DELAYED CHILDBEARING, PREGNANCY SPACING AND IMPACT ON
SUBSEQUENT PREGNANCY OUTCOMES: MISSOURI RESIDENT MOTHERS
1978-1997

by

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A DISSERTATION

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Introduction

The main objective of the study was to examine reproductive health issues among women delaying initiation of childbearing until age 30 or older. Specifically, it examined pregnancy spacing patterns, relationship between pregnancy spacing and subsequent perinatal outcomes as well as racial differences in spacing and adverse perinatal outcomes.

Methods

A retrospective cohort study was conducted using the Missouri maternally linked live birth, fetal death and infant death files 1978-1997. The study sample was limited to mothers residing in Missouri during the study period, having first pregnancy at age 20-50 years, as well as a subsequent second pregnancy. Final study sample included 242,599 singleton sibling pairs. Interpregnancy interval was used as the measure for pregnancy spacing, and was determined as the interval between first and second pregnancy. Interval was categorized into 7 groups (0-5, 6-11, 12-17, 18-23, 24-59, 60-119, \geq 120 months). Perinatal outcomes examined included fetal death, low birth weight, preterm and small-for-gestational age. Bivariate and multivariable approaches were used for analysis, with the Chi-Square and Mantel-Haenszel statistics used to test for significant differences in
proportions. Odds ratios and 95% confidence intervals were estimated for logistic regression analyses.

Results

The mean interpregnancy interval decreased significantly with increasing maternal age at initiation of childbearing (p <0.0001). Mothers delaying initiation of childbearing until age 35 or older had significantly higher rates of short interval <6 months compared to mothers 20-29 at initiation of childbearing (p <0.0001). Among women 35 or older at initiation of childbearing, the significant determinants for interpregnancy interval between first and second pregnancy included maternal educational status, body mass index, first pregnancy adverse outcome and year of delivery. Mothers 30-34 years at first pregnancy were less likely to have a second pregnancy within 6 months, but mothers age 35 or older at initiation of childbearing were more likely to have a second pregnancy within less than 6 months of the first, as compared to mothers 20-29 at initiation of childbearing.

 Mothers 35 or older at first pregnancy had significantly higher rates of adverse perinatal outcomes in the second compared to mothers 20-29. Both advanced maternal age at first pregnancy and short interpregnancy interval (<6 months) were independent risk factors for poor perinatal outcome in subsequent pregnancy, particularly for mothers 35 or older. However, mothers with advanced maternal age at initiation of childbearing as well as short interval had no increased risk for poor perinatal outcome in subsequent pregnancy above that observed for each individual risk factor.
Significantly fewer African Americans delayed initiation of childbearing; however, they had significantly higher rates of adverse perinatal outcomes for both first and second pregnancy compared to whites. No significant racial differences in interpregnancy interval were observed for mothers initiating childbearing at age 35 or older. African Americans had higher odds for adverse perinatal outcome in second pregnancy compared to Whites, however, African Americans delaying initiation of childbearing and having short interpregnancy interval had no increased risk for adverse perinatal outcomes, with the exception for small-for-gestational age births for mothers 30-34 at first pregnancy (OR= 1.91, 95% CI 1.08-3.37).

Conclusion

These study findings maybe of interest to health care providers and policy makers. In efforts to meet the Healthy People 2010 objectives, it is important to identify new areas for possible intervention. With the increasing number of women delaying initiation of childbearing, there is need to pay more close attention to their needs. The pregnancy spacing findings will aid in preconception counseling, and improving contraception use.
DEDICATION

To all mothers who strive to give their children the best start in life
ACKNOWLEDGMENTS

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<tr>
<td>AA</td>
<td>African American</td>
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<td>APH</td>
<td>Antepartum hemorrhage</td>
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<td>API</td>
<td>Asian/Pacific Islander</td>
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<td>ART</td>
<td>Assisted reproductive therapy</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DCB</td>
<td>Delayed childbearing</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>ELBW</td>
<td>Extremely low birth weight</td>
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<td>EPTD</td>
<td>Extremely preterm delivery</td>
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<td>FD</td>
<td>Fetal death</td>
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<td>GA</td>
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<td>HP-2010</td>
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<td>IPI</td>
<td>Interpregnancy interval</td>
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<td>IRB</td>
<td>Institutional review board</td>
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<td>IUGR</td>
<td>Intrauterine growth restriction</td>
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<td>LBW</td>
<td>Low birth weight</td>
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<td>LNMP</td>
<td>Last normal menstrual period</td>
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<td>LR</td>
<td>Logistic regression</td>
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<tr>
<td>MLBW</td>
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<td>NCHS</td>
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<td>OR</td>
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<td>PIH</td>
<td>Pregnancy induced hypertension</td>
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<td>PROM</td>
<td>Premature rupture of membranes</td>
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<td>PTD</td>
<td>Preterm delivery</td>
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<tr>
<td>R-Gindex</td>
<td>Revised graduated index</td>
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<td>SAS</td>
<td>Statistical Analysis Software</td>
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<td>SES</td>
<td>Socio-economic status</td>
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<td>Small-for-gestational age</td>
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<td>VLBW</td>
<td>Very low birth weight</td>
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<td>Very preterm delivery</td>
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INTRODUCTION

Background

Over the last two decades, an increasing number of women in the United States (US) and other developed countries are delaying initiation of childbearing until age 30 or older.\textsuperscript{1-6} This trend is driven in part by increasing number of women pursuing higher education, and entering the work force as well as advances in medical technology. It is postulated that as these factors persist, the proportion of women delaying childbearing will continue to rise. Indeed with continued advances in medical technology, it is expected that more women once considered infertile maybe able to have children albeit at older age.\textsuperscript{1,4,6}

According to the National Center for Health Statistics (NCHS), the mean age at first birth in the US is increasing. In 2003, the mean age was 25.2 years compared to 25.1 years in 2002, 25.0 in 2001 and 24.9 in 2000.\textsuperscript{5} In comparison, the mean age at first birth was 21.4 in 1970.\textsuperscript{7} Similar trends have been seen in other developed nations; in 1970, the mean age at first birth for Sweden was 25.9 years, rising to 27.9 years by 2000.\textsuperscript{7} In Japan, the mean age in 1970 was 25.6 years, and 28.0 in 2000.\textsuperscript{7} Findings from Italy reflect a similar pattern with a mean age at first birth of 30.2 years.\textsuperscript{8}

The changes in age at first pregnancy have contributed to changing pattern in overall birth rates. In the US, births to women in their 30s are at the highest since the mid 1960s.\textsuperscript{5} Similarly births to women in their 40s have also increased markedly, with a 58\%
increase observed since 1990.\textsuperscript{5} During 1995-2000, approximately 30\% of all first time births in the US were to women 30 years or older, with the largest increase noted for women in their 40s.\textsuperscript{9}

The increase in births to women age 30 or older is not without consequences. An increasing body of literature shows that these mothers are at increased risk for poor obstetric outcomes including pregnancy induced hypertension (PIH), gestational diabetes, placental anomalies, operative delivery, as well as maternal mood disorders including anxiety, stress and depression.\textsuperscript{9-16} Rates of poor birth outcomes such as fetal death (FD), preterm delivery (PTD), infant morbidity and mortality are also notably high for these mothers.\textsuperscript{4, 10, 11, 13, 15-22} Because of the noted increasing trend in delayed childbearing (DCB), there is increasing concern among health professionals regarding reproductive health for these mothers. As a result, more attention is being focused on this population of women to gain a better understanding of their reproductive history, and challenges they may face in their quest to have children, and the best approaches to address their special health problems and concerns.\textsuperscript{12}

Problem Statement

Both extremes of maternal age (too young or too old) are associated with poor pregnancy outcomes both for mother and baby.\textsuperscript{1, 11, 14, 23-30} However, the bulk of research has focused mainly on younger mothers, with limited focus on older mothers particularly those delaying initiation of childbearing. In instances where research has examined women who DCB, the focus has been on the first pregnancy and less on subsequent pregnancies. Our understanding of the reproductive history for women who DCB is
limited; for example, among women initiating childbearing in their 30s or older, do they go on to have subsequent pregnancies? What are the potential adverse outcomes that might accompany subsequent deliveries? How do their pregnancy outcomes compare to those of women initiating childbearing in their 20s? While little is known about the pregnancy outcomes of subsequent deliveries, even less is known about the pregnancy spacing patterns for older women and the factors that may influence their pregnancy spacing patterns.

Similarly, limited research has explored racial and/or ethnic differences in pregnancies outcomes for women initiating childbearing in their 30s or older. Research has shown a preponderance of poor outcomes among minority populations compared to Whites in younger women; it is unclear whether the same findings persist for women of advanced maternal age. Moreover, previous research has proposed that minority women, specifically African-Americans (AA), reveal the possible insult of “weathering”, the impact of adverse socio-economic and environmental hardships, which results in a rapid increase in the risk of negative pregnancy outcomes at a sooner age than White women. Additionally, little is understood about the possible differences in birth spacing among different ethnic and racial populations, and what effect this may have on subsequent deliveries in women delaying initiation of childbearing.

With the continuing trend of women delaying initiation of childbearing, it is reasonable to expect that problems associated with these pregnancies are likely to increase over time. Thus there is a need to explore further the reproductive challenges faced by women delaying initiation of childbearing, and have subsequent pregnancies, in order to make their experience of pregnancy and childbearing better. In our efforts to
improve maternal and child health (MCH), understanding of problems related to DCB, and the challenges mothers face in subsequent pregnancies, is necessary in order to identify the best approaches that can address specific needs of these mothers and infants, and to inform policy.

Justification

One of the objectives of Healthy People 2010 (HP 2010) initiative is ‘to improve infant and maternal health, reduce morbidity and mortality as well as racial disparities’. The goals and objectives may not be achieved if the issues affecting women delaying childbearing are not addressed, as the population of women DCB is fast increasing. Findings from this study will help inform providers and policy makers in their efforts to improve maternal and child health.
LITERATURE REVIEW

Trends in Delayed Childbearing

In the US, current findings show a steady increase in births to women in their 30s and 40s, and a modest decline in births to women in their teens and 20s.\(^2\), \(^5\)-\(^7\), \(^9\), \(^12\), \(^33\), \(^34\) Similar patterns are reported in other industrialized nations including Sweden, Italy, and Japan.\(^1\), \(^7\), \(^8\) These trends have been attributed to changes in age demographics, with an increase in the proportion of women in their 30s or older.\(^6\), \(^35\) Data from the NCHS show that from 1970-1986, the population of women 30-34 years increased by 78%, while that for women 35-39 increased by 66%. During the same time period, the population of women 20-24 increased by only 20%.\(^6\)

Because of the changing demographics, there is a noticeable increase in the proportion of women initiating childbearing at older ages. During the period 1995-2000, approximately 30% of all first time births in the US were to women 30 years or older,\(^9\) compared to 15% in 1986 and 4% in 1970.\(^6\) The largest increase is for women in their 40s as indicated in Figure 1. Because of these changes, there is an increasing focus on reproductive health issues among women DCB until age 30 or older, as health providers and policy makers strive to improve reproductive health issues.
Figure 1. Trends in Singleton First Time Births to USA Resident Mothers by Age: 1980-2000

Data Source, Natality Birth Files 1980-2000
Socio-Demographic Characteristics of Women Delaying Childbearing

Women delaying initiation of childbearing are generally married, well educated, and career oriented. Additionally, they have ready access to health care as demonstrated by intensive use of prenatal care services. Furthermore, research shows that most mothers are White; a study done in California looking at women 40 or older, found that 64% of women were White, 14% Hispanic, 17% Asian and only 4% were AA. In countries with less racial/ethnic diversity, regional differences are reported as demonstrated in a study conducted in Italy that found that women in the northern part of the country tended to delay childbearing more compared to their counterparts in the south. These differences are attributed to cultural and religious variations.

Delayed Childbearing and Reproductive Health Outcomes

Maternal age is a known risk factor for poor pregnancy outcomes, with the largest effect seen in women considered to be ‘too young or too old’. Teenage mothers often considered ‘too young’, have increased risk for PTD, low birth weight (LBW), and intrauterine growth restriction (IUGR). Additionally, infants of teen mothers are at increased risk for infant morbidity and mortality compared to infants to mothers in their 20s. Teen mothers also have a higher prevalence of high risk behaviors such as smoking, alcohol and substance use, and poor use of prenatal care, which factors have all been associated with poor pregnancy outcomes.

While the definition of ‘older’ mothers has changed over the years, research shows that women having children at the extremes of maternal age are at increased risk
for poor pregnancy outcomes. Older mothers have increased risk for FD, PTD, LBW, IUGR, chromosomal abnormalities, birth defects and neonatal mortality.\textsuperscript{4, 9, 10, 13, 14, 16, 18, 20-22, 34, 41-43}

Mothers age 30 and older also have higher prevalence of reproductive health risk factors including chronic medical conditions (hypertension, diabetes, heart disease) as well as diseases related to pregnancy (PIH, gestational diabetes). Other problems include placental anomalies leading to antepartum bleeding (APH), and higher rates of operative deliveries.\textsuperscript{9, 10, 13-16, 33, 34, 43-45} Some studies have also reported increased risk of maternal mortality.\textsuperscript{46, 47} Additionally, these mothers have increased risk for mood disorders including stress, anxiety, and postpartum depression in extreme case.\textsuperscript{48} Older mothers particularly first time mothers are notably distressed about their children, and are concerned about ‘doing things right’.\textsuperscript{45, 49}

Conversely, women delaying childbearing are less likely to engage in high risk behavior compared to their younger counterparts and this may mitigate some of the effects of advanced maternal age.\textsuperscript{9, 13, 34} Nevertheless, it is clear that advancing maternal age has far reaching effects on the health of the mother and baby.

Delayed Childbearing and Racial / Ethnic Differences

Research on racial/ethnic differences with respect to women who DCB is very limited; other than the fact that most women are White, there is paucity of information regarding other racial/ethnic differences for this subgroup of women. Few studies have examined racial/ethnic differences in pregnancy outcomes specifically for this unique group of women. Studies that have examined racial/ethnic in reproductive health issues
among women of advanced age, have had mixed results. While one study found no significant racial differences in perinatal outcomes,\textsuperscript{50} other studies have demonstrated racial differences in perinatal outcomes similar to those seen in the younger population.\textsuperscript{51-53} In their study, Khoshnood and colleagues found that AA had twice the rate for LBW compared to White mothers.\textsuperscript{51} Because of the limited studies looking at racial/ethnic differences in reproductive health issues among women DCB, it is difficult to draw conclusions. Furthermore, some studies have key limitations as they examine only AA without comparisons to other race/ethnic groups.\textsuperscript{50}

Addressing racial/ethnic differences in health is a key objective of the HP-2010 initiative,\textsuperscript{32} examining racial differences in pregnancy outcomes for women delaying childbearing is a relevant issue as it will give a better understanding of racial disparities in reproductive health outcomes.

### Pregnancy Spacing Patterns

The relationship between pregnancy spacing and pregnancy outcomes has been of interest to researchers since the 1970s when the relationship between pregnancy spacing and infant mortality was reported.\textsuperscript{54, 55} Since that time, several studies have been done to explore the relationship between pregnancy spacing and pregnancy outcomes.\textsuperscript{56, 57} Over time, the definition of pregnancy spacing has also evolved. Earlier studies focused on birth interval, which was defined as the period between two consecutive pregnancies in a pair.\textsuperscript{57-61} More recent studies look at pregnancy spacing in the context of interpregnancy interval (IPI),\textsuperscript{62-81} defined as the interval between one pregnancy outcome and the conception of the next pregnancy in a pair as demonstrated in Figure 2.
Pregnancy spacing patterns vary from population to population. In the US, changes in birth intervals have been reported. In 1970, the mean birth interval in the US was 41.8 months; by 1977, the birth interval increased to 45.5 months. Current findings indicate a continuing increase in birth interval. Similar findings are reported in other industrialized countries as well. A study done in Denmark found a mean birth interval of 45 months. Studies that examine IPI also show an increase in mean interval. In the US, the median found to be 23.8 months.

Determinates of Pregnancy Spacing

Various factors that are known to influence pregnancy spacing include maternal age, race, educational status, marital status, parity, socio-economic status (SES), previous birth outcomes, breastfeeding status and contraceptive use. Women initiating
childbearing as teens tend to have shorter intervals compared to those starting in their twenties.\textsuperscript{57, 58, 63, 82} The mean birth interval for women having children in their mid or late twenties is 45 months.\textsuperscript{58} A study looking at age at first birth and pace of subsequent fertility, found that women who start childbearing ≥ 25 years have a slower pace of subsequent intervals.\textsuperscript{82} Unfortunately, this study does not expand that category further to look at specific age subgroups.

There is a paucity of information as to what factors influence spacing for women DCB. One study concluded that women who initiate childbearing in their earlier years have higher fertility compared to late starters till midway the reproductive years when late starters being to catch up.\textsuperscript{82} This appears to imply that women DCB may have shorter birth intervals. A study from Denmark found that older mothers had shorter intervals compared to younger mothers.\textsuperscript{75} Parity is another factor known to influence pregnancy spacing.\textsuperscript{55, 58, 82} Intervals between the 1\textsuperscript{st} and 2\textsuperscript{nd} pregnancy are shorter than between the 2\textsuperscript{nd} and 3\textsuperscript{rd} or 3\textsuperscript{rd} and 4\textsuperscript{th}. High SES is associated with longer intervals.\textsuperscript{57, 63, 82, 83} A previous poor pregnancy outcome is associated with a short birth interval, pregnancies that end in FD, abortion, PTD tend to be associated with short pregnancy interval.\textsuperscript{57, 63} Education attainment has also been shown to influence pregnancy spacing. Women with advanced education have longer intervals especially for AA. However, there is evidence suggesting that for White women high educational attainment is associated with shorter intervals.\textsuperscript{58}

Maternal race has also been shown to be associated with pregnancy spacing; women of minority race are known to have shorter intervals compared to Whites, particularly if the mother is young.\textsuperscript{63, 82} This could be because minority women typically
start childbearing at a younger age. There is some evidence suggesting that for older AA women with high education there is a shift in the pattern of birth interval. Older AA women appear to have longer intervals compared to other race groups.\textsuperscript{58}

Relationship between Pregnancy Spacing and Perinatal Outcomes

Various studies indicate that there is an association between pregnancy spacing and adverse perinatal outcomes as indicated in a meta-analysis study.\textsuperscript{84} Both short and long intervals are associated with poor birth outcomes for both mother and baby. Short IPI \textless{}6 months is associated with an increase in risk for LBW and small-for-gestational age (SGA),\textsuperscript{63, 73, 80, 85} PTD,\textsuperscript{60, 74, 80, 85-90} and late term FD.\textsuperscript{78, 80} Additionally, infants born following short IPI are at an increased risk of morbidity and mortality.\textsuperscript{78, 80, 90} Similarly, mothers are also at increased risk for poor pregnancy outcomes.\textsuperscript{91} These findings have been consistent in studies done in both developing and developed countries.\textsuperscript{80, 92, 93} The largest impact of IPI on birth outcomes has been seen in young mothers; mothers 20 years or less with short IPI have increased risk for poor outcomes compared to older mothers.\textsuperscript{60, 90} Mothers with low education status, with short interval also have increased risk for poor outcomes compared to those with high education. Similarly, women of low SES with short IPI tend to have higher risk for poor outcomes.\textsuperscript{60} Racial/ethnic differences in pregnancy spacing and pregnancy outcomes have been reported; AA, Native Americans, and Hispanics with short IPI have increased risk for poor outcomes\textsuperscript{66, 68, 70, 71, 76} compared to Whites. However, few of these studies account for maternal age at initiation of childbearing.
A key question when examining the effect of pregnancy spacing on pregnancy outcomes relates to whether spacing is an independent risk factor or a marker for high-risk pregnancy. Some studies conclude that spacing is more of a risk marker rather than an independent risk factor, as the observed effects are eliminated once confounders are controlled for. Differences in defining pregnancy spacing (birth interval vs. interpregnancy interval) may explain the discrepancies in findings. Additionally, the classification of interval groups is largely arbitrary and varies from study to study and this may affect results as well. Having said that, two key studies reviewing previous research studies support the notion that indeed pregnancy spacing is an independent risk factor for adverse pregnancy outcomes.

The mechanism of how pregnancy spacing affects pregnancy outcomes is still unclear. It is suggested that short intervals are associated with maternal depletion syndrome, as the mother has not had enough time to recover following a previous pregnancy. This hypothesis may be correct although it does not explain why long intervals are also associated with adverse outcomes. Another theory proposed is that short intervals may be associated with folate depletion and this in turn affects pregnancy outcomes. Other suggestions put forth focus on interaction with other risk factors such as maternal age that influence pregnancy outcomes. However, studies that have attempted to explore this relationship found no significant interaction between maternal age and IPI.
Delayed Childbearing and Pregnancy Spacing

Several studies have looked at the impact of delayed childbearing on reproductive outcomes. However, there has been limited focus on pregnancy spacing its association with subsequent pregnancy outcomes in women DCB. We know little about pregnancy spacing patterns in women delaying initiation of childbearing, and the factors that influence their spacing as well as effect on pregnancy outcomes. Previous studies indicate that older mothers have short intervals with a mean of 31 months for women 30-34, and 28 months for women 35-49 having a second pregnancy when compared to younger women who had a mean of 38 months. A Swedish study looking at women delaying childbearing, found that the mean birth interval was 2.7 years between first and second pregnancy. Unfortunately, this study did not account for maternal age at initiation of childbearing.

Factors influencing pregnancy spacing in women DCB are largely unknown. Some of the factors such as education and marital status that are significant in younger women may not be that important since most of the women DCB have high education status and are married. Pregnancy outcome in preceding pregnancy may play a more significant role as seen in younger women. The increased risk for adverse perinatal outcomes among women DCB may have a far significant role in determining pregnancy spacing compared to other risk factors. The effect of pregnancy spacing on subsequent pregnancy outcomes is still unclear, as few studies have examined subsequent pregnancy outcomes in women DCB. In a study among women 30-39 years having two consecutive pregnancies, Forman et al., found an increased risk for late fetal deaths, low birth weight
and preterm delivery.\textsuperscript{4} In a Swedish study, the results suggested a higher risk of poor outcomes in the first pregnancy compared to the 2nd, and that women 35 and older had a higher risk for neonatal death, LBW and PTD in the 2nd pregnancy.\textsuperscript{96} However, none of these studies examined the role of pregnancy spacing. It is not clear whether age alone or some other contributing factors such as short intervals may explain these findings. There is need for further research to explore this issue further given the number of women delaying childbearing is on the rise in much of the developed world.

Challenges in Pregnancy Spacing Research

Research in this area has several limitations primarily methodological issues; definition of interval varies from study to study. Studies that use birth interval may have different findings from those using interpregnancy interval.\textsuperscript{57, 77, 81} In addition, using birth intervals eliminates cases that did not end in a live birth and this may affect estimates obtained. Studies that use IPI as a measure of pregnancy spacing face the challenge of accurately estimating IPI, as it is dependent on knowing the date of last normal menstrual period (LNMP). Similarly, estimates of IPI based on gestational age (GA) may be prone to imprecise estimates if the GA is not accurately estimated. However, with increased use of ultrasound to determine gestational age, more reliable estimates of GA can now be obtained hence use of GA may be a better way for estimating IPI than using LNMP.

Other challenges relate to study designs; most of the studies reviewed use cross sectional or retrospective data, which have some limitations such as selection bias, and recall bias. Furthermore, one is unable to control for all potential confounders in cross sectional or retrospective studies. While prospective studies would be the most ideal, they
are not practical as they are expensive and require long time periods to obtain a large enough sample as short intervals are relatively rare occurrence especially if dealing with a very select sample such as women delaying childbearing.

Another important challenge is determining the cutoff points for pregnancy intervals. Currently there is no standard definition of what is short, long or appropriate. The cutoff limits used are arbitrary; there is no consistency in the literature making it very hard to compare results. There have been attempts to address this issue. In their study, Zhu and colleagues identified intervals at which the risk for adverse outcomes was greatest. They demonstrated that the effect of IPI is J shaped that is, at very low intervals 6 months or less the risk for poor outcomes is high, and reduced between 18-23 months and there after the risk increases again.79, 81 However, few studies have used their proposed cutoff points for meaningful comparisons to be made.

Although the focus has been mainly on short intervals, a few studies have explored long intervals, which are also associated with increased risk for adverse outcomes. The problem with this finding is that there is no biological explanation for the finding, making it difficult to explain the results.

In summary, the literature supports the fact that pregnancy spacing does influence reproductive health outcomes, and is an independent risk factor. Short intervals (birth or interpregnancy) are associated with adverse pregnancy outcomes for both mother and baby. However, limited research has looked at women DCB. Given the increasing trend towards delayed childbearing, it would be worthwhile to examine spacing patterns, and explore the effect on subsequent pregnancy outcomes for this group of women.
RESEARCH QUESTION/ STUDY AIMS

The main objective of this study was to examine reproductive health issues among women delaying initiation of childbearing until age 30 or older. Our major focus was on pregnancy spacing and its relationship with subsequent perinatal outcomes as well as racial differences. Several questions were addressed in this study including:

i. Do women delaying initiation of childbearing until age 30 or older closely space their subsequent pregnancy?

ii. What factors determine pregnancy spacing for women delaying initiation of childbearing until age 30 or older?

iii. Do women delaying initiation of childbearing followed by a closely spaced second pregnancy have increased risk for adverse perinatal outcome?

iv. Are there any racial differences in pregnancy spacing patterns and subsequent pregnancy outcomes among women delaying initiation of childbearing?

The specific aims and hypotheses were:

**Aim 1**

To assess pregnancy spacing patterns among women who delay initiation of childbearing until age 30 or older, and have a second pregnancy.
**Specific Aims**

i. To determine pregnancy spacing patterns among women who initiate childbearing at age 30-34, 35-39 and 40-50, in comparison to women who initiate childbearing in at age 20-29.

ii. To determine factors associated with pregnancy spacing in women who initiating childbearing at age 30-34, 35-39 and 40-50.

iii. To determine whether women delaying initiation of childbearing until age 30-34, 35-39 and 40-50, have shorter interpregnancy interval (<6 months) compared to those initiating childbearing at age 20-29.

**Hypothesis 1**

Women delaying initiation of childbearing until age 30 or older, and go on to have a second pregnancy will have shorter interpregnancy intervals (<6 months) compared to those initiating childbearing age 20-29.

**Rationale**

For a long time, women have been made aware that advancing maternal age is a risk factor for poor birth outcomes.\(^{23-27}\) However, there is an increasing trend of delayed initiation of childbearing. Coupled with the desire for having an ‘ideal’ family women who delay commencement of childbearing may want to space their pregnancies closely in order to minimize the effects of advancing maternal age on pregnancy outcomes. As a result, they may have shorter interpregnancy intervals. Similarly, much research has been conducted to examine factors influencing birth spacing for women in general; however, limited research has been undertaken focusing on women who delay childbearing.
Understanding these issues is essential in addressing pregnancy related factors for women delaying childbearing.

Aim 2

To investigate the relationship between pregnancy spacing and subsequent perinatal outcomes for women delaying initiation of childbearing until age 30 or older.

Specific Aims

i. To determine what proportion of second pregnancies result in FD, LBW, PTD, and SGA among women delaying initiation of childbearing until age 30 or older.

ii. To determine the relationship between IPI and adverse pregnancy outcome (FD, LBW, PTD and SGA) in the second pregnancy for women initiating childbearing at age 30 or older compared to those initiating childbearing age 20-29.

iii. To determine whether women initiating childbearing at age 30 or older, and having short IPI are at increased risk for adverse birth outcomes (FD, LBW, PTD & SGA) in second pregnancy, after controlling for potential confounders.

Hypothesis 2

Mothers delaying initiation of childbearing until age 30 or older, and have a second pregnancy following a short IPI (<6 months) are more likely to be at increased risk for FD, PTD, LBW and SGA; as compared to mothers who initiate childbearing age 20-29 and have a second pregnancy following short IPI.

Rationale

Research has shown that short pregnancy intervals are associated with poor birth outcomes. However, it is unclear what effect this may have on specific pregnancy outcomes (FD, LBW PTD, and SGA) in older mothers who have a subsequent
pregnancy. It is unclear whether women who delay initiation of childbearing have similar or exaggerated effects in subsequent deliveries compared to women initiating childbearing in their 20s.

Aim 3

To examine racial differences in reproductive health outcomes among women delaying childbearing until age 30 or older.

Specific Aims

i. To determine racial difference in pregnancy spacing patterns in relation to age of mother at start of childbearing.

ii. To determine racial differences in perinatal outcomes (FD, LBW, PTD, and SGA), for women initiating childbearing age 30 or older, in comparison to those whose initiating childbearing age 20-29.

iii. To determine racial difference in risk for adverse birth outcomes (FD, LBW, PTD, and SGA), for women initiating childbearing age 30 or older, and have short IPI compared to those initiating childbearing age 20-29 and have short IPI.

Hypothesis 3

African American women who delay initiation of childbearing until age 30 or older have increased risk for adverse birth outcomes (FD, LBW, PTD and SGA) compared to women of other racial/ethnic groups who delay initiation of childbearing after controlling for potential confounders.
Rationale

Current research shows that there are racial disparities in pregnancy and birth outcomes; however the research examines all categories of women and it is unclear whether the same disparities exist in specific subgroups of women. For example, one study suggests that the risk for LBW increases rapidly with age for African American women.\textsuperscript{97} However, the study does not explore outcomes in women delaying initiation of childbearing. Also it has been postulated that the racial differences in birth outcomes can be explained by the weathering hypothesis.\textsuperscript{31,98} According to this hypothesis, African American women are likely to have better outcomes when they start childbearing at a younger age than later. The merit of this hypothesis has not been applied for African American women who start childbearing later in life, and have more than one pregnancy.

MATERIALS AND METHODS

Study Design and Study Population

We conducted a retrospective cohort study using the Missouri maternally linked infant/fetal death files. The database is maintained by the Missouri Department of Health and Senior Services (MDHSS), and contains information on all births that occurred from 1978 to 1997 inclusive. The data are collected prospectively on all mothers delivering in the state during this period. The information is then linked to both fetal and infant death files, creating a maternally linked database. The Missouri vital record system is reliable, and has been adopted as a standard to validate other databases that involve matching and linking procedures.\textsuperscript{99}
Information is obtained from vital records and hospital records, and includes socio-demographic data, information on current pregnancy and any complications, labor and delivery, and birth outcome. Data on the same mother is linked using special linking variables, making it possible to obtain information on all pregnancies to the same mother occurring during the data collection period.

Study Sample

For this study, we considered all records that met the following criteria to be eligible;

Inclusion criteria: Cases meeting the following criteria will be included in the final study sample

1) Mothers 20-50 years old at first pregnancy, delivering in the state of Missouri between 1978-1997
2) Mothers having first two consecutive pregnancies, both occurring in Missouri.
3) Singleton pregnancy

Exclusion criteria: cases were excluded if;

1) Mother was younger than 20 or older than 50 years at first pregnancy
2) Multiple pregnancies
3) If one of the pregnancies was outside the state of Missouri

Variables

Independent Variables

Independent variables for this study included maternal age at first pregnancy, which was estimated from mothers’ date of birth, and child’s date of birth. We
categorized maternal age into 4 age groups; 20-29, 30-34, 35-39 and 40-50. For purposes of this study, a mother having her first pregnancy at age 30 or older was considered to have delayed initiation of childbearing. Maternal race/ethnicity was another variable considered; the dataset has various classifications for mothers’ race and ethnicity, these were grouped in 5 main categories; White, African American, American Indian, Asian Pacific Islander (API), and others. Over 90% of cases were White or African American.

*Intermediate Variable*

Interpregnancy interval was used as the measure for pregnancy spacing in this study. This variable is unique in that it serves both as an independent variable as well as an outcome variable. For purposes of this study, only two consecutive pregnancies are considered. The IPI was computed as the difference between the gestation age of the second pregnancy, and the birth interval between pregnancy one and two. Initially interval was estimated in weeks then converted to months with 13 weeks considered to equal 3 months. Interval categories were created based on the categories proposed by Zhu and colleagues.\(^7\) Categories include 0-5, 6-11, 12-17, 18-23, 24-59, 60-119, and \(\geq 120\). An interval of less than 6 months was considered as short IPI.

*Dependent/Outcome Variables*

Several dependent variables were examined for this study, including FD, LBW, PTD, and SGA. Fetal death was defined as a fetus born at 20 weeks gestation or higher, or birth weight >500gms with no signs of viable life as defined by Missouri’s vital records. Low birth weight was defined as birth weight less than 2,500gms. Infants recorded birth weight in grams was used to determine if infant was LBW. Low birth
weight was categorized into different subgroups; moderately low birth weight (MLBW), 1500-2499gms, very low birth weight (VLBW), 1000-1499gms and extremely low birth weight (ELBW), 500-999gms. Preterm birth was defined as the birth of a baby at less than 37 completed weeks of gestation. Gestational age was estimated as the difference between child’s birth date, and date of last normal menstrual period, initially estimated in days, and then converted to weeks. In situations were the LNMP was missing a day; this was imputed as the 15th. If the month was missing, LNMP was considered as missing.

Using the obtained gestational age, categories of PTD were created; included moderately preterm (MPTD), 32-36 weeks, very preterm (VPTD), 28-31 weeks and extremely preterm (EPTD), 24-27 weeks. Finally, SGA was defined as birth weight that is at or below the 10th percentile of the birth weight distribution of infants at the same gestational age based on US national growth curves. An SGA infant can be born at term or preterm. Both are at increased risk for morbidity and mortality. An algorithm was used to determine SGA infants based on their birth weight, and gestational age.

Confounders

To obtain meaningful results, potential confounders were taken into account. In this study, several confounders were considered and controlled for in the analysis; they included:

*Education Status:* was determined from mothers completed years of education at the time of pregnancy, and maternal age. It was categorized as high, average or low education status for age.
Martial Status: Being unmarried has been linked to poor reproductive outcomes. Mother was considered as single if she was unmarried at the time of pregnancy/delivery.

Prenatal Care Use: Late start of, and inadequate utilization of PNC have been associated with adverse birth outcomes. As such there is need to account for prenatal care use when evaluating adverse birth outcomes. Prenatal care was assessed using the Revised Graduate Index (R-GINDEX), a measure that takes into account timing of start of prenatal care, number of visits and gestational age at delivery. Using this measure, there are 5 categories: no care, missing care, inadequate care, intermediate, adequate care and intensive care.

Medical Risk Factors: Several medical risk factors have been associated with poor birth outcomes. A wide range of medical risk factors are collected as part of the Missouri maternally linked database. For this study, the following medical risk factors were considered; history of hypertension (preexisting and PIH), and diabetes. These factors are selected because previous research has shown a higher rate of these conditions in women who delay childbearing.

Obstetric Risk Factors: Past and present obstetric factors have an impact on pregnancy outcome. Previous research shows that a previous adverse outcome increases the risk of poor outcome in a subsequent pregnancy, and may also influence birth spacing. As such one needs to take this into account when evaluating outcomes in subsequent pregnancy. In this study we controlled for previous adverse outcome (FD, LBW, PTD and SGA).
Other factors considered as confounders related to health behavior during pregnancy such as smoking and alcohol use during pregnancy. Upon evaluation of the database, it was noted that the alcohol variable had almost 50% cases missing; therefore it was not used in the analysis. However, we controlled for smoking even though there are questions about the reliability and validity of the smoking variable when using vital statistics data.

Data Analysis

The Missouri maternally linked file 1978-1997 has a total of 1,577,082 records. A total of 485,118 records (1\textsuperscript{st} and 2\textsuperscript{nd} pregnancy) met the inclusion criteria as demonstrated in appendix C. For further analysis, this sample was split into 2 datasets (1\textsuperscript{st} pregnancy and second pregnancy) each with 242,559 mother infant pairs. Initial descriptive analyses were done on the dataset for first pregnancy while subsequent analyses utilized the dataset for second pregnancy.

Different analysis techniques were used to answer the study questions, and test the hypotheses; including univariate, bivariate, and multivariate (stratified and logistic regression) approaches. For bivariate analysis, the Chi Square statistic was used to test for significant differences in proportion; while for stratified analysis the Mantel-Hansel statistic was used. For the logistic analysis, odds ratios (OR) and 95 % confidence intervals (CI) were estimated. All hypothesis tests were 2-tailed with alpha set at <0.05. All analyses were conducted using Statistical Analysis Software (SAS) version 9.1., Cary NC.
PREGNANCY SPACING AMONG WOMEN DELAYING INITIATION OF CHILDBEARING

by

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ABSTRACT

Introduction

An increasing proportion of women in the US and other countries delay initiation of childbearing until age 30 or older. Little is known about their subsequent pregnancies, particularly in regard to pregnancy spacing.

Objectives

To determine pregnancy spacing patterns, factors associated with pregnancy spacing among women delaying initiation of childbearing until their 30 or older, and if delay in initiation of childbearing is associated with increased risk for short interpregnancy interval of less than 6 months.

Methods

A retrospective cohort study was performed using the Missouri maternal linked file for 1978-1997, inclusive. Analysis was limited to mothers 20-50 years of age at first pregnancy, having two consecutive first and second pregnancies during the data collection period. The sample size included 242,559 mother-infant pairs. Main outcome was interpregnancy interval, which was grouped in 7 categories; 0-5, 6-11, 12-17, 18-23, 24-59, 60-119, ≥120 months.

Results

The mean interpregnancy interval between first and second pregnancy was significantly shorter for women delaying start of childbearing (≥30 years) compared to
20-29 year olds. Observed intervals are 25 (± 17) months for mothers 30-34 years, 21 (± 14) for 35-39 year olds, and 19 (± 16) for 40-50 year olds (p-value <0.0001). A significant trend for shorter intervals was noted as maternal age at first pregnancy increased. Factors associated with interpregnancy interval for women 35 and older at initiation of childbearing include low educational status, adverse outcome in preceding pregnancy, and high body mass index. Mothers 35 years of age and older had a 2-fold increase in risk for short interpregnancy interval.

Conclusion

Older first time mothers are more likely to have a second pregnancy shortly after their first pregnancy, especially if an adverse outcome was present in the first pregnancy. Given the increasing number of older first time mothers, these findings are of relevance to health care providers as they plan care for this unique group of women.

INTRODUCTION

An increasing proportion of women now delay initiation of childbearing until age 30 or older. Mothers delaying childbearing are at increased risk for adverse fetal and maternal outcomes including fetal death, low birth weight, preterm delivery, and maternal stress including postpartum depression. Little is known about their subsequent pregnancies, particularly in relation to pregnancy spacing.

Previous research has revealed that women in developed countries on average desire at least 2 children in their lifetime. Given this baseline statistic, one would anticipate that many women who delay start of childbearing will also have subsequent
pregnancies. However, women initiating childbearing at older age often are aware of their advancing age and the negative effect of the so-called ‘biological clock’. As a result, mothers who delay initiation of childbearing may be inclined to accelerate subsequent pregnancies in an attempt to minimize the effects of the declining fecundability that is inherent with advancing age. It is uncertain if this is the case, however as there is paucity of information on pregnancy spacing patterns for this specific population of women.

Whereas a general population mean interpregnancy interval (IPI) of 23.8 months has been calculated recently, the mean IPI for women delaying initiation of delaying childbearing is unclear. Several studies describe older mothers with shorter interpregnancy intervals compared to their younger counterparts, but these studies do not indicate when mother had her first pregnancy.

Factors associated with pregnancy spacing include maternal age, race, socio-economic status (SES), marital status, education status, smoking, and previous pregnancy outcomes. Young maternal age, single marital status, low SES, non-White race and parity strongly correlate with short intervals. Unfortunately, many of these studies examined all maternal age groups collectively rather than focusing on age specific populations, which have specific and differing characteristics. In addition, methods for measurement of interval and classification of interval groups also vary across these studies. Thus, it is uncertain whether the same factors for pregnancy spacing are significant for women delaying initiation of childbearing.

Understanding pregnancy spacing patterns and factors associated with spacing for older mothers is important, because spacing has been linked to adverse pregnancy outcomes for both the mother and baby including maternal stress and anxiety, fetal death,
low birthweight, preterm delivery and neonatal mortality. Furthermore, pregnancy spacing is a potentially modifiable factor using family planning methods. Given that older mothers already have increased risks for adverse outcomes, if indeed mothers who delay childbearing have short pregnancy intervals, use of effective family planning methods may improve their subsequent reproductive outcomes.

In this paper, we examine issues related to pregnancy spacing and factors that influence spacing for women delaying initiation of childbearing. The main objectives of the study are:

1. To determine the interpregnancy intervals among women delaying initiation of childbearing until age 30 and older, in comparison to those initiating childbearing age 20-29.
2. To determine factors that influence child spacing for women delaying initiation of childbearing until age 30 or older.
3. To determine if women delaying initiation of childbearing are at increased risk for short interpregnancy intervals of less than 6 months compared to women who start childbearing age 20-29.

Our hypothesis for the study is that women who delay start of childbearing until age 30 or older have shorter interpregnancy interval (<6 months) compared to those initiating childbearing at age 20-29.

MATERIAL AND METHODS

The Missouri maternally linked pregnancy outcome cohort files from 1978 through 1997 were used for this study. This dataset contains live birth and fetal death
files linked to infant death files. Additionally, files for siblings have been linked to their biological mother using unique identifiers. The Missouri vital record system is reliable, and has been considered as a standard to validate other databases that involve matching and linking procedures.\textsuperscript{30, 31}

The analyses were limited to cases meeting the following criteria

1. Maternal age 20-50 years at first pregnancy,
2. Mothers with records on two consecutive first and second pregnancies,
3. Singleton pregnancy,
4. Both pregnancies occurred in the state of Missouri

Of the 1,577,082 births in the Missouri database during the study period, 485,118 cases met the study inclusion criteria as shown in Figure 1. Key variables including maternal age, educational status, marital status, body mass index, prenatal care use and perinatal outcomes of the first pregnancy were renamed, and merged to the records for second pregnancy.

For this study, we focused on these key socio-demographic characteristics: race, maternal age, marital status, and educational status at first pregnancy. Maternal age was categorized into four groups; 20-29 (reference group), 30-34, 35-39 and 40-50. We defined delayed initiation of childbearing as a mother aged 30 years or older at first pregnancy. Educational status was estimated based on years completed in school and age of mother at first pregnancy. Three educational status levels were created: high if the mother has completed more years in school than expected for her age; average if mother completed appropriate school level for age, and low mother completed less than expected number of years for age. Race of the mother was categorized into 5 different categories:
White, African American (AA), American Indian (Am Indian), Asian /Pacific Islanders (API) and others. Because the dataset had very few cases recorded as Hispanics, no category for Hispanics was created.

Other variables included health risk indicators such as, prenatal care use and body mass index (BMI) at first pregnancy. Prenatal care (PNC) use was assessed using the Revised Graduated Index (R-GINDEX). The PNC categories using this measure include; intensive (mother received more than the recommended number of visits), adequate (receive recommended number of visits), Intermediate and inadequate (receive less than the recommended visits). The BMI was calculated as the weight (kgs) / height (meters)$^2$ and was categorized into 4 groups based on the CDC classification (< 18.5, 18.5-24.9, 25.0-29.9, $\geq$ 30). Additional obstetric risk factors measured adverse pregnancy outcomes: low birth weight (LBW), defined as birth weight less than 2,500 gms, preterm delivery (PTD), defined as gestational age less than 37 completed weeks, and small-for-gestational age (SGA) defined as birth weight less than the 10$^{th}$ percentile for gestational age based on the US growth curve.

Interpregnancy interval (IPI) between the first and second pregnancy was the main outcome variable. The IPI was computed as the interval between the date of first pregnancy outcome, and date of second pregnancy outcome minus the gestational age of the second pregnancy. Initially the interval was estimated in weeks then converted to months. The assumption was made that 13 weeks equal 3 months. Interval groupings were created based on the categories proposed by Zhu et al., namely, 0-5, 6-11, 12-17, 18-23, 24-59, 60-119, and $\geq$120 months. An interval of less than 6 months was considered to be short, and 18-23 months was used as the reference category.
Univariate, bivariate, stratified analysis and unconditional logistic regression were used to address the study questions. Chi square statistic was used to test for significant difference in proportions, and the Mantel-Haenszel test statistic was used for the stratified analysis controlling for maternal age at first pregnancy. Tests for hypothesis were 2-tailed with a type one error rate fixed at 5%. Descriptive statistics were based on maternal characteristics, and outcomes at first pregnancy. Additional analyses involving race were limited to Whites and AA only, as the other race groups did not have sufficient numbers for meaningful interpretation. All data were analyzed using SAS version 9.1 (Cary, NC).

Approval for this study was obtained from University of Alabama at Birmingham (UAB) Institutional Review Board (IRB), and Missouri Department of Health and Senior Services.

RESULTS

Over the 20-year study period, the annual number of births to women 20-50 years at first pregnancy in Missouri ranged from 1,593 (1996) to 15,855 (1980). Approximately 88% of births were to women age 20-29 years. The study population was predominately white (91%). Fifty two percent of mothers had high educational status based on maternal age, and 87% were married at the time of the first pregnancy. Forty percent of mothers received adequate prenatal care, with 20% reporting history of smoking during the first pregnancy. About 8% of mothers had a BMI $\geq 30$ at first pregnancy. One percent of the first pregnancies ended in stillbirths, 6% in LBW, 8% PTD, and 10% SGA.
The mean interpregnancy interval (IPI) between the first and second pregnancy for the study population was 29.9 ± SD 23.6 months. Mothers initiating childbearing in their 30s had significantly shorter mean intervals compared to mothers initiating childbearing in their 20s (Table I). Roughly 6% of mothers had an IPI of less than 6 months (Tables II). There was a significant trend towards short IPI as the age of the mother at first pregnancy increased (Figure 2).

For the general study population, single marital status, non-white race, low educational status, high BMI, inadequate or no prenatal care, later year of first pregnancy were all significantly associated with interpregnancy interval (p<0.0001). Additionally, an adverse outcome in the first pregnancy was associated with short IPI (Table III). However, on controlling for maternal age at first pregnancy, race, marital status, and prenatal care use were not significantly associated with interpregnancy interval for mothers 35 and older at first pregnancy,

Mothers 35 and older at first pregnancy had an increased risk for short IPI <6 months compared to 20-29 year olds. This risk persisted even after controlling for potential confounders. However, mothers 30-34 at initiation of childbearing had significantly lower risk for short IPI compared to mothers 20-29 year olds (Table IV).

DISCUSSION

We found that mothers delaying initiation of childbearing until age 30 and older have shorter mean interpregnancy intervals between the first and second pregnancy compared to those initiating childbearing in their 20s. This finding confirms previous
and provides support for the theory that women who delay start of childbearing may accelerate their patterns of pregnancy as a catch up strategy.\textsuperscript{35}

Although the risk factors associated with pregnancy spacing for mothers delaying childbearing are similar to those seen in the general population, inadequate prenatal care, maternal race, and marital status were not associated with IPI in older first time mothers. This difference may be due to variations in population, as older first time mothers in the US are generally of White race, married and receive adequate-intensive prenatal care.\textsuperscript{3} The small number of older mothers (40-50 years) may also explain the findings.

Mothers with advancing maternal age at first pregnancy were at increased risk for short IPI (< 6 months), compared to mothers having first pregnancy at 20-29 years even after controlling for confounders. This is especially so for mothers 40 years and older who have a 2 fold risk for having short IPI less than 6 months. These findings confirm those in other studies that indicate increased risk for short IPI in women delaying childbearing.\textsuperscript{14, 21} Reasons for these study findings remain unknown. However, one could speculate that mothers who delay childbearing may want to minimize the effects of advancing age and chose to have their pregnancies in an accelerated fashion. Another possible explanation could relate to increased risk of adverse outcomes seen in women delaying childbearing. Mothers with a poor outcome in the first pregnancy may decide to get pregnant shortly afterwards. As seen in this study, a poor adverse outcome is associated with short IPI. Fertility issues may also play a role; if one has fertility problems and is using fertility treatment, such individuals may not want to wait too long before another treatment cycle.
We found no increased risk for IPI <6 months for mothers age 30-34 at first pregnancy compared to mothers age 20-29. This appears to suggest that perhaps these mothers are not necessarily a high risk group at least for short IPI.

As the data used are collected prospectively, we were able to examine outcomes and risk factors in the same mother overtime hence eliminating the cohort effect. This gives strength to our study. Having said this, given that the data are from a secondary database they are subject to several inherent limitations, including issues of incomplete data and reliability. As the Missouri database covers a long period, there maybe potential differences in the completeness of the data over time evidenced by the low proportion of stillbirths in this study population, which could be because of underreporting.\textsuperscript{36-38} Another important limitation relates to small number of mothers (153) having a first pregnancy at extremes of maternal age (\geq40 years). This may impart instability to the estimates.

Given that the database is based on vital statistics data, some potential cofounders of interest such as use of fertility treatment, are not available hence we are unable to evaluate them. Finally, although the findings are informative on pregnancy spacing in older mothers in Missouri, their generalizability to the national population may be limited.

In conclusion, delayed initiation of childbearing until age 30 and older and especially age 35 and older is associated with short interpregnancy interval between the first and second pregnancy. An adverse outcome in the first pregnancy is an important risk factor for short interval of less than 6 months. These findings have implications for health providers because of the increasing number of women delaying start of
childbearing. Older mothers need preconception counseling about potential risks of closely spaced pregnancies.
REFERENCES


Missouri maternally linked cohort file, 1978-1997 = 1,577,082

Selecting first and second pregnancies = 613,237

Data cleaning to ensure 2 records for each case = 485,118

Eliminating mothers < 20 or >50 years, and multiple births = 917,979

Eliminating all cases with no siblings = 1,104,007

First pregnancy records = 242,559

Second pregnancy records = 242,559

Figure 1. Study Sample Selection: Missouri Maternally Linked Files 1978-1997
Figure 2. Distribution of Interpregnancy Interval by Maternal Age at First Pregnancy: Missouri Resident Mothers 1978-1997
Table 1. Mean Interpregnancy Interval between First and Second Pregnancy: Missouri Resident Mothers 1978-1997.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (n)</th>
<th>Mean (SD)</th>
<th>t-test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mothers, 1st pregnancy 20-50 years</td>
<td>237,044</td>
<td>29.9</td>
<td>(23.6)</td>
</tr>
<tr>
<td>IPI at age 1st Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>212,109</td>
<td>30.7</td>
<td>(24.3)</td>
</tr>
<tr>
<td>30-34</td>
<td>26,593</td>
<td>25.3</td>
<td>(17.4)</td>
</tr>
<tr>
<td>35-39</td>
<td>3,704</td>
<td>20.9</td>
<td>(13.7)</td>
</tr>
<tr>
<td>40-50</td>
<td>153</td>
<td>18.7</td>
<td>(15.6)</td>
</tr>
</tbody>
</table>

Table 2. Distribution of Interpregnancy Interval between First and Second Pregnancy: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>Interpregnancy Interval (Months)</th>
<th>Total N= 242,559</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (n)</td>
</tr>
<tr>
<td>0-5</td>
<td>13,423</td>
</tr>
<tr>
<td>6-11</td>
<td>26,237</td>
</tr>
<tr>
<td>12-17</td>
<td>33,171</td>
</tr>
<tr>
<td>18-23</td>
<td>29,867</td>
</tr>
<tr>
<td>24-59</td>
<td>94,433</td>
</tr>
<tr>
<td>60-119</td>
<td>20,523</td>
</tr>
<tr>
<td>≥ 120</td>
<td>19,383</td>
</tr>
</tbody>
</table>

* May not add up to 100 % because of missing cases
Table 3. Distribution of Interpregnancy Interval by First Pregnancy Outcome: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>First Pregnancy Outcome</th>
<th>% Interpregnancy Interval (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5</td>
</tr>
<tr>
<td>Fetal death*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36.7</td>
</tr>
<tr>
<td>No</td>
<td>5.5</td>
</tr>
<tr>
<td>Low birth weight (&lt; 2500gms) *</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10.5</td>
</tr>
<tr>
<td>No</td>
<td>5.4</td>
</tr>
<tr>
<td>Preterm delivery (&lt;37 weeks) *</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.1</td>
</tr>
<tr>
<td>No</td>
<td>5.4</td>
</tr>
<tr>
<td>Small-for-gestational age (&lt; 10th percentile) *</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.5</td>
</tr>
<tr>
<td>No</td>
<td>5.4</td>
</tr>
</tbody>
</table>

* $\chi^2$ (df = 6); p-value <0.0001; $\alpha$ <0.05

Table 4. Odds Ratios for Short Interpregnancy Interval among Women Delaying Initiation of Childbearing: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>Maternal Age at 1st Pregnancy</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29*</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>30-34</td>
<td>0.88 (0.83-0.93)</td>
<td>0.92 (0.87-0.98)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.32 (1.17-1.50)</td>
<td>1.26 (1.11-1.44)</td>
</tr>
<tr>
<td>40-50</td>
<td>2.26 (1.38-3.70)</td>
<td>1.91 (1.13-3.24)</td>
</tr>
</tbody>
</table>

*Reference group

*Adjusted for year of first pregnancy, maternal race, marital status, educational status, prenatal care, BMI and adverse perinatal outcome at first pregnancy.
INTERPREGNANCY INTERVAL AND SUBSEQUENT PERINATAL OUTCOMES AMONG WOMEN DELAYING INITIATION OF CHILDBEARING

by

SARAH K. NABUKERA, MARTHA S. WINGATE, RUSSELL S. KIRBY, JOHN OWEN, SHAILENDER SWAMINATHAN, GREG R. ALEXANDER, HAMISU M. SALIHU

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Format adapted for dissertation
ABSTRACT

Introduction

Although delayed initiation of childbearing has been associated with adverse perinatal outcomes, it is unclear whether risk persists in a subsequent pregnancy, and how interpregnancy interval affects subsequent perinatal outcomes.

Objectives

To examine second pregnancy perinatal outcomes for women initiating childbearing age 30 or older compared to those initiating childbearing age 20-29. Specific objectives were to determine distribution of adverse perinatal outcomes, and the association between interpregnancy interval and feto-infant mortality and morbidity outcomes.

Methods

Retrospective cohort study using the Missouri maternally linked cohort files 1978-1997. Perinatal outcomes included fetal death, low birth weight, preterm birth and small-for-gestational age. Prediction variables included maternal age at first pregnancy and interpregnancy interval between the first and second pregnancy with interval <6 months considered short.

Results

Compared to mothers 20-29 years at first pregnancy, mothers ≥ 35 years had significantly higher rates of low birth weight (p <0.0001), and preterm delivery (p
<0.0001), however, they had significantly lower rates of small-for-gestational age (p <0.0001). Interpregnancy intervals <6 and ≥60 months were associated with higher rate of adverse outcomes even after controlling for maternal age at first pregnancy. Interval 12-17 months was associated with lowest rate of adverse outcomes for mothers’ ≥35. Both maternal age ≥35 years at first pregnancy and IPI <6 months were independent risk factors for adverse outcome in the second pregnancy, but there was no significant interaction between the two.

Conclusion

Delayed initiation of childbearing is associated with persistent risk for adverse perinatal outcomes in the second pregnancy. Short interpregnancy interval contributes to this risk. With the increasing number of women delaying childbearing until their 30s, providers should consider these risks as they counsel older women concerning their future reproductive plans.

INTRODUCTION

Pregnancy spacing is an established risk factor for adverse maternal and fetal outcomes.1,2 Recent findings demonstrate associations between both short and long interpregnancy intervals and increased rates of adverse outcomes including fetal death (FD), preterm delivery (PTD), low birth weight (LBW), neonatal mortality as well as maternal morbidity and mortality.1-17 However, few of these studies specifically examine the association between pregnancy spacing and subsequent pregnancy outcomes, with regard to timing of first pregnancy.
Whereas maternal age is a known risk factor for adverse pregnancy outcomes, it is uncertain how it interacts with pregnancy spacing particularly for women delaying initiation of childbearing until age 30 or older. Research findings indicate that mothers delaying initiation of childbearing until age 30 or older are at increased risk for adverse perinatal outcomes, as well as short pregnancy intervals of less than 12 months. Given the increasing number of women delaying childbearing, the effect of pregnancy spacing on the subsequent pregnancy outcomes for these women have both clinical and population health implications.

For women delaying initiation of childbearing until age 30 or older, the magnitude of adverse outcomes in subsequent pregnancy is unclear. Although a previous study found that mothers who delay childbearing tend to have better outcomes in the second pregnancy compared to the first pregnancy, this study failed to examine the effect of pregnancy interval on subsequent outcomes. This study seeks to explore this issue.

Our primary objective was to investigate the association between pregnancy spacing and perinatal outcomes in second pregnancy among women delaying initiation of childbearing until age 30 or older. The specific aims were:

i. To determine the proportion of feto-infant morbidity and mortality outcomes in second pregnancy among women delaying initiation of childbearing until age 30-34, or 35-50 compared to mothers initiating childbearing age 20-29.

ii. To determine the relationship between interpregnancy interval (IPI) and feto-infant morbidity and mortality outcomes in second pregnancy for women initiating
childbearing aged 30-34, or 35-50, compared to those initiating childbearing in their 20s.

iii. To determine if mothers delaying initiation of childbearing until age 30-34 or 35-50 and having a short IPI are at increased risk for adverse perinatal outcomes in second pregnancy after controlling for potential confounders.

We hypothesize that mothers delaying initiation of childbearing until age 30 or older, and have a second pregnancy following a short IPI (<6 months) are at increased risk for feto-infant morbidity and mortality as compared to mothers who initiate childbearing age 20-29, with second pregnancy following short IPI.

MATERIALS AND METHODS

We conducted a retrospective cohort study using the Missouri maternally linked cohort files for 1978-1997. The data were collected prospectively on all mothers delivering in the state during the study period. The live birth and fetal death files are linked to infant death files, and births to same mother over the study period are linked using a unique sibling identifying variable making it possible to obtain information on subsequent deliveries to each mother.27 Eligible cases for this study included mothers with singleton first pregnancies, having second singleton pregnancies, who were 20-50 years at first pregnancy, with both pregnancies occurring in the state of Missouri; 242,559 mother-infant pairs met the study inclusion criteria.

Independent variables examined included maternal age at first pregnancy categorized as 20-29 years (reference group), 30-34 and 35-50. We defined delayed initiation of childbearing as occurring to mothers aged 30 and older at delivery of the first
pregnancy. Interpregnancy interval between the first and second pregnancy was the measure for pregnancy spacing used. Interval was estimated as the difference between date of delivery of the second pregnancy and that of the first pregnancy minus the gestational age of the second pregnancy. Initial IPI was computed in weeks then converted to months, with the assumption that 13 weeks is equivalent to 3 months. The intervals were grouped in seven categories namely; 0-5, 6-11, 12-17, 18-23, 24-59, 60-119, ≥120 months as proposed by Zhu et al. An IPI of <6 months was considered as short. Feto-infant mortality & morbidity indices examined included fetal death, small-for-gestational age, low birth weight, and preterm delivery. We defined fetal death according to the Missouri state vital statistics definition as the birth of a fetus ≥20 weeks gestation or at least 500gms, with no signs of viable life. Low birth weight was defined as birth weight less than 2,500gms. The following subgroups were also examined; moderately low birth weight (MLBW), 1500-2499gms; very low birth weight (VLBW), 1000-1499gms; and extremely low birth weight (ELBW), 500-999gms. Preterm delivery was defined as delivery at less than 37 completed weeks of gestation. Gestational age was estimated as the interval in completed weeks from last normal menstrual period to the child’s date of birth. The preterm subgroups included moderately preterm (MPTD), 32-36 weeks; very preterm (VPTD), 28-31 weeks; and extremely preterm (EPTD), 24-27 weeks. Small-for-gestational age was defined as birth weight below the 10th percentile of the birth weight distribution of infants at the same gestational age based on US national growth curves.

Confounding variables considered included educational status, marital status, maternal pregnancy body mass index (BMI) at first pregnancy, smoking history, maternal
race, prenatal care use, poor medical history (chronic hypertension, diabetes), poor obstetric history (past adverse outcome in first pregnancy, and pregnancy induced hypertension). Educational status was estimated based on years completed in school and age of mother at first birth. Three education status levels were created: high if the mother has completed more years in school than the expected for her age; average if mother completed appropriate school level for age, and low if mother completed less than the expected number of years for age. The BMI was calculated as the weight (kgs) / height (meters)$^2$ and was categorized into 4 groups based on the CDC classification ($<18.5, 18.5-24.9, 25.0-29.9, \geq 30$). Prenatal care (PNC) use was assessed using the Revised Graduated Index (R-GINDEX). The PNC categories of this index include intensive, intermediate and inadequate.

Data were analyzed using univariate, bivariate and multivariable techniques. For bivariate analysis, cross tabulations were conducted, the chi-square statistic was used to test for differences in proportion. We tested for trend using the chi-square statistic for trend. Multivariable analyses included stratified analysis and unconditional logistic regression. For the stratified analysis, Mantel-Haenszel statistic was used to test for significant differences in proportions. Several logistic models were tested. First, crude models were fitted without adjusting for confounders. The second set of models examined maternal age and short interpregnancy interval simultaneously, while the third set of models included interaction terms. The final models included significant interactions as well as other confounders (maternal demographic characteristics, medical and obstetric risk factors). Two-tailed statistical tests were conducted with $\alpha < 0.05$. All analyses were performed using SAS version 9.1 (Cary NC). Approval for this study was
obtained from the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB), and from the Missouri Department of Health and Senior Services (MDHSS).

RESULTS

There were 212,109 first time births to mothers aged 20-29, 26,593 to mothers aged 30-34 and 3,857 to mothers aged 35-50. For second births, approximately 65% (n=158,469) were to mothers ages 20-29, 27% (n= 66,478) to mothers 30-34, and 7% (n=17,612) to mothers 35 or older.

Of all second time births, 4% were LBW, and 7% were PTD and SGA, the fetal death rate was 4/1,000 live births plus fetal deaths. Controlling for maternal age at first birth, significant differences in adverse second pregnancy outcomes were observed for mothers ≥ 35 years at first pregnancy compared to mothers 20-29 years, but less so for mothers 30-34 at first pregnancy. Mothers 30-34 and 35-50 at first pregnancy had significantly lower rates of SGA in the second pregnancy (p <0.0001). A significant trend for increasing adverse outcomes with increasing maternal age was observed for VLBW (p= 0.0095), PTD (p = 0.0126), MPTD (p = 0.0458), and EPTD (p = 0.0008). For SGA, there was a significant trend for lower rates of SGA as maternal age at first pregnancy increased (p <0.0001) [Table 1].

In general, interpregnancy intervals <6 months, and 60-119 months were significantly associated with high rates of adverse outcomes (FD, LBW, MLBW, VLBW, ELBW, PTD, MPTD, VPTD, EPTD & SGA) in the second pregnancy, while an IPI of 18-23 months was associated with the lowest rate of adverse outcomes (p <0.0001)
Figure 1]. Controlling for maternal age at first pregnancy, interpregnancy interval was still significantly associated with feto-infant mortality and morbidity outcomes. Mothers with IPI <6 months, and IPI 60-119 months had significantly higher rates of adverse outcomes in the second pregnancy across all age groups (p <0.0001). Distribution followed a J-shape for mothers 20-29 and 30-34 at first pregnancy, with lowest rate of adverse outcomes noted at 18-23 months. However, for mothers 35-50, the J-shape pattern was no longer evident and lowest rate of adverse outcome was noted at interval of 12-17 months (Figure 2).

In the unadjusted logistic models, mothers 30-34 years at first pregnancy had no significantly increased risk for adverse outcomes compared to mothers ages 20-29 year except for EPTD (OR=1.45, 95% CI, 1.11, 1.90). However, mothers 35 years or older at first pregnancy had significantly increased risk for most adverse outcomes examined with the exception of FD, ELBW, and very preterm. For both age groups, there was significantly reduced risk for SGA (Table 2). Interpregnancy interval <6 months was significantly associated with increased risk for adverse second pregnancy outcomes (Table 2).

When maternal age and short IPI were analyzed simultaneously in the logistic model, there was minimal change in the odds ratios (OR) and the crude OR (results not shown). When interaction terms for maternal age and short IPI were included in the models, the risk for adverse outcomes persisted for mothers 35 and older, and for short IPI. However, most of the interactions tested were non-significant, with the exception of ELBW where the interaction for maternal age 30-34 and short interval was significant (OR= 2.03, 95% CI, 1.03, 4.00).
Controlling for other potential confounders in the logistic models had significant impact on the ORs for selected perinatal outcomes. Mothers 30-34 at first pregnancy now had significantly increased risk for FD (OR= 1.37, 95% CI, 1.12, 1.68), LBW (OR= 1.13, 95% CI, 1.05, 1.22), PTD (OR= 1.07, 95% CI, 1.01, 1.13) and EPTD (OR= 1.58, 95% CI, 1.19, 2.12). Mothers 35-50 now had significantly increased risk for FD (OR= 1.78, 95% CI, 1.16, 2.74), and VPTD (OR= 1.70, 95% CI, 1.01, 2.87) [Table 2]. For short IPI, the previously observed risks persisted with the exception of FD and EPTD, which were no longer significant. The interaction term for ELBW was no longer statistically significant; OR= 1.55, 95% CI= 0.72-3.32 (Tables 2).

**DISCUSSION**

Findings from this study indicate delaying initiation of childbearing until age 30 or older is associated with increased rate of adverse perinatal outcomes in the second pregnancy particularly for mothers age 35 or older. Similar to previous general population studies IPI is associated with adverse outcomes even for mothers delaying initiation of childbearing. It is worth noting that previous general population studies indicate that IPI of 18-23 months is associated with lowest rate of adverse outcome. This distribution pattern was evident in this study for mothers 20-29 and 30-34 at initiation of childbearing. However, for mothers 35-50 years, IPI of 12-17 months is associated with lowest rate of adverse outcome in the second pregnancy. The explanation for this difference is unclear and warrants further investigation.

Both delayed initiation of childbearing until age 30 or older, and short IPI less than 6 months are independent risk factors for adverse perinatal outcomes in the second
pregnancy. Mothers 35 or older at start of childbearing have the highest risk compared to mothers ages 20-29 even after controlling for potential confounders. These findings are in contrast to a previous study that found no increased risk for adverse outcomes in a subsequent pregnancy for women delaying childbearing.\textsuperscript{24} The difference in findings could be attributed to population heterogeneity. The study by Cnattingius et al., looked at a Swedish population, which is homogenous, whereas this study looked at a US population that is typically more diverse. Furthermore, their study did not consider the effects of pregnancy interval as a confounder.

Mothers delaying initiation of childbearing and having a second pregnancy following a short IPI <6 months are not at significantly higher risk for adverse perinatal outcomes compared to mothers 20-29 years having a second pregnancy following short IPI as evidenced by non significant interactions. This finding suggests that delaying childbearing and having subsequent pregnancy within <6 months confers no added risk beyond that seen individually for advanced maternal age and short IPI. This finding could be as a result of interaction with other risk factors not examined in this study, or due to the small number of mothers 35 or older at first pregnancy (n= 3857), and relatively rare events examined, which may influence the parameter estimates.

It suffices to say that women initiating childbearing at age 30-34 are not necessarily different from mothers 20-29 at start of childbearing. Significant differences become apparent from age 35 or older and perhaps these are the mothers who need to be considered high risk with respect to maternal age at initiation of childbearing. Given current statistics indicating rapidly increasing birth rates among women 35 and older,
group,\textsuperscript{23} health care providers should become more aware of their potential pregnancy risks and advise these patients appropriately.

Our findings also have implications for preconception care; with growing focus on preconception care, there is need to integrate these findings as part of preconception counseling, to enable women make informed decisions about their reproductive choices as when to start childbearing and timing of subsequent pregnancies.

The study draws strength from its longitudinal design that enabled us examine reproductive outcomes in the same mother over time thus eliminating cohort differences. We obtained information concerning the mothers’ first pregnancy and used these data to control for potential confounders. That said, our study is subject to several limitations. Since we used a secondary database, there are potential risks for missing information and misclassification of variables leading to loss of data.\textsuperscript{33,34} Because of the small number of cases initiating childbearing at the extremes of maternal age, it necessitated us combining maternal age groups (35-50) who may have unique differences to them, which may mask some associations. The dataset spans a long period, during which time there have been changes in medical practices for example use of fertility treatment, or changes in behavioral factors, which may influence our outcomes of interest. Unfortunately, we were unable to control for such changes but that is certainly something worth exploring in future research. Finally, as the dataset used was from one state, the findings may not be generalizable to all populations; however, these findings are likely characteristic of US gravidas.

In conclusion, as providers and public health professionals strive to meet the Healthy People 2010 objectives associated with improved birth outcomes, issues related
to pregnancy spacing need to be addressed as an independent risk factor. Health care providers should encourage women to space pregnancies adequately through use of effective family planning methods to minimize some of the potential effects of closely spaced pregnancies.
REFERENCES


27. Herman AA, Mccarthy BJ, Bakewell JM, Et Al. Data linkage methods used in maternally-linked birth and infant death surveillance datasets from the United States (Georgia, Missouri, Utah And Washington State), Israel, Norway, Scotland And Western Australia. Paediatr Perinat Epidemiol. 1997;11 (Suppl 1):5-22.


Table 1. Distribution of Adverse Perinatal Outcomes in Second Pregnancy by Maternal Age at First Pregnancy: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>Adverse Perinatal Outcome 2nd Pregnancy</th>
<th>Maternal Age at First Pregnancy (%)</th>
<th>Trend p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-29 (n=212,109)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-34 (n=26,593)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35-50 (n=3,857)</td>
<td></td>
</tr>
<tr>
<td>Fetal death</td>
<td>3.9</td>
<td>0.0732</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>4.0</td>
<td>0.6166</td>
</tr>
<tr>
<td>Moderately low birth weight</td>
<td>3.2</td>
<td>0.2737</td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>0.3</td>
<td>0.0095‡</td>
</tr>
<tr>
<td>Extremely low birth weight</td>
<td>0.3</td>
<td>0.4742</td>
</tr>
<tr>
<td>Preterm</td>
<td>7.3</td>
<td>0.0126‡</td>
</tr>
<tr>
<td>Moderately preterm</td>
<td>6.8</td>
<td>0.0458‡</td>
</tr>
<tr>
<td>Very preterm</td>
<td>0.3</td>
<td>0.7263</td>
</tr>
<tr>
<td>Extremely preterm</td>
<td>0.2</td>
<td>0.0008‡</td>
</tr>
<tr>
<td>Small-for-gestational age</td>
<td>7.0</td>
<td>&lt;0.0001‡</td>
</tr>
</tbody>
</table>

* Fetal death rate/1,000 live births plus fetal deaths
‡ Statistically significant Chi Square trend test
Figure 1. Proportion of Adverse Second Pregnancy Outcomes by Interpregnancy Interval: Missouri Resident Mothers 1978-1997
Figure 1. Legend

LBW = low birth weight
MLBW = moderately low birth weight
VLBW = very low birth weight
ELBW = extremely low birth weight
PTD = preterm delivery
MPTD = moderately preterm delivery
VPTD = very preterm delivery
EPTD = extremely preterm delivery
SGA = small-for-gestational age

Figure 2. Legend

LBW = low birth weight
ELBW = extremely low birth weight
EPTD = extremely preterm delivery
SGA = small-for-gestational age
Figure 2. Distribution of Adverse Second Pregnancy Outcomes by Interpregnancy Interval and Maternal Age at First Pregnancy: Missouri Resident Mothers 1978-1997
<table>
<thead>
<tr>
<th>Perinatal Outcome 2&lt;sup&gt;nd&lt;/sup&gt; Pregnancy</th>
<th>Unadjusted Odds Ratio* (95% CI)</th>
<th>Adjusted Odds Ratio† (95% CI)</th>
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</thead>
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<td>Maternal age at First Pregnancy ‡</td>
<td>Short IPI§</td>
</tr>
<tr>
<td></td>
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<td>35-50</td>
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<tr>
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<td>1.45</td>
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<td></td>
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<td>(0.94-2.22)</td>
</tr>
<tr>
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<td>0.84</td>
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<tr>
<td></td>
<td>(0.76-0.84)</td>
<td>(0.73-0.96)</td>
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<tr>
<td>Low birth weight</td>
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<td>1.38</td>
</tr>
<tr>
<td></td>
<td>(0.87-1.00)</td>
<td>(1.20-1.59)</td>
</tr>
<tr>
<td>Moderately low birth weight</td>
<td>0.89</td>
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</tr>
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<td>(1.10-1.51)</td>
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<td>Very low birth weight</td>
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<td>1.89</td>
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<tr>
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<td>(0.93-1.43)</td>
<td>(1.25-2.87)</td>
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<td>(1.28-1.59)</td>
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<td>(1.24-1.56)</td>
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<td>(0.98-2.57)</td>
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<td>Extremely preterm</td>
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<td>1.91</td>
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<tr>
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<td>(1.11-1.90)</td>
<td>(1.07-3.39)</td>
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</tbody>
</table>
CI = Confidence interval
‡ 20-29 reference group
§ IPI = Interpregnancy interval (Reference category ≥ 6 months)
* Logistic models tested for maternal age and IPI individually
¶ Logistic model includes significant interaction term
† Logistic models adjust for significant interaction terms, as well as confounders; race, educational status, marital status, BMI, smoking, PNC, chronic hypertension, diabetes, pre-eclampsia, adverse outcome in first pregnancy and year of first pregnancy.
RACIAL DISPARITIES IN PERINATAL OUTCOMES AND PREGNANCY SPACING AMONG WOMEN DELAYING INITIATION OF CHILDBEARING

by

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ABSTRACT

Introduction

Reducing racial/ethnic disparities is a key objective of the *Healthy People 2010* initiative. Unfortunately, racial disparities among women delaying initiation of childbearing have received limited attention. As more women in the US are delaying initiation of childbearing, it is important to examine racial disparities in reproductive health outcomes for this subgroup of women.

Objective

To examine racial disparities in perinatal outcomes, interpregnancy interval, and to assess the risk for adverse outcomes in subsequent pregnancy for women delaying initiation of childbearing until age 30 or older compared to those initiating childbearing at age 20-29.

Methods

We conducted a retrospective cohort study using the Missouri maternally linked cohort files 1978-1997. Study sample included 239,930 singleton sibling pairs for Whites and African Americans. Outcome variables included first and second pregnancy perinatal outcomes (fetal death, low birth weight, preterm delivery and small-for-gestational age) and interpregnancy interval between first and second pregnancy. Independent variables included maternal age at first pregnancy and race. Analysis strategies used involved stratified analyses and multivariable unconditional logistic regression; interactions
between maternal race, age and interpregnancy interval were examined in the regression models.

Results

Compared to Whites, African American mothers initiating childbearing at age 30 or older had significantly higher rates of adverse outcomes in the first and second pregnancy (p <0.0001). Generally, African Americans had significantly higher rates of second pregnancy following intervals <6 months compared to Whites; however, no significant racial differences were noted in interpregnancy interval distribution pattern after controlling for maternal age at first pregnancy. African Americans delaying initiation of childbearing had significantly higher risk for adverse perinatal outcomes in the second pregnancy compared to whites after controlling for potential confounders, however there were no significant interactions between maternal age at first pregnancy, race and short interpregnancy interval.

Conclusion

Although African Americans were less likely to delay initiation of childbearing than were white women, their risk for adverse perinatal outcomes was much greater. As health care providers strive to address racial disparities in birth outcomes, there is need to pay attention to this unique group of women as their population continues to increase.
INTRODUCTION

Addressing racial disparities is an important key objective of the Healthy People (HP) 2010 initiative (1). Research has shown racial disparities in reproductive health risk factors as well as perinatal outcomes in the general population (2-4). However, limited research has examined racial disparities for women delaying initiation of childbearing until age 30 or older.

Previous studies indicate that women delaying initiation of childbearing until age 30 or older are at increased risk for adverse perinatal outcomes, including preterm delivery (PTD), low birth weight (LBW) and fetal death (FD) (5-8). Additionally these women have increased risk for short interpregnancy intervals of <6 months (9-11). The few studies that have examined racial disparities in this group of women have mixed findings. Whereas one study did not find any racial differences in outcomes (12), others found that nonwhite older mothers had higher rates of poor outcomes compared to whites (3, 4, 13-15). Most of these studies failed to account for maternal age at the start of childbearing.

Few studies have examined racial differences in pregnancy spacing for women delaying initiation of childbearing and its association to subsequent pregnancy outcome. General population studies show that AA mothers are more likely to have short IPI compared to Whites (16, 17). A previous reported suggested that older AA have longer pregnancy intervals compared to whites (18).

The lowest rate of adverse outcomes is seen at IPI of 18-23 months for both Whites and AA, while highest rate is observed at <6 months (19). In their study Rawlings and colleagues found that AA with IPI <9 months had higher prevalence for PTD while
for whites highest rate was seen at IPI <3 months (16). Other studies found that IPI did not appear to increase the risk for SGA (17), or PTD (20), for Whites and AA. Unfortunately, none of these studies took into account maternal age at first pregnancy, a potential confounding factor.

We sought to address some of these issues by examining racial differences in this unique population of women. Our specific objectives were:

i. To examine racial differences in first pregnancy perinatal outcomes (FD, LBW, and SGA) among women initiating childbearing at age 30 or older, in comparison to women initiating childbearing age 20-29.

ii. To determine racial differences in perinatal outcomes in second pregnancy among women initiating childbearing age 30 or older, in comparison to those starting childbearing age 20-29.

iii. To examine racial differences in interpregnancy interval (IPI) patterns for women delaying initiation of childbearing until age 30 or older, in comparison to women initiating childbearing age 20-29.

iv. To determine racial differences in risk for feto-infant mortality and morbidity outcomes in second pregnancy, among women initiating childbearing at age 30 or older, and having short interpregnancy intervals (<6 months), compared to those initiating childbearing in their 20s, after controlling for potential confounders.

We hypothesize that there are racial differences in interpregnancy interval patterns and perinatal outcomes among women initiating childbearing age 20-29, compared to those initiating childbearing age 30 or older. Additionally, there are racial differences in risk for adverse feto-infant mortality and morbidity outcomes between women initiating
childbearing in their 20-29, with short IPI, and those initiating childbearing age 30 or older with short IPI, after controlling for potential confounders.

MATERIALS AND METHODS

We conducted a retrospective cohort study using the Missouri maternally-linked live birth/fetal death and infant death files. The database contains information on all live births, fetal and infant deaths occurring to state residents from 1978 to 1997 inclusive. The data were collected prospectively, and births to same mother are linked together using a unique sibling identifier (21). Cases that met the following criteria were included in the study sample; maternal age 20-50 years at first pregnancy and having 2 consecutive singleton pregnancies during the study period both occurring in Missouri. A total of 242,559 sibling pairs met these inclusion criteria.

Variables

Main independent variables included maternal age at first pregnancy, maternal race and interpregnancy interval. Dependent variables included FD, LBW and subgroups, PTD and subgroups as well as SGA. Confounders examined included socio-demographic factors such as year of delivery, educational status, and marital status. Other confounders were prenatal care use (PNC), smoking, body mass index (BMI), hypertension (primary and pregnancy induced), diabetes and previous adverse pregnancy outcome in first pregnancy.

Maternal age was measured as the completed age at first pregnancy, and was categorized as 20-29 (reference group), 30-34, and 35-50. For this study, mothers age 30
or older at first pregnancy were considered to have delayed initiation of childbearing.

Race was limited to White and AA mothers, as other race groups were too small for meaningful analysis. Interpregnancy interval was the measure for pregnancy spacing used in this study, and was calculated as the difference between date of second pregnancy outcome and date of first pregnancy outcome minus the gestational age of the second pregnancy. Initial computations were in weeks, and then converted to months. The assumption was that 13 weeks equals 3 months (22). Interval groups were created based on the recommendation by Zhu et al., and included: 0-5, 6-11, 12-17, 18-23, 24-59, 60-119, ≥120 months (22). Fetal death was defined as birth of fetus ≥ 20 weeks gestation or 500gms, expressed as a rate per 1,000 live births plus fetal deaths. Low birth weight was defined as birth weight less than 2,500gms. The subgroups examined included: moderately low birth weight (MLBW), 1500-2499gms, very low birth weight (VLBW), 1000-1499gms and extremely low birth weight (ELBW), 500-999gms. Preterm delivery was defined as delivery at than 37 completed weeks of gestation. The subgroups examined included moderately preterm delivery (MPTD), 32-36 weeks, very preterm delivery (VPTD), 28-31 weeks and extremely preterm delivery (EPTD), 24-27 weeks. Small-for-gestational age was defined as birth weight at or below the 10th percentile of the birth weight distribution of infants at the same gestational age based on US national growth curves (23).

Educational status was estimated from years of education completed by the first pregnancy, and maternal age. Education status was classified as high if the mother had completed higher than expected number of years for age, average if completed appropriate school years for age and low if mother has completed few years based on her
age (24). Prenatal care use was assessed based on the revised graduated index (R-GINDEX) measure, which takes into account timing of start of prenatal care, number of visits and gestational age at delivery. Using this measure, 5 categories were considered: no care, missing care, inadequate care, intermediate, adequate care and intensive care (25).

Analysis

The final sample used for analysis had 239,930 maternal-infant pairs (White & African Americans). Descriptive analyses were conducted to obtain distribution of key variables for the study population. Subsequent analyses involved multivariable analysis approaches (stratified analysis and unconditional logistic regression). For bivariate analysis, chi-square statistic was used to test for significant differences in proportions, while the Mantel-Haenszel chi square statistic was used for the stratified analyses. Several logistic regressions models were constructed; initial model looked at maternal race, maternal age at first pregnancy, and IPI. Additional models included interactions between maternal age, maternal race, and IPI as well as potential confounders. All hypothesis tests were two tailed with alpha (α) set at <0.05 All analyses were performed using Statistical Analysis Software (SAS) version 9.1. Cary NC

Approval for the study was obtained from the University of Alabama at Birmingham Institutional Review Board and from the Missouri Department of Health and Senior Services
RESULTS

Over the study period, there were 221,383 first time births to White mothers, and 18,548 to AA aged 20-50 years. Significant racial differences were observed in all key socio-demographic factors and health risk factors with AA having significantly higher rates compared to Whites. The racial differences persisted even after controlling for maternal age at first pregnancy (Table 1).

In general, racial differences were observed for adverse first pregnancy outcomes, with AA having significantly higher rates of FD (8.4/1,000 vs. 4.6/1,000); LBW (11.3% vs. 5.0%); PTD (13.4% vs. 7.1%), and SGA (18.6% vs. 9.1%); [p <0.0001]. The rate of adverse outcomes increased with maternal age at first pregnancy for both Whites and AA. However, the increase was more pronounced for AA particularly for LBW and PTD as displayed in Figure 1.

The rate of adverse perinatal outcomes in the second pregnancy was also significantly higher for AA compared to Whites for the whole study population (p <0.0001). Controlling for maternal age at first pregnancy, the racial differences persisted with AA having significantly higher rates of adverse outcomes compared to Whites. However, among mothers 35 or older at first pregnancy we found no significant racial differences for FD (p = 0.2611), VLBW (p = 0.2980), ELBW (p = 0.0960) and VPTD (p = 0.3680) [Table 2].

For IPI, the mean interval in general was significantly longer for AA mothers compared to that of Whites mothers (35.3±30.2 vs. 29.5±22.9); p <0.0001. The mean IPI decreased with increasing age at first pregnancy (p <0.0001). Comparing across race groups, among 30-34 year olds, AA had significantly longer mean IPI compared to...
Whites (28.2±22.1 vs. 25.2±17.1) [p <0.0001]. However, for mothers 35-50 at first pregnancy, no significant difference in mean IPI among Whites and AA was observed (20.9±13.8 vs. 20.3±12.9; p = 0.5899).

Significant racial differences were seen across IPI strata, with AA generally having higher rates of IPI <6 months compared to White mothers (p <0.0001). However when controlling for maternal age at first pregnancy, there were no significant racial differences in IPI distribution (Mantel-Haenszel p = 0.9048). Within maternal age specific categories, significant racial differences in IPI distribution were seen for mothers 20-29 and 30-34 years at first pregnancy (Table 3).

Examining the association between IPI and subsequent perinatal outcome in second pregnancy, significant racial differences were also observed. Mothers with short IPI (<6 months) and long interval (60-119 months) had higher rates of LBW, PTD and SGA, particularly for AA. For AA, lowest rates of LBW & SGA were observed at IPI 12-17 months (Figure 2). Within race specific categories, short intervals were significantly associated with all adverse perinatal outcomes examined for Whites, however for AA, no significant differences in rate of adverse outcomes was observed for VLBW (p = 0.2511), ELBW (p = 0.3039), VPTD (p = 0.3977) and EPTD (p = 0.1319).

The first logistic model examined risk for adverse 2nd pregnancy outcome controlling for maternal age at first pregnancy, race and IPI. African Americans had significantly increased risk for all outcomes tested. Similarly IPI <6 months was significantly associated with an increased risk for adverse outcomes with the exception of FD (Table 4).
Subsequent logistic models examined maternal race, age at first pregnancy and short IPI (<6 months) as well as interactions and potential confounders. These models revealed that AA mothers remained at increased risk for adverse outcomes in the second pregnancy. Generally most of the interactions tested were not significant, with the exception of the interaction between maternal age 30-34, short IPI, and race when modeling for SGA (OR 1.75, 95% CI= 1.07-2.82). This interaction remained significant even after controlling for other potential confounders (OR 1.91, 95% CI= 1.08-3.37) [Table 5].

DISCUSSION

Similar to previous general population research (3, 4, 15, 26), we found evidence of racial disparities in perinatal outcomes both in the first and second pregnancy for mothers delaying initiation of childbearing. Although the proportion of AA mothers delaying initiation of childbearing until age 30 or older was much lower than for Whites, these mothers had far higher prevalence for adverse outcomes, and the disparities increased with increasing maternal age. The reasons to explain these findings are still largely unknown even in the general population. Previous studies have suggested various theories to explain the racial disparities including among others socio-economic (SES) factors, health behavior factors (27, 28), genital infections during pregnancy (29), and maternal stress (30), as well as differences in developmental trajectories over time (31).

While these factors may explain observed racial disparities in general when looking at women delaying childbearing some of these factors may play a minimal role. For example women delaying initiation of childbearing generally have high education,
and fewer health behavior risk factors compared to their younger counterparts (8). Thus, SES and health behavior risk factors may not explain the racial differences observed in women delaying childbearing. Likewise, although genital infections contribute significantly to adverse perinatal outcomes, and may explain racial disparities, there is no evidence to suggest that nonwhite women delaying initiation of childbearing have higher rates of infection compared to Whites to account for the observed disparities.

On the other hand, maternal stress may explain some of the observed racial disparities. Research has associated maternal stress with adverse perinatal outcomes. It has been argued that nonwhite women experience greater stress over their life time which in turn increases their risk for adverse perinatal outcomes with advancing maternal age. This process has been termed the ‘weathering’ hypothesis (32-34). Additionally, mothers delaying initiation of childbearing may have increased risk for stress and anxiety (35). The cumulative effect of maternal stress coupled with differences in the environment (31), may play an important role in the racial disparities among women delaying childbearing. While the merits of this theory are beyond the scope of this study, further research should examine the impact of maternal stress on racial disparities in women delaying initiation of childbearing.

Interestingly, we found that AA delaying initiation of childbearing had significantly longer mean IPI compared to whites. This finding so offer some support to previous report that older AA mothers may have longer pregnancy intervals (18). Nevertheless, we found no significant racial differences in interpregnancy interval patterns among women delaying initiation of childbearing.
In general IPI was associated with racial disparities in perinatal outcomes particularly at intervals <6 months. This finding supports previous population studies that found short IPI to be associated with racial differences in pregnancy outcomes (16, 19). Interesting, for AA the relationship between IPI and adverse perinatal outcomes did not demonstrate the J-shaped pattern that had been previously reported in general population studies (22). However, for white mothers a J-shape was evident; the explanation for this finding is unknown.

The effect of IPI on subsequent perinatal outcomes among women of different race groups delaying initiation of childbearing is unclear. No significant interactions were seen between maternal age at start of childbearing, race and IPI, suggesting that AA mothers delaying initiation of childbearing with short IPI do not appear to have elevated risk for adverse outcomes compared to Whites. We were unable to examine patterns of delayed childbearing and IPI among other race/ethnic groups. This is a limitation of this study as it has been reported that some nonwhite population particularly Asians tend to delay initiation of childbearing (36). Future research using a larger and more diverse sample may reveal disparities between White women and women of other race/ethnic groups.

This study draws strength from the fact that it is among the few studies exploring racial differences in pregnancy outcomes among women delaying initiation childbearing and their pregnancy spacing patterns using a large longitudinal database. The study used a cohort design, thus enabling us to examine perinatal outcomes in the same women over time eliminating the cohort effect. Nevertheless, there were some limitations; the study used a secondary database making it prone to missing or incorrect data, resulting in loss
of information, which may reduce the effective sample size (37,38). Furthermore, the sample of mothers initiating childbearing at age 35 or older was relatively small especially for AA as the population of the state of Missouri is predominately White. Analysis for this age category is prone to imprecise estimates and may explain the non-significant associations as noted for pregnancy spacing patterns. Finally, there are issues related to generalizability as the data used are from only one state. Having said that, the findings do provide an insight to what may be happening among the general US population.

In summary, while the number of AA women delaying initiation of childbearing is small, they are at increased risk for adverse perinatal outcomes in the first and subsequent pregnancy. With the HP-2010 objective of addressing racial disparities in birth outcomes, it is important for providers to pay attention to this unique population of women. Further research aimed at understanding risk factors associated with racial disparities may identify potential areas for intervention as health care providers strive to address racial disparities in reproductive health.
REFERENCES


Table 1. Maternal Characteristics by Maternal Race and Age at First Pregnancy: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th>20-29</th>
<th>30-34</th>
<th>35-50</th>
<th>Mantel Haenszel p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White % (n=192,885)</td>
<td>AA % (n=17,198)</td>
<td>White % (n=24,905)</td>
<td>AA % (n=1,181)</td>
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<td>Marital status</td>
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<td></td>
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<td></td>
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<td>Education status</td>
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<td>48.9</td>
<td>44.8</td>
<td>78.1</td>
<td>71.9</td>
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<td>45.8</td>
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<td>12.1</td>
<td>9.6</td>
<td>6.4</td>
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<td>69.6</td>
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<td>Prenatal care use</td>
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<tr>
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<tr>
<td>Inadequate</td>
<td>4.0</td>
<td>10.2</td>
<td>1.4</td>
<td>4.0</td>
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Figure 1. Proportion of Adverse First Pregnancy Outcomes by Maternal Race and Age at First Pregnancy: Missouri Resident Mothers 1978-1997
Table 2. Rate Ratios for Adverse Second Pregnancy Outcomes by Maternal Race and Age at First Pregnancy: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>Second Pregnancy Perinatal Outcome</th>
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<th>35-50</th>
<th>Mantel Haenszel p-value</th>
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</thead>
<tbody>
<tr>
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<td>AA/White Rate Ratio</td>
<td>p-value</td>
<td>AA/White Rate Ratio</td>
<td>p-value</td>
</tr>
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<td>Fetal death*</td>
<td>2.5</td>
<td>&lt;.0001</td>
<td>2.9</td>
<td>&lt;.0001</td>
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<tr>
<td>Small-for-gestational age</td>
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<td>2.2</td>
<td>&lt;.0001</td>
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<td>Low birth weight (&lt;2500 gms)</td>
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<td>2.6</td>
<td>&lt;.0001</td>
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<td>Extremely low birth weight (500-999 gms)</td>
<td>5.0</td>
<td>&lt;.0001</td>
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<td>&lt;.0001</td>
</tr>
<tr>
<td>Very low birth weight (1000-1499 gms)</td>
<td>2.3</td>
<td>&lt;.0001</td>
<td>4.3</td>
<td>&lt;.0001</td>
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<tr>
<td>Moderately low birth weight (1500-2499 gms)</td>
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<td>&lt;.0001</td>
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<td>Preterm (&lt;37 weeks)</td>
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<td>&lt;.0001</td>
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<td>Extremely preterm (24-27 weeks)</td>
<td>6.0</td>
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<td>Moderately preterm (32-36 weeks)</td>
<td>2.2</td>
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* Fetal death rate/1000 live births plus fetal deaths
Table 3. Distribution of Interpregnancy Interval by Maternal Race and Age at First Pregnancy: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>Interpregnancy Interval (Months)</th>
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<th>30-34*</th>
<th>35-50†</th>
<th>Mantel Haenszel p-value</th>
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<td></td>
<td>White %</td>
<td>AA %</td>
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<td>White %</td>
</tr>
<tr>
<td>0-5</td>
<td>5.5</td>
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</tr>
<tr>
<td>18-23</td>
<td>12.7</td>
<td>8.8</td>
<td>0.69</td>
<td>14.3</td>
</tr>
<tr>
<td>24-59</td>
<td>40.6</td>
<td>36.6</td>
<td>0.90</td>
<td>38.4</td>
</tr>
<tr>
<td>60-119</td>
<td>8.8</td>
<td>15.4</td>
<td>1.75</td>
<td>4.4</td>
</tr>
<tr>
<td>≥ 120</td>
<td>8.1</td>
<td>8.1</td>
<td>1.00</td>
<td>8.5</td>
</tr>
</tbody>
</table>

AA = African American
* p <0.0001
† p = 0.1288
Figure 2. Distribution of Adverse Second Pregnancy Outcomes by Maternal Race and Interpregnancy Interval: Missouri Resident Mothers 1978-1997

LBW = low birthweight, PTD = preterm; SGA = small-for-gestational age; AA = African American
Table 4. Odds Ratios for Adverse Second Pregnancy Outcome Controlling for Maternal Race, Age at First Pregnancy and Interpregnancy Interval: Missouri Resident Mothers 1978-1997

<table>
<thead>
<tr>
<th>Perinatal Outcome</th>
<th>Race*</th>
<th>Maternal Age 1st Pregnancy†</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Interpregnancy Interval (Months) §</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>30-34</td>
<td>0-5</td>
<td>6-11</td>
<td>12-17</td>
</tr>
<tr>
<td>FD</td>
<td>2.40</td>
<td>1.20</td>
<td>1.14</td>
<td>0.81</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>(2.02-2.85)</td>
<td>(0.98-1.45)</td>
<td>(0.98-2.34)</td>
<td>(0.86-1.51)</td>
<td>(0.62-1.04)</td>
</tr>
<tr>
<td>SGA</td>
<td>2.37</td>
<td>0.84</td>
<td>1.73</td>
<td>1.39</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>(2.27-2.49)</td>
<td>(0.80-0.89)</td>
<td>(0.77-1.03)</td>
<td>(1.60-1.87)</td>
<td>(1.30-1.49)</td>
</tr>
<tr>
<td>LBW</td>
<td>3.05</td>
<td>1.03</td>
<td>1.52</td>
<td>1.04</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>(2.89-3.21)</td>
<td>(0.96-1.10)</td>
<td>(1.32-1.76)</td>
<td>(1.39-1.67)</td>
<td>(0.96-1.13)</td>
</tr>
<tr>
<td>MLBW</td>
<td>2.99</td>
<td>0.97</td>
<td>1.50</td>
<td>1.09</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>(2.73-3.08)</td>
<td>(0.90-1.05)</td>
<td>(1.20-1.67)</td>
<td>(1.36-1.67)</td>
<td>(0.99-1.20)</td>
</tr>
<tr>
<td>VLBW</td>
<td>2.54</td>
<td>1.26</td>
<td>1.65</td>
<td>0.93</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>(2.12-3.06)</td>
<td>(1.02-1.57)</td>
<td>(1.40-2.34)</td>
<td>(1.23-2.21)</td>
<td>(0.70-1.24)</td>
</tr>
<tr>
<td>ELBW</td>
<td>4.29</td>
<td>1.11</td>
<td>1.40</td>
<td>0.89</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>(3.61-5.10)</td>
<td>(0.87-1.41)</td>
<td>(0.92-2.57)</td>
<td>(1.04-1.89)</td>
<td>(0.67-1.19)</td>
</tr>
<tr>
<td>PTD</td>
<td>2.45</td>
<td>1.04</td>
<td>1.67</td>
<td>1.40</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>(2.34-2.56)</td>
<td>(0.99-1.10)</td>
<td>(1.37-1.66)</td>
<td>(1.55-1.80)</td>
<td>(1.31-1.49)</td>
</tr>
<tr>
<td>MPTD</td>
<td>3.99</td>
<td>1.03</td>
<td>2.41</td>
<td>1.70</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>(3.34-4.75)</td>
<td>(0.80-1.33)</td>
<td>(1.09-2.89)</td>
<td>(1.71-3.39)</td>
<td>(1.23-2.34)</td>
</tr>
<tr>
<td>VPTD</td>
<td>2.28</td>
<td>1.04</td>
<td>1.61</td>
<td>1.38</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>(2.81-2.39)</td>
<td>(0.98-1.09)</td>
<td>(1.28-1.61)</td>
<td>(1.49-1.74)</td>
<td>(1.29-1.48)</td>
</tr>
<tr>
<td>EPTD</td>
<td>4.10</td>
<td>1.59</td>
<td>2.10</td>
<td>1.42</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>(3.28-5.13)</td>
<td>(1.21-2.10)</td>
<td>(1.19-3.78)</td>
<td>(1.38-3.19)</td>
<td>(0.96-2.11)</td>
</tr>
</tbody>
</table>
CI= Confidence Interval; AA= African American
*Reference race group = White
†Reference age group = 20-29 years
§Reference IPI = 18-23 months
FD=fetal death; LBW= low birth weight, MLBW=moderately low birth weight, VLBW=Very low birth weight; ELBW=extremely low birth weight; PTD=preterm; MPTD=moderately preterm; VPTD= very preterm, EPTD=extremely preterm; SGA=small-for-gestational age

Table 5. Adjusted Odds Ratios for Adverse Second Pregnancy Perinatal Outcomes: Missouri Resident Mothers; 1978-1997

<table>
<thead>
<tr>
<th>Adverse Perinatal Outcome Second Pregnancy</th>
<th>Adjusted OR (95% CI)*</th>
<th>African American**</th>
<th>Short IPI &lt; 6 months†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal death</td>
<td>2.02 (1.63-2.51)</td>
<td>1.06 (0.81-1.38)</td>
<td></td>
</tr>
<tr>
<td>Small-for-gestational age‡</td>
<td>1.95 (1.84-2.07)</td>
<td>1.12 (1.04-1.20)</td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>2.35 (2.20-2.51)</td>
<td>1.21 (1.11-1.31)</td>
<td></td>
</tr>
<tr>
<td>Moderately low birth weight</td>
<td>2.24 (2.08-2.41)</td>
<td>1.15 (1.04-1.26)</td>
<td></td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>1.61 (1.29-2.01)</td>
<td>1.38 (1.07-1.78)</td>
<td></td>
</tr>
<tr>
<td>Extremely low birth weight</td>
<td>3.27 (2.63-4.07)</td>
<td>1.43 (1.09-1.88)</td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>1.92 (1.82-2.03)</td>
<td>1.15 (1.08-1.23)</td>
<td></td>
</tr>
<tr>
<td>Moderately preterm</td>
<td>1.81 (1.71-1.91)</td>
<td>1.12 (1.05-1.20)</td>
<td></td>
</tr>
<tr>
<td>Very preterm</td>
<td>2.75 (2.21-3.43)</td>
<td>1.52 (1.17-1.98)</td>
<td></td>
</tr>
<tr>
<td>Extremely preterm</td>
<td>3.02 (2.28-4.02)</td>
<td>1.37 (0.97-1.95)</td>
<td></td>
</tr>
</tbody>
</table>

*Model adjusted for significant interaction, and other confounders (marital status, educational status, prenatal care use, body mass index, smoking, chronic hypertension, diabetes, pregnancy induced hypertension, past adverse outcome, and year first birth).
**Reference age group = White
†Reference IPI ≥ 6 months
‡Model included significant interaction for maternal age 30-34, IPI <6 months, and race.
GENERAL SUMMARY

In this study, we found substantial differences in interpregnancy interval patterns between women initiating childbearing at age 20-29 and those initiating childbearing at age 30 or older. First time mothers age 35 or older tended to have second pregnancies at shorter intervals than mothers age 20-29. The IPI was associated with year of first pregnancy, body mass index, educational status and preceding pregnancy outcome for mothers 35 and older at first pregnancy. For this group of mothers, we found no significant racial differences in spacing patterns, contrary to previous reports among younger women. While mothers 35 and older had significantly higher odds of becoming pregnant again within less than 6 months of a preceding one, those age 30-34 at first pregnancy had relatively lower odds of short interpregnancy interval compared to mothers 20-29 years of age at initiation of childbearing. These findings support our hypothesis that mothers DCB are more likely to have short interval between pregnancies.

Mothers delaying initiation of childbearing until age 30 or older had an increased risk for adverse perinatal outcomes in the second pregnancy, particularly those 35 and older. This contrasts with a previous study that found no such increased risk. The contrasting results may be due to variations in study populations and differences in methodology used. Nevertheless, it is evident that the risk for adverse outcomes experienced by older mothers in the first pregnancy persists in the second pregnancy.

A relatively lower number of AA mothers delayed initiation of childbearing until age 30 or older. These women had significantly higher rates of adverse perinatal
outcomes for both the first and second pregnancies. Rates of adverse perinatal outcomes increased with increasing maternal age. This finding provides some support for the weathering hypothesis that older AA mothers have far worse outcomes compared to their younger counterparts.\textsuperscript{31,98}

Short interpregnancy interval of less than 6 months, maternal age 35 or older at first pregnancy, and nonwhite race all were found to be independent risk factors for adverse perinatal outcome in the second pregnancy after controlling for confounders. However, we found no significant interactions neither between maternal age at initiation of childbearing and short IPI, nor with maternal race. By implication, mothers with both of these risk factors do not have an exaggerated risk for adverse perinatal outcomes beyond that anticipated from these factors individually. Nonetheless, perinatal care providers should pay attention to these risk factors, particularly short IPI, as it is a potentially modifiable risk factor through use of appropriate family planning methods. Additionally, as providers continue to find ways to address racial disparities in reproductive health outcomes, it is essential that they are aware of the contribution of older first time AA mothers to racial disparities in perinatal outcomes.

This study draws strength from its longitudinal design, which enabled us examine reproductive outcomes in the same mothers over time, hence eliminating the cohort effect. Furthermore, it utilized one of the best maternally linked databases in the country.\textsuperscript{99} Because we examined pregnancy spacing using previously recommended cut-off points for IPI,\textsuperscript{73} we were able to compare our findings with those of previous studies to make meaningful conclusions.
Major limitations include the utilization of a secondary database that included missing data as well as misclassification for some variables. These factors result in loss of data and reduce the effective sample size.\textsuperscript{105,106} Additionally, there are issues relating to generalizability because these data reflect the experience of a single US state. However, the findings do provide an insight as to what may be happening among US gravidas. Finally, the database covered a long time during which several changes in medical practice such as fertility treatment have occurred. Unfortunately, we were unable to account for these changes in this study.

To summarize, significant differences in IPI and adverse perinatal outcomes in second pregnancy generally become apparent among mothers 35 or older at first pregnancy. Mothers 30-34 years did not differ greatly from 20-29 olds in regard to pregnancy spacing and risk for adverse perinatal outcomes. Mothers 35 years or older at initiation of childbearing are a more high risk group, and warrant more clinical and public health attention. Having said that, it is imperative that all women receive sufficient information regarding their reproductive risks to enable them make informed decisions concerning when to initiate childbearing and how to space their pregnancies. Finally, these findings are of relevance both to patient care and preconception counseling of women as they plan their families. With continued trend towards preconception counseling, there is need to integrate our study findings as part of preconception care services.

Because of the increasing number of women delaying childbearing, understanding their reproductive history is essential in order to design interventions that target this unique population. Further research should examine issues relating to racial/ethnic
differences utilizing a more diverse study population, as this study was unable to explore this issue exhaustively given the limited diversity of the study population. Another area for potential research is examining relationship between changes in medicine practices such as fertility treatment, pregnancy spacing and perinatal outcomes. It is known that mothers delaying childbearing may have issues relating to infertility. It is still unclear how this may influence their pregnancy spacing patterns, and perinatal outcomes. Further research can explore the relationship between maternal stress on pregnancy spacing and outcomes. Mothers delaying childbearing have been shown to have increased levels of stress and anxiety; it would be worthwhile examining this relationship further as stress may be potentially modifiable. Finally, population based studies are needed to understand the mechanism by which pregnancy spacing affects pregnancy outcomes to identify new areas for future intervention.
GENERAL REFERENCES


APPENDIX A

PREVIOUS STUDIES
<table>
<thead>
<tr>
<th>Author / Title</th>
<th>Study question /hypothesis /objectives</th>
<th>Study design</th>
<th>Study population &amp; sampling</th>
<th>Data collection</th>
<th>Data analysis</th>
<th>Study outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebanoff MA, 1988. Short interpregnancy interval and the risk of LBW.</td>
<td>To investigate the effect of potential confounders on the relationship btw IPI &amp; LBW.</td>
<td>Prospective cohort study</td>
<td>55,000 pregnancies enrolled from 1959-1966. Included 1st &amp; 2nd pregnancy to a women during the study period, with information of IPI, BW, confounders under investigation. Final sample = 5938</td>
<td>Data collected on socio-demographics, IPI (end of 1st pregnancy to 1st day of LNMP). BW, IPI grouped in 3 month intervals</td>
<td>Univariate to determine mean weight at each IPI. Trend analysis Linear regression Analysis of covariance Multiple logistic regression</td>
<td>Short intervals of 3 months associated with increased risk of LBW. Effect attenuated after controlling for confounders. IPI is more of a risk marker rather than a risk factor.</td>
</tr>
<tr>
<td>Miller JE. 1991. Birth intervals &amp; perinatal health. Investigation of three hypotheses</td>
<td>To investigate 3 hypotheses explaining relation btw birth intervals &amp; birth outcomes. Hypotheses include; -confounding effect of</td>
<td>Retrospective cohort study, using data from 3 countries (Sweden, US, Hungary)</td>
<td>Second order or higher births, with information on the variables of interest. -Birth interval (from birth to sampled birth) estimated in years. Conception interval (US) -socio-demographic data -health behavior</td>
<td>Logistic regression with or without controlling for confounders.</td>
<td>Prematurity accounts for a large proportion of poor outcomes related to short birth intervals (&lt;12 months). However even after controlling for prematurity short</td>
<td></td>
</tr>
<tr>
<td>Rawlings JS, et al., 1995.</td>
<td>Investigate the relation of pregnancy interval to outcome of second pregnancy in a two consecutive singleton pregnancies</td>
<td>Retrospective cohort from 1983-1993</td>
<td>Racially diverse population of women in military families. 1922 women were enrolled in the study</td>
<td>Determine outcome (LBW, PTD, SGA) of 2nd pregnancy, race, and IPI, obtained by subtracting the gestation age if the 2nd birth from the birth interval. IPI computed in weeks then converted to months.</td>
<td>Chi-square tests, t-test, and stepwise logistic regression</td>
<td>intervals still significantly contribute to poor perinatal outcomes. Appropriate birth interval 24-48 months. Short IPI more prevalent in black women compared to white women. In black women, IPI &lt;9 months was associated with higher prevalence of PTD. For white women, only intervals of &lt;3 months were associated with high prevalence of PTD, LBW. 46% of black women had intervals less than 9 months, while 4.2 percent of white women had intervals less than 3 months.</td>
</tr>
</tbody>
</table>

Adams MM, et al. To examine the population data collected from stratified short interval of...
The relationship of interpregnancy interval to infant birth weight and length of gestation among low risk women, Georgia.

- Short interpregnancy intervals are associated with a higher risk for PTB in both black and white women. Excluded multiple births, PG, 2 pregnancies minus gestation age of most recent, difference in means & student t-test - Chi square estimation - Stepwise logistic regression. Pregnancy within ≤ 3 months IPI is associated with increased risk for PTB, no racial difference. At other intervals, AA were at increased risk, effect eliminated after controlling for confounders (mothers age, education, PNC, father's name, race). Interactions with LBW & PTD were also done.

Ekwo EE, et al., 1997. The relationship of IPI to the risk of PTB to black & white women. Retrospective cohort study, delivering at the University of Chicago.

- Analysis by race, logistic regression. Controlled for confounders (mothers age, education, PNC, father's name, race). Interactions with LBW & PTD were also done.

Data from women delivering at least one live birth, 10-24 months after delivery of previous baby. Categories included; ≤3 months, 4-6 months, 7-9 months, 10-24 months, 25-36 months, 37-48 months, >48 months. LBW, PTD, SGA & IPI was computed, and 9 categories created. Interactions btw race & IPI were also done.

Retrospective cohort study, 23,388 women, racially diverse, Had births bw 1980-1992 in GA vital records. LBW, PTD, SGA & IPI was computed, and 9 categories created. Interactions btw race & IPI were also done.

Ekwo EE, et al., 1998. The relationship of IPI to the risk of PTB to black & white women. A short interpregnancy interval is associated with a higher risk for PTB. Black women more frequently have short intervals between two successive pregnancies than white women. Retrospective cohort study. Data from women delivering at least one live birth, 10-24 months after delivery of previous baby. Categories included; ≤3 months, 4-6 months, 7-9 months, 10-24 months, 25-36 months, 37-48 months, >48 months. LBW, PTD, SGA & IPI was computed, and 9 categories created. Interactions btw race & IPI were also done.
from another hospital, incomplete data, pregnancies with previous abortion or miscarriage, missing information on some variables. Final sample was 761 women.

<p>| James AT, et al., 1999. | To examine the role of IPI on the elevated risk of term SGA for black women | Retrospective cohort study; 1922-1980 | Hospital based sample of women who delivered term births. (578 AA, &amp; 3400 White) | From medical records &amp; vital stats. SGA, IPI (estimated from LNMP, and date of last delivery). IPI measured in months, 7 categories created. | Limited to white and black mothers. Univariate analysis for outcome comparing White &amp; AA, estimated RR &amp; 95% CI. Logistic regression &amp; OR | Black women twice as likely to have short IPI&lt;6 months, &amp; long intervals &gt; 60 months. At every IPI interval, AA had higher rate of SGA, especially at intervals &lt;6 months. IPI did not increase risk for SGA among black |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Study Design</th>
<th>Data Collection</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu BP, et al., 1999.</td>
<td>The effect of the interval between pregnancies on perinatal outcomes</td>
<td>Retrospective cohort study</td>
<td>Live births to multiparous women in Utah btw 1989-1996</td>
<td>Information obtained from birth certificate &amp; medical records. Included information on GA, BW, past OB history, age, PNC use, MS, education status, race/ethnicity, smoking &amp; residence</td>
<td>Stratified analysis &amp; logistic regression. No interactions included. Intervals less than 3 months, &amp; greater than 24 months were associated with greatest risk of adverse outcomes. Risk lowest for intervals 18-23 months.</td>
</tr>
<tr>
<td>Conde-Augdelo A, et al., 2000.</td>
<td>Maternal morbidity and mortality associated with interpregnancy interval: cross-sectional study.</td>
<td>Retrospective cross sectional study</td>
<td>IPI, (short &lt;6 months, long &gt;59 months) Maternal death, pre-eclampsia, eclampsia, GDM, APH, PPH, PROM</td>
<td>-Bivariate analysis assessing each outcome in each category of IPI Estimated OR, 95% CI Ref category =18-23. -Logistic regression</td>
<td>3% had IPI &lt;6mnths, 20% &gt;59 months. IPI &lt;5 months associated with increased maternal mortality, third trimester bleeding, PROM, and anemia. Women with long interval increased risk for pre-eclampsia &amp; eclampsia</td>
</tr>
<tr>
<td>Fuentes-Afflick E, et al., 2000.</td>
<td>IPI and the risk of PT infants.</td>
<td>Retrospective cohort study</td>
<td>-IPI (number of months btw delivery of previous birth and conception of current</td>
<td>Bivariate analysis with chi-square estimation,</td>
<td>Intervals &lt;18 months associated with increased risk for PTD. Risk</td>
</tr>
</tbody>
</table>
To investigate the relation between IPI and adverse perinatal outcomes. To determine any racial differences persist even after controlling for confounders.

<p>| Zhu B, et al., 2001. Effect of the interval btw pregnancies on perinatal outcomes among white &amp; black women. | Retrospective cross sectional study | Vital stat data from Michigan state, between 1993-1998, looked at live births | Multiple logistic regressions, no interactions | The risk for delivering LBW, preterm and SGA infant was lowest if the IPI was 18-23 months. Same for both race groups. Short intervals (&lt;6 months), and long intervals ≥120 months associated with highest risk for both race groups. |
| <strong>Al-Jasmi F, et al., 2002.</strong> Effect of IPI on risk of spontaneous preterm birth in Emirati women, UAE. | <strong>To identify the relationship between IPI &amp; spontaneous PTB, in a homogeneous population after controlling for potential confounders.</strong> | <strong>Matched Case-control study, done in a small city in UAE.</strong> | <strong>Study population included all births recorded between 1997-2000 at 3 area hospitals. Cases restricted to those delivering PT, with no OB complications reported. Matched each case to control. Sample = 256.</strong> | <strong>Data obtained from hospital labor &amp; delivery records, &amp; PNC records. Determined socio-demographics, mean birth interval, IPI (birth interval – GA) gravidity,</strong> <strong>-Differences in proportions, significance tested with Wilcoxon rank test for continuous variables, &amp; X² for categorical variables. -Multivariable logistic regression.</strong> | <strong>Short intervals significantly associated with spontaneous PTD even after controlling for potential confounders.</strong> |</p>
<table>
<thead>
<tr>
<th>Author / Title</th>
<th>Study question /hypothesis /objectives</th>
<th>Study design</th>
<th>Study population &amp; sampling</th>
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<th>Data analysis</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dafopoulos KC, et al., 2002. Interpregnancy interval and the risk of preterm birth in Thrace, Greece.</td>
<td>To examine the influence of short IPI on PTD in two ethnic groups in Greece</td>
<td>Retrospective cross-sectional study</td>
<td>652 urban &amp; 578 rural. Delivering at regional hospital.</td>
<td>-IPI=Birth interval – gestational age, estimated in wks then converted to months. -GA, -confounders (age, PNC, smoking,</td>
<td>T-tests, RR &amp; 95% CI.</td>
<td>PT &amp; IPI more common in Muslims (rural) than Christians. Associated more with interval &lt;6 months</td>
</tr>
<tr>
<td>Smith GCS, et al., 2003. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study.</td>
<td>To determine whether short IPI is an independent risk factor for adverse outcome</td>
<td>Retrospective cohort study</td>
<td>Conducted in Scotland, enrolled 89,143 having second pregnancy btw 1992-1998.</td>
<td>Outcomes, IUGR, EPTD, MPTD, perinatal death. IPI, Data obtained from perinatal database Other variables (age, smoking, MS, height, SES</td>
<td>-Measures central tendency for continuous data using Mann-Whitney test. -Chi-square testing (Fisher’s exact testing) Multivariate logistic regression, evaluated interactions as well</td>
<td>1st pregnancy ending in IUGR, EPTD, MPTD or perinatal death were more likely to be followed by short IPI. Short IPI (&lt; 6 months) associated with EPTD, MPTD, neonatal death, but not IUGR or stillbirth</td>
</tr>
<tr>
<td>Stephansson O, et al., 2003. Influence of IPI on the</td>
<td>To investigate whether interpregnancy interval is</td>
<td>Population retrospective study of women</td>
<td>Women having 1st &amp; 2nd Child Information on SB, gestation age, birth weight, sex, date of delivery,</td>
<td></td>
<td>Unconditional logistic regression used, adjusted fro IPI,</td>
<td>Short intervals (0-3 months) are associated with increased risk for</td>
</tr>
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<tr>
<td>Conducted in Scotland, enrolled 89,143 having second pregnancy btw 1992-1998.</td>
<td>Outcomes, IUGR, EPTD, MPTD, perinatal death. IPI, Data obtained from perinatal database Other variables (age, smoking, MS, height, SES</td>
<td>-Measures central tendency for continuous data using Mann-Whitney test. -Chi-square testing (Fisher’s exact testing) Multivariate logistic regression, evaluated interactions as well</td>
<td></td>
<td>1st pregnancy ending in IUGR, EPTD, MPTD or perinatal death were more likely to be followed by short IPI. Short IPI (&lt; 6 months) associated with EPTD, MPTD, neonatal death, but not IUGR or stillbirth</td>
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</table>

<p>| Study design | Study population &amp; sampling | Data collection | Data analysis | Study outcome |
|--------------|-----------------------------|-----------------|---------------|---------------|----------------|
| Population retrospective study of women | Women having 1st &amp; 2nd Child Information on SB, gestation age, birth weight, sex, date of delivery, |                              | Unconditional logistic regression used, adjusted fro IPI, | Short intervals (0-3 months) are associated with increased risk for |
| Subsequent risk of stillbirth and early neonatal death. | Associated with increased risk of stillbirth and early neonatal death. | Delivering in Sweden between 1983-1997 | Mortality, SGA, &amp; IPI = time lapsed between birth of first child, and estimated conception date of the following child. Other info included maternal characteristics | Maternal age, smoking, education status, MS, country of origin, DM, HT, year of second delivery | SB, &amp; early neonatal death. Risk disappeared after controlling for confounders. Long IPI (72 months) associated with increased risk that persisted after controlling for confounders |</p>
<table>
<thead>
<tr>
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<td>Conde-Agudelo A, et al., 2005. Effect of IPI on perinatal outcomes in L. America</td>
<td>To determine whether IPI is assoc. with increased risk of adverse birth outcomes in cohort of Latin American Women.</td>
<td>Multi-site prospective cohort</td>
<td>Women delivering btw 1983-2005. Limited to singleton births. Final sample = 1,125,430</td>
<td>Socio-demographics, medical factors, birth outcomes</td>
<td>Determined rates of outcomes by IPI category. OR &amp; 95% CI estimated as well. Reference interval= 18-23 months.</td>
<td>Median IPI = 27.8 months. IPI of &lt;12 months more in younger women, late start of PNC, &amp; women with h/o SB, poor previous outcome. Older women had longer intervals, as well those with high BMI. Infants of mothers with short intervals had excess of neonatal death, fetal death, LBW, PT &amp; SGA. IPI was found to be an independent risk factor.</td>
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<tr>
<td>Conde-Agudelo A, et al., 2005. Effect of the interpregnancy interval after an abortion on maternal and perinatal health in L. America</td>
<td>To investigate whether the length of the interval btw an abortion &amp; next pregnancy is associated with increased risk of adverse maternal &amp; perinatal outcomes in L. America</td>
<td>Retrospective cohort study using a multi country perinatal database. Births from 1985-2002 included.</td>
<td>Limited to women with singleton births whose previous pregnancy ended in an abortion</td>
<td>-socio-demographics, past OB, medical, IPI (in months; ≤2, 3-5, 6-11, 12-17, 18-23, 24-59, ≥60)</td>
<td>Determined rates and differences in proportions. Logistic regression to assess association (OR)</td>
<td>An interval of, 6 months following abortion is associated with increased risk for poor maternal &amp; perinatal outcome.</td>
</tr>
<tr>
<td>Hsieh TT, et al., 2005. The impact of IPI and previous PTB on the subsequent risk of PTD.</td>
<td>To examine the impact of IPI &amp; a previous preterm birth on the subsequent risk of a preterm birth.</td>
<td>Retrospective cohort study</td>
<td>4072 women delivering at the hospital had at least 2 consecutive pregnancies btw 1991-1997.</td>
<td>Demographic data, medical &amp; obstetric history, perinatal outcome. IPI (estimated from DOB of previous pregnancy, &amp; LNMP</td>
<td>Multi-level analysis with logistic regression - OR, PAR,</td>
<td>Pregnancy following interval &lt;12 months had increase risk for PTD. Also had increased risk if the 1st pregnancy had ended in a PTD. Lowest risk noted for 18-48. Previous term delivery was associated with PTD in the 2nd preg. if the IPI was &lt; 6 months</td>
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To examine the association between birth spacing and relative risk of adverse perinatal outcomes. To evaluate if association is due to confounding

Systematic literature review with meta analysis was conducted.

Included all published studies that examined birth spacing and the perinatal outcomes, and gave a summary of the effect, gave riskiest and optimal intervals. Conference proceedings and personal contact with known researchers.

Included -studies with cohort, case control, or cross sectional design. -Defined interval -controlled for age, and SES. Excluded -Lit reviews -Letters to editor -used Univariate analysis only -no control for age or SES

Abstracted data -Author, title, year, geo-region, design, study population, sample size, outcome measures, birth spacing used, categorization of interval, data collection methods, exposure measurement, ascertainment of outcome, confounders controlled for, OR

Converted interval measures to months to have uniform unit. Used 3 analytical tools -meta regression analysis -pooled ORs -dose response regression slopes

-130 studies found, -63 excluded -67 met inclusion criteria -20 studies in US. Intervals <6 months have increased risk for poor outcomes. Optimal period 18-23 months. Long intervals of 59 months also associated with increased risk.
APPENDIX B

INSTITUTIONAL REVIEW BOARD APPROVAL FORMS
Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH/GCP Guidelines. The Assurance became effective on November 24, 2001 and expires on February 14, 2009. The Assurance number is FWA00005900.

Principal Investigator: NABOKERA, SARAH KOLO
Co-Investigator(s):
Protocol Number: 2060098002
Protocol Title: "Delayed Childbearing, Pregnancy Spacing and Impact on Subsequent Pregnancy Outcomes: A Prospective Cohort Study, 1976-1997"

The IRB reviewed and approved the above named project on 09/08/02. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 09/08/02

Date IRB Approval issued: 09/08/02

Marilyn Dusa, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unexpected risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
APPENDIX C

STUDY SAMPLE ESTIMATION
Missouri maternally linked file, 1978-1998
= 1,577,082

Eliminating cases without siblings
= 1,104,007

Eliminating teens, > 50 years & multiple births
= 919,979

Selecting 1st & 2nd pregnancy records
= 613,237

Cleaning to ensure all cases have 2 records
= 485,118

First pregnancy records
= 242,559

Second pregnancy records
= 242,559