref	1.20	(1.03-1.38)	1.05	(0.86-1.29)	1.02	(0.73-1.42)	1.20	(0.70-2.04)	1.59	(0.79-3.20)
Presence of Congenital Anomaly	1.67	(0.12-6.70)	1.11	(0.99-1.25)	1.11	(1.05-1.19)	0.99	(0.94-1.05)	ref	1.03	(0.97-1.10)	1.13	(1.05-1.23)	1.23	(1.09-1.40)	1.20	(0.97-1.49)	1.56	(1.17-2.08)
Apgar score at 5 min <7	1.73	(0.95-3.15)	1.47	(1.41-1.54)	1.32	(1.29-1.36)	1.10	(1.07-1.12)	ref	1.00	(0.97-1.02)	1.14	(1.11-1.19)	1.29	(1.22-1.36)	1.29	(1.17-1.41)	1.46	(1.28-1.66)
Birthweight <2500 g	1.77	(1.30-2.41)	1.37	(1.34-1.40)	1.16	(1.14-1.18)	1.01	(0.99-1.02)	ref	1.08	(1.07-1.10)	1.26	(1.24-1.28)	1.43	(1.40-1.47)	1.58	(1.51-1.65)	1.83	(1.71-1.94)
Gestational age <37 weeks	2.05	(1.59-2.64)	1.32	(1.30-1.35)	1.11	(1.10-1.13)	1.01	(0.99-1.02)	ref	1.10	(1.09-1.11)	1.27	(1.26-1.29)	1.42	(1.39-1.45)	1.52	(1.46-1.57)	1.76	(1.67-1.86)
Gestational age >40 weeks	1.20	(0.92-1.57)	1.17	(1.14-1.19)	1.19	(1.17-1.20)	1.12	(1.12-1.13)	ref	0.88	(0.88-0.89)	0.83	(0.82-0.84)	0.81	(0.79-0.82)	0.85	(0.81-0.88)	0.89	(0.83-0.93)

*** Instances of zero events occurring.

Table 5. Logistic Regression Model for Paternal Age Adjusted ORs

Adverse Outcome	Paternal age (years)																		
	Under 15		15-19		20-24		25-29		30-34	35-39		40-44		45-49		50-54		55-98	
	AOR ^a	95% CI	AOR ^a	95% CI	AOR ^a	95% CI	AOR ^a	95% CI		AOR ^a	95% CI	AOR ^a	95% CI	AOR ^a	95% CI	AOR ^a	95% CI	AOR ^a	95% CI
Assisted Ventilation	1.15	(0.61-2.17)	1.11	(1.06-1.16)	1.05	(1.03-1.07)	1.02	(1.00-1.04)	ref	1.02	(1.00-1.04)	1.15	(1.120-1.18)	1.19	(1.14-1.25)	1.22	(1.13-1.31)	1.30	(1.17-1.45)
Assisted Ventilation >6hrs	1.18	(0.38-3.68)	1.06	(0.98-1.14)	1.03	(0.98-1.07)	1.02	(0.99-1.06)	ref	1.05	(1.01-1.09)	1.21	(1.15-1.27)	1.35	(1.25-1.45)	1.35	(1.19-1.54)	1.09	(0.88-1.35)
NICU Admission	1.42	(0.98-2.06)	1.05	(1.02-1.08)	0.97	(0.96-0.99)	0.97	(0.96-0.98)	ref	1.07	(1.06-1.09)	1.22	(1.19-1.24)	1.34	(1.30-1.37)	1.39	(1.32-1.45)	1.54	(1.44-1.64)
Use of Surfactant	***		1.15	(1.02-1.29)	1.02	(0.96-1.08)	1.02	(0.96-1.07)	ref	1.05	(0.99-1.11)	1.20	(1.12-1.30)	1.30	(1.16-1.46)	1.34	(1.10-1.63)	1.23	(0.90-1.68)
Use of Antibiotics	1.91	(1.01-3.58)	1.27	(1.20-1.33)	1.13	(1.10-1.16)	1.06	(1.03-1.08)	ref	0.99	(0.97-1.02)	1.06	(1.02-1.09)	1.17	(1.11-1.24)	1.15	(1.05-1.27)	1.13	(0.98-1.31)
Seizure	***		1.17	(0.75-1.82)	1.20	(0.95-1.51)	1.04	(0.85-1.27)	ref	1.06	(0.85-1.32)	1.17	(0.89-1.55)	1.26	(0.81-1.96)	1.65	(0.85-3.22)	1.73	(0.64-4.66)
Birth Injury	***		1.17	(0.86-1.60)	1.30	(1.10-1.53)	1.16	(1.01-1.34)	ref	1.23	(1.05-1.43)	1.05	(0.85-1.30)	0.95	(0.66-1.38)	1.08	(0.59-1.97)	1.62	(0.77-3.42)
Presence of Congenital Anomaly	1.28	(0.18-9.10)	1.17	(1.02-1.33)	1.15	(1.07-1.23)	0.98	(0.93-1.04)	ref	1.05	(0.99-1.12)	1.17	(1.07-1.27)	1.30	(1.14-1.48)	1.26	(1.01-1.59)	1.51	(1.10-2.07)
Apgar score at 5 min <7	1.12	(0.50-2.51)	1.30	(1.24-1.37)	1.18	(1.15-1.21)	1.04	(1.01-1.06)	ref	1.01	(0.98-1.04)	1.14	(1.10-1.18)	1.23	(1.17-1.30)	1.17	(1.06-1.29)	1.30	(1.13-1.49)
Birthweight <2500 g	1.39	(0.96-2.01)	1.16	(1.13-1.20)	1.03	(1.02-1.05)	0.97	(0.95-0.98)	ref	1.08	(1.07-1.10)	1.23	(1.21-1.25)	1.35	(1.31-1.39)	1.43	(1.37-1.50)	1.59	(1.48-1.69)
Gestational age <37 weeks	1.57	(1.17-2.12)	1.11	(1.08-1.13)	0.97	(0.96-0.98)	0.95	(0.94-0.96)	ref	1.11	(1.10-1.12)	1.26	(1.25-1.28)	1.37	(1.34-1.41)	1.41	(1.36-1.47)	1.64	(1.55-1.73)
Gestational age >40 weeks	1.31	(0.97-1.78)	1.21	(1.18-1.23)	1.22	(1.21-1.24)	1.13	(1.12-1.14)	ref	0.89	(0.88-0.90)	0.84	(0.83-0.85)	0.82	(0.80-0.84)	0.87	(0.84-0.91)	0.88	(0.83-0.94)

^a Models adjusted for paternal race, Hispanic origin and paternal education level: men aged 30-34 are the reference group.

*** Instances of zero events occurring.

Figure 1. Point Estimates for Assisted Ventilation for Maternal Age

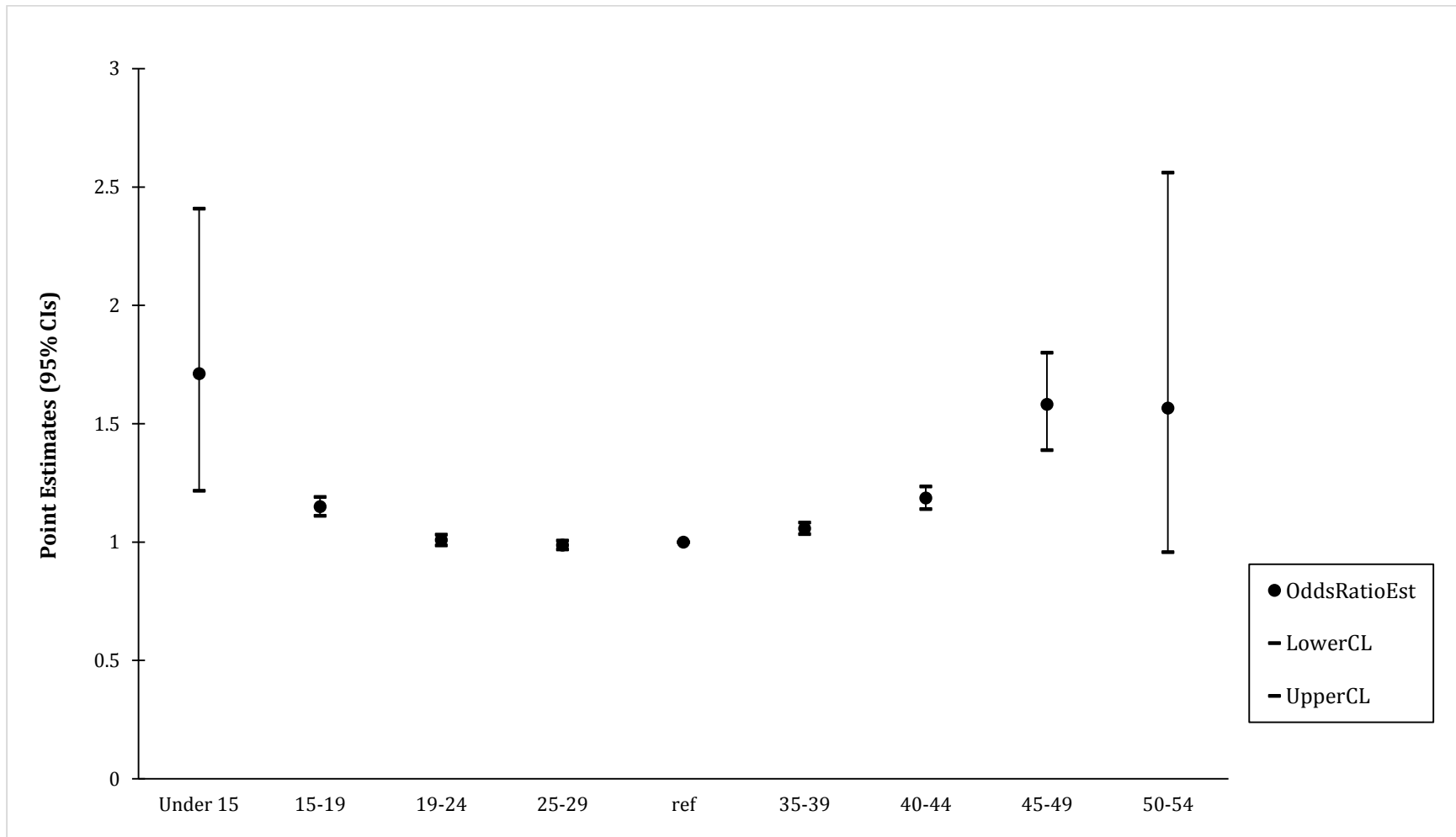


Figure 2. Point Estimates for <37 Weeks Gestational Age for Maternal Age

