Fetomaternal Outcomes of Grand Multiparas
Over Two Decades in Mali

By
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2010

_______________________ (date) _______
Advisor: Russell Harris, MD

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Second Reader: Phyllis Leppert, MD, PhD
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Manuscript

Fetomaternal outcomes of grand multiparas over two decades in Mali

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Article condensation:

A higher odds for placental abnormalities, perinatal death, and high birthweight, but lower odds for maternal death found for multiparas in Mali.

Short version of article title:

Fetomaternal outcomes of grand multiparas
Abstract

Objective: To analyze the association between grand multiparity and maternal and perinatal morbidity and mortality.

Study design: Cross-sectional study of 18,697 singleton births at a tertiary care hospital in Mali (1985-2003) compared outcomes between 3,617 grand multiparas (para ≥5) and 9,723 pauciparas (para 1-4). Odds ratios [OR] were adjusted for maternal age, prenatal care utilization, socioeconomic status, and region of origin.

Results: Grand multiparas were older, poorer, and less likely to have accessed prenatal care. Grand multiparas had a lower adjusted odds of maternal death (adjusted OR, 0.66; 95% CI, 0.45-0.97), but higher odds of perinatal death (adjusted OR, 1.33; 95% CI, 1.12-1.59), placental abnormalities (adjusted OR, 1.57; 95% CI, 1.21-2.05), and high birthweight (adjusted OR, 1.42; 95% CI, 1.05-1.92).

Conclusion: The healthy person effect may explain grand multiparas’ lower odds of maternal death. Reducing grand multiparity and improving grand multiparas’ access to prenatal care may improve population-level perinatal outcomes.

Ibrahima TEGUETE, Amelia W. MAIGA, and Phyllis C. LEPPERT

Key words: Grand multiparity
Mali
Pregnancy outcomes
Introduction

The International Federation of Gynecology and Obstetrics (FIGO) and most recent literature define grand multiparity as parity ≥5.\textsuperscript{1-4} Recent attention to a global decline in maternal mortality rates has reemphasized the presumed causality between population-level multiparity and maternal mortality.\textsuperscript{5-6} Grand multiparity has historically been associated with numerous maternal and perinatal adverse outcomes, including maternal death,\textsuperscript{7-9} post-partum infection,\textsuperscript{7, 9} uterine rupture,\textsuperscript{10} post-partum hemorrhage\textsuperscript{1, 9-10} placental abnormalities,\textsuperscript{1-2, 11-13} toxemia,\textsuperscript{10, 14} stillbirth,\textsuperscript{4, 9, 15-16} neonatal death,\textsuperscript{3, 17-18} low birthweight or prematurity,\textsuperscript{19} and high birthweight or macrosomia.\textsuperscript{2, 20} A 2005 review cited widespread poor study design and heterogeneous outcome definitions, but did find evidence for a higher risk of placental pathologies and increased birthweight with increasing parity.\textsuperscript{2}

However, researchers from developed countries with uniform prenatal care have challenged the characterization of high multiparity as an independent risk factor, highlighting the potent confounding effects of increased maternal age and differential socioeconomic status and prenatal care.\textsuperscript{14, 21-22} Many of these studies tending towards the null hypothesis are limited in sample size, making valid conclusions about rare outcomes like mortality and uterine rupture difficult.\textsuperscript{2} In contrast, some well-powered studies have demonstrated a persistent link between grand multiparity and feto-neonatal risks even after accounting for confounders.\textsuperscript{3, 16-17, 19} Grand multiparity remains highly relevant in most African countries where the total fertility rate exceeds five.\textsuperscript{21} Immigrant populations in developed countries have similarly high birth rates.\textsuperscript{24} In light of the globally insufficient and conflicting literature, we need robust studies from contexts where grand multiparity is most prevalent today.
The primary aim of the present study was to determine whether grand multiparity is independently associated with maternal and perinatal mortality, placental abnormalities, obstetric complications, and abnormal neonatal birth weight after adjusting for confounders. Second, we explored any dose-response relationships between parity and specific adverse outcomes. Finally, we evaluated how a reduction in the average parity of multiparous Malian women between 1985 and 2003 contributed to a reduction in perinatal mortality over this time.

Methods

This cross-sectional study was conducted at Point G National Hospital, a tertiary referral facility in Bamako, the capital city of Mali. One of the poorest countries in the world, Mali ranks 178 out of 182 on the United Nations Human Development Index. The current total fertility rate in Mali is 6.5 children per woman, down from 7.4 in 1990. Point G is an academically-affiliated referral center that provides emergency obstetric and gynecologic care to women referred or evacuated from health centers across Mali, in addition to routine prenatal and delivery care to a catchment area of approximately 10% the population. Pregnant women are also frequently cared for by the surgery, urology, anesthesia, and internal medicine departments.

The initial study population was all pregnant women admitted to Point G National Hospital between January 1, 1985 and December 31, 2003 (n=19,253). Multiple births (n=556) were excluded to avoid confounding, leaving 18,697 singleton births. Of the 18,076 women (96.7%) with parity data, 3,617 grand multiparas (para ≥5) and a comparison group of 9,723 pauciparas (para 1-4) were identified. Nulliparas (n=4,736) were not included in the comparison group due to their higher obstetric risk. No further exclusion criteria were applied for assessing maternal outcomes. Before comparing perinatal outcomes, we excluded gestations ending <28
weeks (n=1,617), including all spontaneous and therapeutic abortions (n=840), and molar (n=43) and ectopic (n=570) pregnancies. Ten additional ectopic pregnancies discovered after 28 weeks gestation were also excluded, giving a final perinatal population of 17,070.

As previously described, data from all relevant department records were integrated into a single computer database to minimize under-reporting. In neighboring Burkina Faso, 70% of in-hospital maternal deaths were missed using obstetric records only. Data were double abstracted by two independent trained individuals to ensure accuracy, with discrepancies resolved by a third party. Due to the 19-year period from which data were collected and the lack of a unique identifier for each woman, some may have contributed more than one delivery to the study. Maternal and perinatal mortality and morbidity outcomes, admission type, pregnancy type (i.e., ectopic, abortion, molar, or normal), week of gestation, parity, birth interval, and basic socio-demographic data were collected. Follow-up data after hospital discharge were not available except in rare cases of re-admission. Research protocols and data were approved by the ethics committee of the Faculty of Medicine, Pharmacy, and Dentistry at the University of Bamako. Institutional review board exemption was obtained from Duke University on the basis of a de-identified database.

The primary outcomes of this study were maternal and perinatal mortality. We defined maternal mortality using the World Health Organization definition as “the death of a woman while pregnant or within 42 days after termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.” However, deaths after hospital discharge were not captured. Perinatal mortality included stillbirths and early neonatal deaths (up to 13 days); 90.1% (283 of 314) of neonatal deaths occurred within the first week.
Secondary obstetric outcomes included placental abnormalities (a composite of previa and abruption, defined clinically), uterine rupture (determined during cesarean), post-partum infection (defined clinically), post-partum hemorrhage (≥500 ml blood loss within 24 hours after delivery), eclampsia (defined clinically), and cesarean delivery. We also compared average neonatal birth weights and proportions of low birthweight (<2500 g) and high birthweight (>4000 g) infants. Because reliable dating techniques like early ultrasound are infrequent in Mali, we were unable to reliably distinguish between small for gestational age and preterm infants. We thus used the composite outcome of low birthweight. Similarly, high birthweight infants included both large for gestational age and post-term infants.

We defined parity as the number of previous pregnancies either ≥22 weeks or resulting in an infant ≥500 g (stillborn or live). Parity was the principal covariate, divided into para 1-4 and para ≥5. We also used parity as a categorical variable (para 1-4, 5-6, 7-9, and ≥10). Great-grand multiparas were defined as those with ≥10 prior pregnancies. Covariates included as potential confounders were maternal age (both as a simple continuous variable and as number of years over age 30), socioeconomic status (low, medium, and high), region of origin (greater Bamako area vs. outside Bamako), and prenatal care utilization (any vs. none). Covariates were checked for association with each outcome using Pearson’s correlation coefficient. Relative socioeconomic status was determined using a culturally-appropriate algorithm that paired a woman’s profession with that of her partner. Region of origin was an additional proxy for socioeconomic status. While maternal smoking status is another potent confounder, the female smoking rate in Mali is negligible (<3%) and contributes minimally to adverse fetomaternal outcomes.
We first characterized the study population in terms of basic demographics and mode of admission. Means or medians were reported for continuous variables and percentages for categorical variables. Next, we compared unadjusted outcomes between grand multiparas and pauciparas using Student’s t-test (or the Wilcoxon rank-sum test for nonparametric data) for continuous outcomes and Pearson’s chi-square test for categorical outcomes. We then constructed multivariable models (multiple linear regression for birth weight, logistic regression for the dichotomous outcomes) with the four confounders. Results are expressed as odds ratios with 95% confidence intervals. All models were run in duplicate with a time cohort adjustment to assess for temporal effects. Multiple imputations (n=5) were done to account for missing data, and all models were re-run on this imputed dataset. Results are from the original dataset unless otherwise noted. Stata version 11 (Stata Corp, College Station TX, USA) was used for all analyses. P values <.05 were considered statistically significant.

Dose-response analysis involved comparing the rates of each significant outcome by individual parity group, with P values calculated from the likelihood ratio test for the difference of the adjusted probabilities. Great-grand multiparas (para ≥10) were pooled due to small sample size. Finally, we correlated mean institutional parity with institutional perinatal mortality rates, both unadjusted and adjusted for parity, after stratifying the study population into four time cohorts of roughly equivalent observations (1985-1988, 1989-1992, 1993-1997, and 1998-2003). Nulliparas were excluded to avoid confounding. In addition to confounders, we also adjusted perinatal mortality for changes in referral patterns over time. Previous work demonstrated that increases in the proportion of referred cases masked a significant drop in institutional maternal mortality.26
Results

Of the 18,076 women with parity data, 26.2% were nulliparas, 53.8% pauciparas, 20.0% grand multiparas, and 1.6% great-grand multiparas (Table 1). This distribution did not differ substantially in the perinatal study population. In comparison to pauciparas, grand multiparas were significantly older and of lower socioeconomic status. They were more likely to be from outside Bamako and to have been evacuated from another facility to the hospital, and less likely to have accessed prenatal care (Table 2). The age distribution by parity group was particularly illuminating because of the minimal overlap: three-quarters of pauciparas were under age 30, whereas three-quarters of grand multiparas were over 30.

The unadjusted maternal mortality rate (MMR) in grand multiparas was significantly higher than that in pauciparas (2.7% vs. 1.5%, p<.01) (Table 3). Eighty-three (20.4%) of the 407 maternal deaths occurred in women with missing parity data, but age was recorded for 71 (85.5%) of these 83. The difference in MMR remained significant after distributing these 71 deaths among parity groups based on estimations derived from the differential age distribution of nulliparas, pauciparas, and grand multiparas (3.2% vs. 1.8%, p<.01). The top three causes of maternal mortality were uterine rupture (25.7%), post-partum hemorrhage (21.0%), and post-partum infection (19.8%). After adjusting for confounders, grand multiparas had a significantly lower odds of maternal death (adjusted OR, 0.66; 95% CI, 0.45-0.97) (Table 4).

Excluding pregnancies ending <28 weeks, there were 1,911 perinatal deaths. Perinatal death was more frequent in grand multiparas than in pauciparas (17.9% vs. 9.1%, p<.01) (Table 3), and this association persisted on multivariable analysis (adjusted OR, 1.33; 95% CI, 1.12-1.59) (Table 4). Dose-response analysis showed a U-shaped relationship between perinatal
mortality and parity, with the lowest adjusted odds in women of para 2 and the highest in para $\geq 4$ (Fig 1). An absolute 2.5% reduction in the adjusted institutional perinatal mortality rate (PMR) (from 7.5% in 1985-1988 to 5.0% in 1998-2003) paralleled an absolute 0.58 reduction in mean institutional parity (3.63 to 3.05). Further adjusting the change in PMR for parity reduced this absolute PMR reduction to 2.2% (7.3% minus 5.1%). This difference of 0.3% (2.5% minus 2.2%) in the absolute PMR reduction over time can be thus solely attributed to parity reductions.

Placental abnormalities included 390 cases of previa and 158 abruptions (7 had both). Grand multiparas had twice the rate of placental abnormalities than did pauciparas (5.8% vs. 2.6%, $p<.01$) (Table 3). In the adjusted analysis grand multiparas remained at higher odds for placental abnormalities (adjusted OR, 1.57; 95% CI, 1.21-2.05) (Table 4). Adjusted odds ratios for previa and abruption were 1.41 (95% CI, 1.04-1.92) and 2.07 (95% CI, 1.28-3.36). Odds of abruption also correlated with parity; women of para 5-6, 7-9, and $\geq 10$ had adjusted odds ratios of 1.98 (95% CI, 1.14-3.44), 1.99 (95% CI, 1.03-3.84), and 3.91 (95% CI, 1.40-10.93), respectively. Grand multiparas under age 35 had a particularly high adjusted odds of placental abnormalities at 1.70 (95% CI, 1.26-2.32), whereas this association was not significant for women $\geq 35$ ($p=.19$). Dose-response analysis demonstrated a clear positive step-wise interaction between parity and placental abnormalities, beginning with 3.1% at a parity of 5 and increasing to 6.1% among great-grand multiparas (Fig 1).

Women delivering via cesarean were more likely to be diagnosed with any placental abnormality (70.6% vs. 29.4%, $p<.01$), and three times as likely to be diagnosed with previa (76.6% vs. 23.4%, $p<.01$). Adjusting for cesarean delivery in the models strengthened the association between grand multiparity and placental abnormalities from an adjusted odds ratio of 1.57 to 1.84 (95% CI, 1.41-2.40).
The mean neonatal birth weight was 2983 grams. In the unadjusted analysis grand multiparas had significantly heavier babies than did pauciparas (3058 g vs. 3016 g, p<.01) (Table 3). In the multivariable analysis, birth weight as a continuous outcome was not associated with grand multiparity (p=.39). However, grand multiparas were at higher odds for high birthweight infants (adjusted OR, 1.45; 95% CI, 1.07-1.95) (Table 4). High birthweight infants had twice the mortality rate than normal weight infants (PMR 20.1% vs. 8.4%, p<.01).

Grand multiparas had significantly higher unadjusted rates of uterine rupture (5.4% vs. 2.7%, p<.01) and post-partum hemorrhage (PPH) (4.6% vs. 2.5%, p<.01) (Table 3). Upon multivariable analysis, grand multiparas had a lower adjusted odds ratio of cesarean delivery than pauciparas (0.54; 95% CI, 0.47-0.62) (Table 4). Other obstetric complications did not differ significantly between pauciparas and grand multiparas on multivariable analysis.

Discussion

This cross-sectional study of 18,697 women delivering at a tertiary referral facility in Mali sought to determine whether grand multiparity is independently associated with serious fetomaternal outcomes. After adjusting for confounders, paucipara mothers were actually 52% more likely than grand multiparas to die. Grand multiparity did confer a 33% increased odds of perinatal death and a 59% increased odds of placental abnormalities over that in pauciparas. Confirming previous studies,2, 20 grand multiparas were also 42% more likely to deliver high birthweight (>4000 g) infants. This represents the largest published study of grand multiparas in Africa to date and the only to employ multivariable analysis (MEDLINE; 1952-May 2010; search terms: “grand multipar*” AND [“pregnancy outcome OR pregnancy complications”]).
Strengths of our study include its large sample size allowing for comparison of rare complications and our ability to adjust for all recognized confounders. While our study’s observational nature precludes conclusions on causality, including time as a covariate in the models did not change any conclusions, reducing the likelihood of temporal bias. We do rely on data from a single institution, but our population is reasonably representative of the Malian health care system as >30% of women were referred or evacuated from outside facilities. The major limitation of our study is the potential for measurement bias. We were limited to comparing in-hospital mortality rates, and were unable to meaningfully compare birth intervals, as they were missing for 39% of observations in our study and self-reported intervals lack precision in Mali. Previous authors have hypothesized that grand multiparity may be a proxy risk factor for an abbreviated birth interval.15, 18

Recent global reductions in maternal mortality have been attributed to decreasing parity.5-6 This study does not support that assumption. Our surprising finding of a negative association between grand multiparity and maternal mortality confirms the paramount importance of maternal age, prenatal care utilization, and socioeconomic status on grand multiparas’ outcomes. Two additional factors may be at play. The “healthy person effect” means women who experience obstetric complications in earlier deliveries are more likely to end their childbearing early either voluntarily or involuntarily (e.g., by perishing during a delivery).15 Pauciparas were also 85% more likely to deliver via cesarean. Women delivering via cesarean had a 5.5% MMR as compared to 0.8% in those delivering vaginally.

Our most clinically relevant finding was the strong correlation between increased parity and perinatal mortality that persisted even after adjusting for the potent confounder of maternal age.30 This confirms other reports,3, 17 including a recent U.S. epidemiologic study demonstrating
a strong dose-response relationship between increasing parity >10 and stillbirth risk.\textsuperscript{16} We hypothesize the reduction in institutional PMR during our study period to be due in part to a decrease in the mean parity of multiparous women and in part to better care at Point G Hospital and the improved condition of referred and evacuated patients. In 1994 a National Perinatality Program reorganized the referral system to better link primary health centers to facilities like Point G, dramatically reducing the institutional MMR.\textsuperscript{31} While prospective studies must establish causality, population-level reductions in parity may also reduce perinatal mortality.

Grand multiparas, particularly those <35 years, were at increased odds of placental abnormalities in our study, confirming two population-based studies’ findings.\textsuperscript{3, 13} Increasing maternal age increases previa risk by changing uterine blood flow.\textsuperscript{13} Similarly, in young grand multiparas the cumulative effects of many deliveries may prematurely age the uterus and increase the subsequent risk of developing previa.\textsuperscript{32} Although hypertension has long been hypothesized to place a causal role in placental abruption in grand multiparas,\textsuperscript{11} women with abruption in our study did not have higher blood pressure readings. Rather, nutritional deficiencies may play a role in the pathophysiology of abruption.\textsuperscript{33-34} Grand multiparity may either be a marker for or a direct cause of poor nutrition. Multiple pregnancies and long periods of breastfeeding may deplete nutritional stores, and grand multiparas may prioritize the nutritional needs of their growing families over their own intake.

Although previous studies in populations with good obstetric care have downplayed the fetomaternal morbidity and mortality risks of placental abnormalities,\textsuperscript{10, 12, 21, 30} others have correlated antepartum fetal death with both placental abnormalities and grand multiparity.\textsuperscript{4} More than half (50.9\%) the pregnancies in our population with placental complications ended in perinatal death, and previa and abruption carried 8\% and 12\% maternal case fatality rates.
discrepancy likely reflects the higher proportion of clinically non-significant cases detected in more developed settings where ultrasound examinations are part of routine prenatal care. However, it should also serve as a call to action for improving prenatal coverage for grand multiparas as a means to reduce the fetomaternal implications of placental problems.

In conclusion, our findings are important for clinical and public health practice in Africa and beyond. First, providers should communicate the increased odds of fetomaternal complications (including perinatal mortality) for pregnancies after the fifth delivery, and provide appropriate contraceptive options to patients. Policies that succeed in reducing population-level fertility rates below five may reduce perinatal mortality rates. Second, access to quality prenatal care for grand multiparas must be prioritized, particularly in low-income settings. Prospective studies are needed to evaluate the potential causal linkages between placental abnormalities, perinatal mortality, and increasing parity, in addition to exploring the risks and benefits of screening for placental abnormalities in grand multiparas.

**Acknowledgements:** To Russell Harris, MD for reviewing the manuscript and providing valuable feedback, and to Amadou Dolo, MD, head of the Department of Obstetrics and Gynecology at Point G National Hospital, for his constant encouragement and support for the updating of the database during the study period.
**Figures**

**Figure 1:** Dose-Response Analysis. (Adjusted for maternal age, socioeconomic status, region of origin and prenatal care utilization; $P$ values calculated using *predxcat*.)
### Table 1: Study Population Distribution by Parity

<table>
<thead>
<tr>
<th>Parity</th>
<th>n</th>
<th>Percent</th>
<th>Cumulative n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4,736</td>
<td>26.2%</td>
<td>4,736 (26.2)</td>
</tr>
<tr>
<td>1</td>
<td>3,622</td>
<td>20.0%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2,685</td>
<td>14.9%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1,940</td>
<td>10.7%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1,476</td>
<td>8.2%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1,119</td>
<td>6.2%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>830</td>
<td>4.6%</td>
<td>1,949 (10.8)</td>
</tr>
<tr>
<td>7</td>
<td>655</td>
<td>3.6%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>436</td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>291</td>
<td>1.6%</td>
<td>1,382 (7.7)</td>
</tr>
<tr>
<td>10</td>
<td>139</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>43</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>16</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>8</td>
<td>&lt;0.1%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>&lt;0.1%</td>
<td>286 (1.6) 3,617 (20.0)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Entire study population&lt;sup&gt;a&lt;/sup&gt; (N=18,697)</td>
<td>Pauciparas (para 1-4) (n=9,723)</td>
<td>Grand multiparas (n=3,617)</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Median&lt;sup&gt;b&lt;/sup&gt; parity (interquartile range)</td>
<td>2 (0-4)</td>
<td>2 (1-3)</td>
<td>6 (5-8)</td>
</tr>
<tr>
<td>Median&lt;sup&gt;b&lt;/sup&gt; birth interval&lt;sup&gt;c&lt;/sup&gt; in months (interquartile range)</td>
<td>24 (15-36)</td>
<td>24 (15-36)</td>
<td>24 (16-36)</td>
</tr>
<tr>
<td>Mean maternal age in years (range)</td>
<td>26.4 (13-50)</td>
<td>26.1 (13-48)</td>
<td>34.1 (16-50)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Low</td>
<td>14.2%</td>
<td>12.8%</td>
<td>23.1%</td>
</tr>
<tr>
<td>- Medium</td>
<td>42.6%</td>
<td>39.9%</td>
<td>40.2%</td>
</tr>
<tr>
<td>- High</td>
<td>43.2%</td>
<td>47.3%</td>
<td>36.7%</td>
</tr>
<tr>
<td>Region of origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bamako</td>
<td>78.2%</td>
<td>80.7%</td>
<td>70.9%</td>
</tr>
<tr>
<td>- Outside of Bamako</td>
<td>21.8%</td>
<td>19.3%</td>
<td>29.1%</td>
</tr>
<tr>
<td>Prenatal care utilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>84.1%</td>
<td>86.8%</td>
<td>76.4%</td>
</tr>
<tr>
<td>- No</td>
<td>15.9%</td>
<td>13.2%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Mode of admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Self-admitted</td>
<td>68.7%</td>
<td>71.0%</td>
<td>66.2%</td>
</tr>
<tr>
<td>- Referred from other center</td>
<td>12.6%</td>
<td>14.0%</td>
<td>9.8%</td>
</tr>
<tr>
<td>- Evacuated from another center</td>
<td>18.7%</td>
<td>15.0%</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

<sup>P</sup> values calculated from Student’s t-test, Wilcoxon rank-sum test, or two-sided Fisher’s exact test, as appropriate.

<sup>a</sup> Provided for comparison only; includes nulliparas, pauciparas (para 1-4), and grand multiparas (para ≥5). Statistical tests compare grand multiparas to pauciparas only. Percentages are by column.

<sup>b</sup> Median values reported due to positive skew of data distribution; mean values are 2.5, 2.1, and 6.7, respectively, for parity and 30.1, 30.8, and 29.3 months, respectively, for birth interval.

<sup>c</sup> Birth interval was missing for 39% of all observations in the study population (excluding nulliparas).
### Table 3: Unadjusted Maternal, Obstetric and Feto-neonatal Outcomes by Parity Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire study population (N=18,697)</th>
<th>Pauciparas (para 1-4) (n=9,723)</th>
<th>Grand multiparas (n=3,617)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal mortality^a</td>
<td>407 (2.2)</td>
<td>148 (1.5)</td>
<td>97 (2.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Placental abnormalities</td>
<td>541 (3.0)</td>
<td>248 (2.6)</td>
<td>206 (5.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>540 (2.9)</td>
<td>260 (2.7)</td>
<td>194 (5.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Post-partum infection</td>
<td>1,235 (6.6)</td>
<td>574 (5.9)</td>
<td>233 (6.4)</td>
<td>.25</td>
</tr>
<tr>
<td>Post-partum hemorrhage</td>
<td>494 (2.6)</td>
<td>244 (2.5)</td>
<td>167 (4.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>196 (1.1)</td>
<td>53 (0.6)</td>
<td>11 (0.3)</td>
<td>.09</td>
</tr>
<tr>
<td>Cesarean</td>
<td>4,358 (25.4)</td>
<td>2,276 (24.9)</td>
<td>848 (25.1)</td>
<td>.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire study population (N=17,070)</th>
<th>Pauciparas (para 1-4) (n=9,082)</th>
<th>Grand multiparas (n=3,369)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal mortality</td>
<td>1,911 (11.3)</td>
<td>822 (9.1)</td>
<td>599 (17.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean birth weight in grams (SD)</td>
<td>2983 (579)</td>
<td>3016 (551)</td>
<td>3058 (647)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Low birthweight infants</td>
<td>2,387 (14.2)</td>
<td>1,115 (12.4)</td>
<td>463 (13.9)</td>
<td>.03</td>
</tr>
<tr>
<td>High birthweight infants</td>
<td>364 (2.2)</td>
<td>181 (2.0)</td>
<td>141 (4.2)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise noted.

P values calculated from Student’s t-test for mean birth weight and two-sided Fisher’s exact test for all other variables.

^a Although parity was only missing in 3.3% of all observations, it was not recorded for 83 (20.4%) of maternal deaths
Table 4: Adjusted Maternal, Obstetric and Feto-neonatal Outcomes by Parity Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Para 5-6 (n=1,949)</th>
<th>Para 7-9 (n=1,382)</th>
<th>Para ≥10 (n=286)</th>
<th>All grand multiparas (para ≥5) (n=3,617)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal mortality</td>
<td>0.81 (0.53-1.23)</td>
<td>0.42 (0.24-0.74)</td>
<td>0.17 (0.05-0.56)</td>
<td>0.66 (0.45-0.97)</td>
</tr>
<tr>
<td>Placental abnormalities</td>
<td>1.46 (1.08-1.97)</td>
<td>1.65 (1.15-2.37)</td>
<td>1.60 (0.86-2.98)</td>
<td>1.57 (1.21-2.05)</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>1.27 (0.94-1.73)</td>
<td>0.81 (0.54-1.23)</td>
<td>0.49 (0.21-1.17)</td>
<td>1.14 (0.86-1.51)</td>
</tr>
<tr>
<td>Post-partum infection</td>
<td>0.94 (0.75-1.19)</td>
<td>0.84 (0.62-1.13)</td>
<td>1.29 (0.73-2.29)</td>
<td>0.90 (0.73-1.11)</td>
</tr>
<tr>
<td>Post-partum hemorrhage</td>
<td>1.22 (0.89-1.67)</td>
<td>1.54 (1.06-2.25)</td>
<td>1.01 (0.50-2.07)</td>
<td>1.30 (0.99-1.72)</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>0.48 (0.18-1.29)</td>
<td>0.48 (0.14-1.63)</td>
<td>0.69 (0.07-7.05)</td>
<td>0.52 (0.23-1.20)</td>
</tr>
<tr>
<td>Cesarean</td>
<td>0.55 (0.47-0.65)</td>
<td>0.50 (0.41-0.62)</td>
<td>0.23 (0.15-0.35)</td>
<td>0.54 (0.47-0.62)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1.23 (1.01-1.51)</td>
<td>1.37 (1.07-1.76)</td>
<td>1.01 (0.62-1.65)</td>
<td>1.33 (1.12-1.59)</td>
</tr>
<tr>
<td>Low birthweight infants</td>
<td>1.08 (0.90-1.30)</td>
<td>1.05 (0.83-1.33)</td>
<td>0.92 (0.58-1.47)</td>
<td>1.09 (0.93-1.28)</td>
</tr>
<tr>
<td>High birthweight infants</td>
<td>1.46 (1.04-2.03)</td>
<td>1.31 (0.85-2.02)</td>
<td>1.53 (0.65-3.59)</td>
<td>1.42 (1.05-1.92)</td>
</tr>
</tbody>
</table>

Data are OR (95% CI). Pauciparas (para 1-4) were used as the reference group.
Adjusted for maternal age, socioeconomic status, region of origin, and prenatal care utilization; odds ratios calculated using logistic regression models.
Addendum #1: Introduction

Definition of Grand Multiparity

The fetomaternal hazards of extreme parity have been vigorously debated for the past nearly 150 years in the scientific literature. While some attribute the term to the early French literature, Bethel Solomons is generally said to have first introduced the term “grand multipara” in the 1930s, correlating increased parity with pregnancy complications and describing a steady rise in maternal mortality in women with five to ten previous pregnancies. Shortly thereafter, Eastman demonstrated grand multiparity to be a risk factor for perinatal mortality as well. The term grand multipara is defined variably in the early literature as a woman having delivered at least four to eight prior late-term pregnancies. The International Federation of Gynecology and Obstetrics (FIGO) and more recent studies use a definition of parity of at least five. Another term, “great-grand multipara”, commonly refers to a woman who has delivered at least 10 prior term pregnancies. This latter term is more consistently applied throughout the literature than is grand multipara.

Methods

In order to identify relevant studies on the fetomaternal risks of grand multiparity, an abbreviated systematic literature review was conducted in the following manner. An electronic search of MEDLINE and other bibliographic databases (Web of Science, EMBASE, and CAB) was conducted in January 2010 using the keywords “parity”, “multipar*”, “grandmultipar*”, “pregnancy outcome”, “pregnancy complication”, “mortality”, “birth outcome”, “obstetric outcome”, and “fetal outcome”. A total of 1150 articles were identified using this initial strategy.
After reviewing the abstracts of these articles for relevancy and eliminating duplicates, approximately 120 full-text articles were selected for review. The search was not time-limited, and only articles published in either the English or French language with full text versions available (either electronic or hardcopy) were selected for review. Further studies, including those published prior to 1954 and not yet included in the MEDLINE database, were identified by hand searching the bibliographies of key articles. Several additional articles newly indexed to MEDLINE between January 2010 and June 2010 were also included by repeating the literature search strategy on a weekly basis.

A total of 163 articles were reviewed and critically appraised. An evidence table was constructed that contained relevant information from each of the studies, including the type of study design, sample size, comparison group used, outcomes evaluated, inclusion and exclusion criteria, statistical methods employed, confounders adjusted for, results, and study strengths and limitations. A screen shot of a portion of the evidence table is shown below.
Critical Appraisal

Maternal and obstetric risk

Numerous previous studies have highlighted the various maternal risks of grand multiparity, including maternal death, postpartum infection, uterine rupture, antepartum and postpartum hemorrhage, placental abnormalities, pre-eclampsia and eclampsia, other hypertensive disorders, and diabetes. Similarly, obstetric complications, such as malpresentation, prolonged labor and dystocia, increased rate of cesarean delivery, premature rupture of membranes (PROM), and cord prolapse have been linked to increased parity.

Writing from Scotland in 1865, Duncan is generally recognized to be the first to have linked high parity to maternal mortality, describing an increase in both maternal death and fatal postpartum infection rates with parity above nine, compared to the general obstetric population. Several decades later, Peckham and Solomons reviewed obstetric records from the U.S. and Ireland, respectively, and both described a dose-response relationship between parity and maternal death among multiparas (i.e., all women excluding nulliparas). Interestingly, Peckham excluded all referred emergency cases and limited observations to viable deliveries in an effort to better represent the U.S. child-bearing population at the time. Another large cross-sectional study from the U.S. observed a threshold effect at a parity level above eight, with those women at increased odds of maternal death. A higher rate of maternal death in women of parity ≥7 was also reported from a small retrospective study from Trinidad. In addition, a 1977 review of crude maternal mortality rates in the U.S. from 1919-1969 demonstrated that grand multiparas (parity above 6-7) surpassed nulliparas in terms of odds of maternal death.
With the exception of the 1977 study that employed bivariate methods, all of these early studies listed above were essentially descriptive in nature and failed to adjust for any important confounders such as maternal age and socioeconomic status. In 1955 Oxorn et al. looked at 1056 grand multiparas (defined here as parity ≥7) and linked grand multiparity to maternal death, postpartum infection, and postpartum hemorrhage. While this study did make an effort to stratify observations into two groups by maternal age, they failed to fully take other confounders into consideration in the analysis, and thus the potential for selection bias was high. In their 2005 large retrospective U.S. population-based cohort study, Yasmeen et al. were the first and only to document a significantly increased odds of maternal death in grand multiparas (defined here as parity 5-9) compared to pauciparas (para 2-4) even after adjusting for multiple confounders using multivariable analysis. Specifically, odds ratios were adjusted for maternal age, ethnicity (primarily Hispanic and non-Hispanic Caucasian), and payer type.

Preeclampsia and eclampsia are typically considered diseases of nulliparity, and even some very early studies, such as Peckham’s report from 1933, have failed to show an association between grand multiparity and eclamptic diseases. However, some authors have actually reported higher rates or odds of eclamptic diseases in grand multiparas. Writing in 1965, Israel and Blazar documented an increased risk of eclamptic disease in grand multiparas (defined as para ≥7) as compared to all other deliveries (para ≤6). Theirs was a mid-sized retrospective study using bivariate statistics, although observations were stratified by both maternal age (≤34 and ≥35) and race (African-American and Caucasian). While the authors also observed higher odds of other maternal complications (postpartum hemorrhage, uterine rupture, and placental abnormalities) in grand multiparas, there was no difference in maternal mortality, likely because
the overall low maternal mortality rate (0.05%) and relatively small sample size increased the likelihood of a type II error.

Another retrospective study from Australia in the late 1970s found an association between hypertension, preeclampsia, and grand multiparity (defined here as para ≥5). Although the study authors attempted to take maternal age into consideration by analyzing the bivariate relationship between maternal age and hypertension (which, at p=0.17, was not statistically significant), they acknowledged the need for larger sample size and multivariable modeling to definitively explore this association. In more recent years, a prospective Israel study concurred that grand multiparas (para ≥7) were at higher odds of preeclampsia than were pauciparas (para 2-6); these observations were stratified by socioeconomic status only. Finally, a small retrospective case control study in Jordan of great-grand multiparas (defined here as para ≥9) compared to pauciparas (para 1-4) also found unadjusted odds of preeclampsia to be higher in those women of higher parity. No studies have yet demonstrated a robust association between high parity and eclamptic disease upon multivariable analysis.

Postpartum hemorrhage is among the causes of maternal mortality that was earliest linked to increased parity. A number of small American studies have shown the odds of postpartum hemorrhage to increase with increasing parity. Although these were all based on descriptive statistics, Nelson et al. did note the rate of prenatal care utilization to be comparable between grand multiparas (defined as para ≥7) and the general clinic population, and the observations in their study were also almost uniformly African-American (95%). Another larger U.K. study described a similar rate of postpartum hemorrhage between grand multiparas (para ≥5) and other observations (para <5), but noted postpartum hemorrhage to be more severe in grand multiparas, as the rate of fetal death was significantly higher in grand multiparas with
this complication. As mentioned previously, Israel and Blazar also documented a higher odds of postpartum hemorrhage in grand multiparas (para $\geq 7$) than in other women (para $\leq 6$), after stratifying by age and race. Finally, a small retrospective case control study from Nigeria demonstrated an increased odds of postpartum hemorrhage in grand multiparas (para $\geq 5$) compared to age-matched paucipara controls (para 2-4).

Two additional studies identified high parity as a risk factor for postpartum hemorrhage, although neither was designed to study the association between parity and this complication specifically. Al-Kadri et al. reported a 17% adjusted increased risk of postpartum hemorrhage among women of higher parity in a small case-control study from Saudi Arabia. Similarly, a population-based study of post-partum hemorrhage in Zimbabwe found grand multiparas (para $\geq 5$) to have a 1.9 relative risk (RR) of post-partum hemorrhage (95% CI: 1.0, 3.5) than pauciparas (para 2-4), but this RR dropped to a non-significant 1.1 (95% CI: 0.49, 2.4) after adjusting for maternal age. Of note, both of these studies employed multivariable analysis to adjust for confounders, whereas the earlier studies listed above relied on either bivariate or, more commonly, simple descriptive statistical methods.

Uterine rupture is another serious obstetric complication and was one of the primary causes of maternal death in the majority of studies examined. A small retrospective study of poor Caucasian women in Kentucky found grand multiparas (para $\geq 7$) to be at higher odds of several obstetric complications, including uterine rupture, than either pauciparas (para 0-3) or the rest of the obstetric population (para 0-6). While statistical analysis was limited to bivariate tests, observations were also stratified by maternal age. A similar study from South Africa reached the same conclusions, although these authors did not stratify or otherwise account for differential
maternal age distribution. The study by Israel and Blazar also documented a higher odds of uterine rupture in grand multiparas (para ≥7) after stratifying by age and race.10

A case series of 133 uterine ruptures between 1958 and 1960 found that women of higher parity (para ≥3) were three times as likely to have traumatic uterine rupture as women of lower parity (para 0-2), and ten times as likely to have spontaneous uterine rupture.47 Statistics were purely descriptive, and no effort was made to account for any confounders in the analysis. Two additional small studies focusing on uterine rupture, one a retrospective case series from Kuwait and the second a prospective case control study from Nigeria, also associated uterine rupture with grand multiparity.50-51 One Israeli study comparing obstetric outcomes in great-grand multiparas (para ≥10) to those in other grand multiparas (para 6-9) found great-grand multiparity to be an independent risk factor for uterine rupture after adjusting for maternal age.70 However, these conclusions were based on data from a single clinic, and the different control group (grand multiparas rather than pauciparas or the general obstetric population) limits the external validity of this study.

Comparatively more has been written on the association between placental abnormalities and grand multiparity. Placental abnormalities typically include placenta previa, placental abruption, retained placenta, and various composite outcome definitions. As early as 1933, Peckham commented on the high prevalence of placenta previa in his large retrospective study, stating that “previa is not only a disease of multiparity but essentially one whose incidence increases in direct relation to parity.”43 Eastman also partially attributed the increased risk of maternal death in women of parity above eight to higher rates of placenta previa.35 A Finnish study in a high-risk population found higher odds of placental abnormalities (previa, abruption, and retained placenta each considered separately) in grand multiparas (para ≥7) than in the rest
of the observations (para ≤ 6) after stratifying by maternal age. In this same study, the difference between the two groups was not statistically significant for either uterine rupture or maternal mortality, although the rates of those two outcomes were probably too low to meaningfully compare. A descriptive French study also concluded that placental abnormalities (low placenta and retained placenta, considered separately) were more common in grand multiparas.32

A small retrospective cohort study from Norway concluded that women of higher parity (para ≥ 4) had a tendency towards delivering preterm infants due to higher rates of placenta previa and placental abruption.57 This study was limited by small sample size and bivariate analysis. Brunner et al. out of Saudi Arabia reported on one of the only prospective case control studies on grand multiparity, concluding that grand multiparas (para ≥ 4) were at higher risk of placental complications than were pauciparas (para 1-2).12 Although the analysis was only bivariate, paucipara controls were age-matched and the study population was a socioeconomically homogenous group with uniform free access to medical care (including prenatal care).

The interactions between age, parity, and placental abnormalities have been addressed by a few studies. A case series of 219 severe placental abruptions from Ireland found grand multiparity (para ≥ 5) to be a risk factor for severe abruption only in women over the age of 40. However, although the study authors used multivariable analysis to adjust for maternal age, they failed to adjust for differential socioeconomic status, despite the fact that there was a higher rate of abruption in the lower socioeconomic group and that parity was differentially distributed among socioeconomic groups.11 In contrast, a more recent population-based prospective study in
Nova Scotia found higher parity (para ≥3) to be a risk factor for placenta previa and placental abruption only in younger women (< 35 years).\textsuperscript{13}

A U.S. study on placenta previa determined that while age over 30 was a stronger risk factor for previa, grand multiparity (defined as para ≥4) also independently conferred an odds ratio of 1.7 relative to the nullipara control group.\textsuperscript{60} This was a well-designed study that adjusted for a large number of potential confounders, including race, education, socioeconomic status, previous cesarean delivery, smoking status, fetal gender, and maternal age. In contrast, a smaller case control study on placenta previa from Jordan found previa to be associated with higher parity (para ≥3) but not with increasing maternal age.\textsuperscript{58} No adjustment for confounders was made in this latter study.

A small study comparing a wide variety and large number of adverse birth outcomes in great-grand multiparas (para ≥10), other grand multiparas (para 5 -9), and pauciparas (para 2-4) found placental abruption to be more common in women of the highest parity (great-grand multiparas).\textsuperscript{1} Although all women were over 35 and of similar socioeconomic status, no adjustment for confounders was attempted, and the authors also failed to adjust for multiple testing. Finally, a small Finnish retrospective case control study of placenta previa identified grand multiparity as an independent risk factor for previa, with an impressive adjusted odds ratio of 5.8.\textsuperscript{62} Although this study was able to adjust for a large number of maternal demographics and comorbidities, and carefully defined placenta previa, grand multiparity was not defined, making comparison to other studies difficult.

In contrast to the above summary of studies, more recent literature, primarily from more developed countries like Israel\textsuperscript{79-81}, Finland\textsuperscript{21, 56} and Hong Kong\textsuperscript{82}, have challenged the assertion that grand multiparity entails maternal hazards. A small Israeli study of great-grand multiparas
(para ≥10) from 1968 concluded advanced parity to be “an obstetric challenge but not a prohibitive risk.” Two decades later, a slightly larger study of grand multiparas (para ≥6) in the same country concluded grand multiparity was not an obstetric risk factor in a healthy and economically stable population with good obstetric care. The assertion that women of higher parity who receive good perinatal care are “basically healthy” was reiterated by another Israeli study in great-grand multiparas (para ≥9) compared to multiparas (para ≥2).

One common limitation of all of the above three studies is sample size and a susceptibility for type II error. For example, even a larger Finnish study that was enriched in a high-risk obstetric population failed to make any meaningful conclusions on maternal mortality and uterine rupture due to low complication rates. An interesting longitudinal cohort study of great-grand multiparas (para ≥10) in Finland with their prior deliveries used as controls again concluded that extremely high parity was not a major problem with good prenatal and obstetric care. Finally, a small retrospective cohort study from Hong Kong comparing obstetric outcomes in grand multiparas (para ≥5) to overall hospital rates reached the same conclusion that grand multiparity was not a significant maternal risk factor with modern medical care. There were no cases of maternal mortality in this study.

Fetal and neonatal risk

Grand multiparity has also been associated with specific fetal and neonatal risks, including increased rates of stillbirth, neonatal death, spontaneous abortions, low birthweight or prematurity, increased birthweight or macrosomia, neonatal jaundice, low APGAR scores, and fetal malformations. Increased parity is also a well-established risk factor for multiple births.
While grand multiparity was linked to maternal mortality in the scholarly literature as early as the 19th century, in an impressively large retrospective cross-sectional study, Eastman et al. first demonstrated grand multiparity to be a risk factor for perinatal mortality in 1940. Perinatal mortality is a composite term that includes both stillbirths and neonatal deaths. A decade later, another smaller study confirmed this association between stillbirth rates and higher parity. Although this second study did attempt minimal stratification by maternal age, both relied on descriptive analysis, as did Miller’s study of grand multiparas (para ≥6) in 1954 that showed the stillbirth rate to increase in the higher parity brackets. Miller, however, should be credited for providing a comprehensive methods description compared to his contemporaries, as well as for increasing his study’s external validity by including some midwife-assisted home births among his observations.

Another Canadian study in 1955 reinforced the association between grand multiparity (para ≥7) and fetal death after stratifying by maternal age, although the overall fetal mortality rate dropped from 15% to 9% over the 20-year period from which the study derived data. There was no attempt to evaluate the presence of temporal bias in this study. The previously-cited study by Nelson et al. also found twice the stillbirth rate in grand multiparas (para ≥7) than in the general clinic population in a uniformly poor, African-American population with non-differential prenatal care access. Baird et al. examined the causes of so-called “obstetric deaths” (roughly equivalent to perinatal deaths but only including stillbirths and neonatal deaths within the first week of life) via autopsy and found the mortality due to prematurity or low birthweight to be highest in young grand multiparas (para ≥3). However, the authors were again unable to adjust for socioeconomic status, and acknowledged the possibility that most of the young multiparas were also from lower socioeconomic classes, which would mean significant selection bias.
More recent studies, while variable and flawed in some ways, have continued to demonstrate an association between higher parity and perinatal death. A 1989 population-wide survey of all grand multiparas (para ≥6) delivering in Israel hospitals over a three month period linked grand multiparity to perinatal death, although the latter term was not defined and all deaths beyond 26 weeks of gestation were included (versus the more common cut-off point of 28 weeks gestation).

No true adjustments for confounders were made, but the authors ran bivariate tests to evaluate the association between the outcomes evaluated and maternal age, and determined maternal age to be partially responsible for the link between parity and perinatal death. This study included records from 30 different facilities, which while increasing the external validity of its findings also makes this study more susceptible to measurement bias due to the heterogeneous outcome and covariate definitions used and the differential distribution of grand multiparity among the facilities.

Another study based on 30 years of obstetric records from a single Canadian institution primarily highlighted the risk of fetal death with increased maternal age, but also documented an (unadjusted) odds ratio of 1.7-1.8 in women of higher parity (para ≥3), with a 30-year-old para 1-2 within medical risk factors as the reference group. The study population was overwhelmingly white and had access to prenatal care, but was socioeconomically diverse; no comment was made on any association between parity or maternal age and the outcome of interest. In contrast to most previous studies, cases of perinatal deaths were robustly defined, with autopsies performed in 97% of deaths. In 2005, a hospital-based Saudi cohort of stillbirths identified grand multiparity (para ≥5) as one of many factors independently associated with unexplained fetal deaths, with an odds ratio of 1.19.
One of the most robust studies of perinatal outcomes, a large population-based cross-sectional study of more than 500,000 grand multiparas (para 4-8) in Australia found grand multiparas to be at higher odds of perinatal death (and of a questionable composite outcome “obstetric complications”) even after adjusting for maternal age, smoking status, and socioeconomic status on multivariable analysis. While women of parity \( \geq 9 \) were excluded, thus limiting the generalizability of the study findings to great-grand multiparas, one strength of this study was the ability to capture all deliveries, including out-of-hospital births assisted by midwives. A second population-based study, this one from the U.S., also found a 1.5 odds of perinatal death after adjusting for multiple confounders (maternal age, ethnicity, source of payment, among others). A third well-designed study that also adjusted for confounders on multivariable analysis documented a dose-response relationship between high parity (para \( \geq 5 \)) and stillbirth rates, particularly in great-grand multiparas (para \( \geq 10 \)). Unlike most previous studies, this last study was well-powered enough to allow meaningfully commentary on this subpopulation of great-grand multiparas.

In a rare early study originating from Africa, a large retrospective cohort study from Sudan published in 1980 also found the rate of both stillbirth and neonatal death to be higher in grand multiparas (para \( \geq 6 \)) than in pauciparas (para 2-4). While unadjusted for confounders, these results have perhaps the best current external validity of any study in light of the fact that grand multiparity now remains most relevant on a population level in Africa. A more recent retrospective case-control out of Nigeria limited to gestations \( \geq 28 \) weeks found an increased odds of perinatal death in grand multiparas (para \( \geq 5 \)). However, confounders were not adjusted for beyond the use of age-matched controls.
A few studies have examined sets of sibships rather than general obstetric records. In his classic 1968 paper on stillbirth and birth order, James documented a higher risk of stillbirth above parity of three within sibships, but noted the strong possibility that maternal age and socioeconomic status confounded this association. An Israeli study of 657 sibships determined grand multiparity (para \( \geq 7 \)) to be a risk factor for stillbirth but not for low birthweight. Although they only used bivariate statistics, the study population \textit{a priori} included a subpopulation of 97 sibships from a socioeconomically and racially homogenous ultraorthodox community; results were identical in this subpopulation to those in the overall study population.

Higher parity has also been associated with fetal morbidity, most notably abnormal neonatal birth weight. An early French study suggested the presence of an association between higher parity (para \( \geq 6 \)) and prematurity. At that time, prematurity was defined by the size or weight of the infant, thus the more contemporary interpretation of their outcome would be low birthweight. Reporting in 1955, Petry et al. did not find low birthweight to be more common in grand multiparas (para \( \geq 7 \)) among poor Kentucky whites, but did find this complication to carry a higher neonatal mortality rate in grand multiparas. Low birthweight was significantly more common in grand multiparas (para \( \geq 5 \)) from a small retrospective Nigeria study, but no adjustment for confounders was made to strengthen this conclusion. The best evidence for an association between high parity and low birthweight comes from a U.S. epidemiologic study by Aliyu et al. that documented a dose-response relationship between high parity and proportion of low birthweight infants after adjusting for multiple confounders. The authors suggested that higher parity might work by shortening gestation rather than by physical size restriction (i.e., small for gestational age). In contrast to the above reports, the well-done Israeli sibship study from 1987 described earlier did not find low birthweight to be associated with grand multiparity.
Although birthweight data in this study was collected retrospectively by maternal recall, the validity of this measurement was tested in a subgroup and found to be accurate within 200 grams in 87% of cases.

Perhaps paradoxically, grand multiparity has also been linked to high birthweight or macrosomia. In fact, some studies have shown grand multiparas to be at higher odds of having both low and high birthweight infants (i.e., to be less likely to have normal weight infants). As early as 1952, an impressive multivariable analysis from the U.K. showed a positive correlation between birthweight and parity, best observed after adjusting for maternal age, which was negatively correlated with birthweight. A more recent U.S. prospective case-control study compared mostly Hispanic grand multiparas (para 5-10) to age-matched pauciparas (para 2-4), and found a higher odds of macrosomia at 1.58 ($P < 0.03$) in grand multiparas. However, this study was primarily designed to compare intrapartum complications, and the authors did not adjust for prenatal care or socioeconomic status despite demonstrating that these variables were differentially distributed among parity groups. Some of the best evidence for a higher risk of macrosomia comes from an interesting longitudinal cohort study from Finland that used patients as their own controls through parity stages and found birth order to be an independent predictor of birthweight even until the tenth delivery. Women of parity $\geq 12$ were excluded due to small sample size. Acknowledging the risk of temporal bias in light of the 20-year study period, the authors adjusted birthweight for the secular trend and showed this positive association between parity or birth order and birthweight to be robust.

As with maternal risk, the validity of these feto-neonatal risks has also been challenged in more recent years, with authors highlighted the confounding effect of differential socioeconomic status and prenatal care on assessing feto-neonatal morbidity and
mortality outcomes in grand multiparas. Authors of an Israeli review even went so far as to say “the term dangerous multipara should be removed from the medical literature,” citing problems with selection bias in previous studies that showed an increased risk in grand multiparas. 

A small prospective Saudi study from 1992 found no difference in perinatal mortality rates between grand multiparas (para ≥4) and age-matched paucipara controls (para 1-2) with similar prenatal care utilization patterns. The same study did find a higher frequency of placental complications in grand multiparas, and with an overall perinatal mortality of less than 1%, this first finding could be attributed to a type II error. Another slightly larger prospective study from Israel found no difference between perinatal mortality and low birthweight rates in grand multiparas (para ≥7) and pauciparas (para 2-6) after stratifying by socioeconomic status, arguing instead that these outcomes correlated with low socioeconomic status and thus could be solely explained by adjusting for this confounder. A third study from the United Arab Emirates comparing great-grand multiparas (para ≥10) to other grand multiparas (para 5-9) and pauciparas (para 2-4) concluded that extreme grand multiparity was not a risk factor for adverse perinatal outcomes in a setting with favorable socioeconomic conditions and prenatal care. While this study was relatively well powered compared to previous ones in the great-grand multipara population, the authors did not attempt a dose-response analysis and attributed the increase in stillbirth rate among great-grand multiparas to so-called “defaulters” who did not seek adequate prenatal care. In fact, their own data suggested that great-grand multiparas had 3.56 times the odds of stillbirth than pauciparas (95% CI: 1.49-8.51).

The above reports concur with a retrospective Australian study from 1977 that reported that the stillbirth rate was not higher in grand multiparas (para ≥5) than in the rest of the obstetric population (para 0-4). Another earlier small Saudi study reached the same conclusion. Of
note, both of these studies pooled primiparas (i.e., para=0) with pauciparas as the comparison group, which likely resulted in a bias towards the null.

Lastly, an interesting Israeli study compared perinatal outcomes in grand multiparas (para ≥7) from low socioeconomic background to another group of grand multiparas coming from a high socioeconomic background, and cited the finding that the latter group had significantly better neonatal morbidity and mortality indices as evidence that the “environment” of the grand multipara (i.e., low socioeconomic status) explained any independent risk attributed to this factor, rather than an inherent biological mechanism. Although these findings demonstrate the need to account for the confounder of socioeconomic status, they do not necessary negate the possibility of grand multiparity as an independent risk factor. Furthermore, it is unclear how well these findings can be generalized to other contexts beyond Israel.

**Summary**

Several discrete challenges exist in interpreting and comparing the body of literature on the fetomaternal risks of high parity. First, the definition of grand multiparity (or high parity) varies widely from parity above three to parity above eight. Great-grand multiparity is more consistently taken to mean parity above ten, but some studies instead use parity above nine as a definition. Second, outcome definitions used are not consistent across studies, and in fact many studies fail to adequately define the outcomes used. Third, the comparison group is not consistent across studies. Fourth, interpretation of many studies, particularly in the light of specific adverse outcomes, is complicated by the fact that most were not designed to answer specific questions, but rather sought to explore the association between high parity and adverse birth outcomes in
general by testing a wide range of separate negative outcomes, often upwards of 20+. None of the studies mentioned adjusting for multiple testing.

In general, studies reaching the conclusion that grand multiparas are at higher odds or risk of adverse fetomaternal outcomes than are women in the comparison group were more likely to be susceptible to selection bias by virtue of the fact that potential confounders were differentially distributed between parity groups and unaccounted for by either study design or analysis. Issues of measurement bias apply to the vast majority of studies that are retrospective or cross-sectional in nature, particularly those that pooled and analyzed data from more than one source. The direction of this bias is very difficult to ascertain with the minimal information provided in most method sections.

Studies tending towards the null hypothesis were often limited in sample size, making valid conclusions about rare outcomes like mortality and uterine rupture difficult. On the other hand, recent large-scale studies have documented a persistent link between grand multiparity and fetomaternal risk even after accounting for confounders in multivariable analysis.\textsuperscript{3, 16-17, 19} For example, a cross-sectional study of more than 500,000 women from Australia did find those with \( \geq 4 \) prior pregnancies to be at higher risk of obstetric complications even after adjusting for confounders.\textsuperscript{17} The inclusion of primiparas in the comparison group was another common limitation of studies reaching the null hypothesis due to type II error.

In addition to the threats to internal validity mentioned above, it is particularly important to note the generalizability of studies on grand multiparity given the diversity of contexts in which grand multiparas currently give birth. In particular, very few studies have been completed using data from the African continent. While per-woman fertility rates below three in the U.S. and other middle and high income countries have made grand multiparity seem to be a
“disappearing” risk factor, it remains highly relevant on a population level in most African countries where the average total fertility rate is above five.\textsuperscript{23}

A comprehensive review published in 2005 cited widespread problems with conflicting evidence, heterogeneous outcome definitions, and poor study design, but did find evidence for a higher risk of medical complications and placental pathologies among women of extreme parity, in addition to sufficient evidence for increased birthweight in infants born to grand multiparas.\textsuperscript{2} Since that review was released, more substantial evidence for perinatal mortality and morbidity risk in grand multiparas has been released, but is far from conclusive.

**Research Question**

Despite the large number of studies conducted in a variety of countries and populations, the globally insufficient and conflicting nature of the data necessitates the dissemination of well-powered and well-designed studies from the developing world where grand multiparity is most relevant today.

The primary research objective of the present study was to determine whether grand multiparity is independently associated with maternal and perinatal mortality. The secondary research objective was to determine whether grand multiparity is independently associated with fetomaternal morbidity (specifically, placental abnormalities, obstetric complications, and abnormal neonatal birth weight). To that end, the PICO (population, intervention, comparison, and outcome) formatted research question was the following: **In pregnant Malian women delivering at Point G National Hospital between 1985 and 2003, are the odds of specific perinatal morbidity and mortality outcomes higher in grand multiparas (para ≥5) than in pauciparas (para 1-4)?**
Addendum #2: Discussion

Despite its flaws, the present study is significant in that it represents the largest published study of grand multiparas in Africa to date and the only to employ multivariable analysis (MEDLINE; 1952-July 2010; search terms: “grand multipar*” AND [“pregnancy outcome OR pregnancy complications”]). The four main conclusions of this study are as follows:

1. Grand multiparas are at higher odds of perinatal death than are pauciparas
2. Grand multiparas are at higher odds of placental abnormalities than are pauciparas
3. Grand multiparas are at higher odds of high birthweight than are pauciparas
4. Pauciparas are at higher odds of maternal death than are grand multiparas

In this study, grand multiparas had a 33% increased odds of perinatal death and a 59% increased odds of placental abnormalities over those in pauciparas. These two findings are related. Yasmeen et al. also found grand multiparas (para 5-9) to be at higher adjusted odds of both placental abruption (odds ratio 1.3) and perinatal death (odds ratio 1.5) than pauciparas (2-4), even after taking maternal age, ethnicity, and payment source into account on multivariable analysis. This U.S. study was conducted in a very different population yet reached nearly identical conclusions, suggesting that our findings may complement and increase the generalizability of that study. Moreover, another large population-based study from Australia also concluded that grand multiparas (para 4-8) were at higher odds of perinatal death (odds ratio 1.21, 1.20, 1.30, and 1.56 for parity=4, 5, 6, and 7-8, respectively) after adjusting for multiple confounders. Although both of these population-based studies excluded great-grand multiparas, a recent U.S. epidemiologic study was well-powered enough to demonstrate a true dose-response relationship between extreme parity (para ≥10) and stillbirth. Thus, this study confirms and
extends the generalizability of previous findings linking grand multiparity to perinatal mortality and placental abnormalities to the African context where grand multiparity is most relevant today.

Increased parity has already been hypothesized to increase a woman’s risk of developing placenta previa via changes in uterine blood flow patterns. This pathophysiology is similar to that by which maternal age increases previa risk, implying that young multiparas may in fact prematurely age their uterus through repeated deliveries, as suggested by Palliez et al. in 1971. Placental abruption in women of higher parity is traditionally thought to be mediated by hypertension, but this study suggests otherwise. As early as 1968, De Valera demonstrated hypertension to be less important to the etiology of severe placental abruption in grand multiparas with in women of lesser parity. Similarly, in this study, high blood pressure readings at the time of hospital admission were not associated with placental abruption. An alternative pathophysiological pathway must then explain the strong independent association between grand multiparity and placental abruption. Interestingly, a prospective study of placental abruption and perinatal death from 1977 identified growth retardation patterns in the deceased fetuses and neonates consistent with antenatal undernutrition, which may reflect maternal nutritional deficiencies. The same authors (Naeye et al.) conducted a similar study in Ethiopia and found the same evidence of undernutrition in that context, in addition to documenting an association between maternal poverty and fatal abruptions.

Nutritional deficiencies or abnormalities may mediate the interaction between high parity and placental abruption via a number of different pathways. First, poverty or low socioeconomic status is likely a significant confounder, as highlighted by the second study by Naeye et al. described above. Grand multiparas are typically both of lower socioeconomic status and more
apt to suffer from severe placental abruption. However, the persistent and robust association between abruption and high parity, which was confirmed on dose-response analysis, suggests other factors may be at play. Grand multiparity may directly deplete nutritional stores by virtue of the cumulative impact of breastfeeding and childbearing on the body. This interaction may be confounded by a shortened birth interval in grand multiparas compared to non-grand multiparas. Finally, grand multiparity may indirectly contribute to maternal undernutrition if these women intentionally divert increasing proportions of the household food source to their offspring and thus consume diminishing calories themselves. This last mechanism may be specific to the Malian or African context, or at the very least may likely contribute less to the etiology of placental abruption in grand multiparas from the higher socioeconomic classes.

The correlation between placental abnormalities and perinatal mortality was clear in our population, as more than half (50.9%) of the pregnancies with placental complications ended in perinatal death in this study. These findings mirror those of Oron et al., who determined both grand multiparity (para $\geq 5$) and placental abruption to be independent risk factors for antepartum fetal death (i.e., stillbirth). Those authors hypothesized that placental abnormalities were more likely to be a direct cause of death (via both acute and chronic mechanisms), and grand multiparity was more likely to be a risk factor in part mediated by placental abnormalities. More work is needed to establish a causal and temporal relationship between high parity (or late birth order), placental abnormalities (notably abruption), and perinatal mortality.

Grand multiparity was also independently associated with high birthweight, with grand multiparas shown to be 42% more likely than pauciparas to deliver high birthweight infants. This compares to an unadjusted 58% increased odds of macrosomia in the study by Toohey et al., which used the same cut-off of para $\geq 5$ for defining grand multiparity. As noted in the first
addendum, two other studies have also associated grand multiparity with high birthweight. It is difficult to compare our findings numerically to those of Juntunen et al. because they evaluated birthweight as a continuous variable only, rather as a dichotomous variable as we did in our study. High birthweight clearly correlates with perinatal mortality, but whether this association is either directly or indirectly causal in nature remains to be determined.

In a surprising twist, this cross-sectional study demonstrated that paucipara mothers were actually 52% more likely than grand multiparas to die during or shortly after pregnancy. As discussed in the first addendum, several studies have documented an increased odds of maternal death in grand multiparas, and others have shown no association between high parity and maternal death (although many of these had a tendency towards type II error). The present study is actually the first study to demonstrate a statistically significant negative association between grand multiparity and maternal death, likely because no previous studies that adjusted for multiple confounders have been done in a study population that is large and high-risk enough in which to meaningfully evaluate maternal mortality rates.

Hogan et al. recently reported in the Lancet that substantial progress has been made towards reducing global maternal mortality rates. In that article’s discussion section and in the accompanying editorial, much emphasis was placed on the presumed causal association between high parity or high fertility rates and maternal mortality on a population level as a means of explaining this decrease in maternal mortality rates. The present study does not support a causal etiology between high fertility and maternal mortality, and in fact reveals the true association between high parity and maternal mortality to be negative in nature. Instead, the correlation between reductions in parity and reductions in maternal mortality observed by Hogan
et al. is likely mediated by socioeconomic advancement or development on a population level in these countries.

It is important to note that the findings of the present study do not negate the fact that most grand multiparas in Mali – as elsewhere – remain poorer, older, and less likely to access prenatal care than are other women. Thus, while reducing parity rates uniformly across a cross-sectional of the population would not be expected to have a favorable impact on maternal death rates, reducing parity rates disproportionally among poorer women who are less likely to access prenatal care would in fact likely reduce population-wide maternal death rates. Interpretation of this study finding should thus be done cautiously.

One of the principal limitations of this study was the inability to meaningfully compare birth intervals between parity groups. Previous authors have hypothesized that grand multiparity may be a proxy risk factor for an abbreviated birth interval. In his classic 1968 study on stillbirth, neonatal death and birth intervals, James associated stillbirths with long birth intervals (within sibships) and neonatal deaths with short birth intervals (also within sibships). He also highlighted the potentially strong confounding role of parity, maternal age, social class, and previous stillbirths or unrecognized spontaneous abortions. In a companion paper, he even suggested that “women who are predisposed to produce stillbirths (may) have more pregnancies than other women on the average” or, in other words, “stillbirth-prone women are more fertile than others.” Or, as other authors have suggested, women who experience a perinatal death may elect to continue childbearing sooner than those with a successful first outcome, which over time would mean that perinatal death motivates women to effectively become grand multiparas.
This study is also limited by study design. Observational cross-sectional studies such as the present one are potentially subject to measurement and temporal biases, among others. For obvious reasons, however, experimental studies are not possible in addressing the principal research question of interest here, as it is neither ethical nor feasible for researchers to assign women to parity groups for the purpose of a study. Longitudinal or sibship studies, whether prospective or retrospective, have the potential to better control for selection bias and evaluate the true etiology behind any association between increased parity and placental abnormalities and/or perinatal death. Previous authors have cautioned against drawing interpretations from large pooled datasets and rather highlighted the need to evaluate data from individual sibships. However, with the exception of two small retrospective longitudinal studies, both of which collected data on past deliveries using maternal recall, such sibship studies are rare in the literature.

One of the population-level implications of this study’s findings is an impetus to reduce the proportion of grand multiparas as a means of reducing overall perinatal mortality. If this reduction is accomplished by disproportionally reducing the parity levels among poor grand multiparas not typically accessing prenatal care, maternal mortality rates may react favorably. Prospective obstetric registries in Mali and other countries may help determine whether an intervention to reduce parity rates accomplishes its objective with regard to perinatal mortality rates. Further research opportunities range from exploring the risks and benefits of screening for placental abnormalities in grand multiparas, to understanding the pathophysiological basis of an association between increased parity, placental abnormalities (both previa and abruption), and perinatal death.
Bibliography


