The risk of stillbirth and infant death stratified by gestational age in women with gestational diabetes

Melissa G. Rosenstein, MD; Yvonne W. Cheng, MD, MPH; Jonathan M. Snowden, PhD; James M. Nicholson, MD; Amy E. Doss, MD; Aaron B. Caughey, MD, PhD

OBJECTIVE: We sought to compare the different mortality risks between delivery and expectant management in women with gestational diabetes mellitus (GDM).

STUDY DESIGN: This is a retrospective cohort study that included singleton pregnancies of women diagnosed with GDM delivering at 36-42 weeks’ gestational age in California from 1997 through 2006. A composite mortality rate was developed to estimate the risk of expectant management at each gestational age incorporating the stillbirth risk during the week of continuing pregnancy plus the infant mortality risk at the gestational age 1 week hence.

RESULTS: In women with GDM, the risk of expectant management is lower than the risk of delivery at 36 weeks (17.4 vs 19.3/10,000), but at 39 weeks, the risk of expectant management exceeds that of delivery (relative risk, 1.8; 95% confidence interval, 1.2–2.6).

CONCLUSION: In women with GDM, infant mortality rates at 39 weeks are lower than the overall mortality risk of expectant management for 1 week; absolute risks of stillbirth and infant death are low.

Key words: expectant management, gestational diabetes, infant mortality, stillbirth


Gestational diabetes mellitus (GDM) affects 5-7% of pregnancies in the United States, and in 2005 was diagnosed in 5.3% of all California pregnancies.1 This condition is characterized by newly recognized hyperglycemia occurring in pregnancy, and is associated with an elevated risk of macrosomia, shoulder dystocia, hypoglycemia, cesarean delivery, and future maternal type 2 diabetes, among other maternal and neonatal morbidities.2,3 When O’Sullivan et al4 first recognized this condition in the 1960s, they observed an increased incidence of stillbirth among women with GDM who were undiagnosed or suboptimally treated. Subsequent early studies and those in the developing world have also demonstrated an increased risk of stillbirth associated with GDM.5,6 As screening, diagnosis, and treatment of GDM have become more widespread, however, the association between GDM and perinatal mortality has become less clear. More recent studies in Italy, Israel, and Sweden report a lack of association.7,8 Due to this conflicting evidence, there is continuing controversy about the optimal timing of delivery for women with GDM.9

When considering the optimal time for delivery to improve perinatal outcomes, the risk of stillbirth must be weighed against the risk of neonatal and infant morbidity and mortality. While GDM has been shown to be associated with macrosomia and neonatal hypoglycemia, this has not consistently been shown to contribute to higher neonatal and infant death rates.8 Although some studies find that macrosomia is independently associated with increased mortality,7 other data suggest that neonates born large for gestational age actually have a lower postneonatal death rate when compared with neonates who were average for gestational age or small for gestational age.10,11 Thus, examining only short-term morbidities may not fully account for the true mortality risk associated with GDM.

We have previously demonstrated in a large dataset of California births that using a novel composite mortality calculation to estimate the risk of expectant management at term can be useful in quantifying the risks faced by a pregnant woman and her care provider when trying to determine the optimal time of delivery.12 In this study, we...
apply this novel methodology to the specific subpopulation of women with GDM to determine their optimal delivery time from a mortality perspective.

**Materials and Methods**

We designed a retrospective cohort study of singleton births to women diagnosed with GDM identified through the California Vital Statistics Birth Certificate Data linked with the California Patient Discharge Data as well as Vital Statistics Death Certificate Data and Vital Statistics Fetal Death File from 1997 through 2006. Linkage of data was performed by the California Office of Statewide Health Planning and Development Healthcare Information Resource Center under the State of California Health and Human Services Agency. The resultant linked datasets include maternal antepartum and postpartum hospital records for the 9 months prior to delivery and 1 year postdelivery as well as birth records and all infant admission and re-admissions occurring within the first year of life. Linkage for the mother/baby pair was achieved using the “record linkage number,” an alphanumeric encrypted code unique to the mother and the baby. Institutional review board approval was obtained from the Committee on Human Research at the University of California, San Francisco; the institutional review board at Oregon Health and Science University; and the California Office of Statewide Health Planning and Development and the Committee for the Protection of Human Subjects. The reporting of births and deaths in California is nearly 100% complete and the California Health and Human Services Agency performs rigorous statistical quality checks. Since the linked dataset did not contain potential patient privacy and identification information, informed consent was exempted.

Women with a diagnosis of GDM were identified using the International Classification of Diseases, Ninth Revision (ICD-9) codes. ICD-9 codes used for the identification of GDM include: 648.8, 648.80, 648.81, 648.82, 648.83, and 648.84. We excluded women with a diagnosis of prepregnancy diabetes mellitus using ICD-9 codes: 648.0, 648.01, 648.02, 648.03, and 648.04. These ICD-9 codes were taken from maternal medical records but do not specify how or when the diagnosis of GDM was made. The California Diabetes and Pregnancy Program, administered by the California Department of Health, oversees the diagnosis and management of most pregnant women with diabetes in the state. During the time frame that these patients were cared for, they recommended, at a minimum, universal screening of GDM with a 1-hour 50-g glucose challenge test, followed by a 3-hour 100-g glucose tolerance test if the screening value was >140 mg/dL. Other exclusion criteria were multiple gestations and births with congenital anomalies as determined by diagnosis codes on the birth certificate and the infant’s medical record (ICD-9 codes Q00-Q99).

In this database, length of gestation in days was calculated by subtracting the date of last normal menstrual period (LMP) from the date of birth of the linked infant. If a negative value was obtained, 1 year was subtracted from the date of LMP and the interval was recomputed. Gestational age was then converted into weeks and treated as an ordered categorical variable. If date of LMP was missing or was nonsensical, the mother/infant pair was excluded from analysis. For this study, we included births between 36-42 completed weeks; 36 weeks’ gestational age included births ranging from 36 weeks and 0 days to 36 weeks and 6 days; and 42 weeks’ gestational age included births from 42 weeks 0 days to 42 weeks 6 days.

The purpose of this study was to compare the mortality risks (including both stillbirth and infant death) associated with delivery at a given week of gestation, as compared to expectant management (ie, continuing the pregnancy for another week and then delivering 1 week later). More specifically, the mortality risk of delivery at a given week was defined as the rate among those infants born at that week of gestation. The mortality risk of a week of expectant management was defined as the risk of stillbirth over that week plus the mortality risk experienced by infants born in the subsequent week of gestation. This comparison was made at varying gestational ages among women with GDM. Neonatal death (death within 28 days of birth) has typically been the metric included in estimates of perinatal death rates, but recent data demonstrate that term infants who die within the first year of life are more likely to do so in the postneonatal period (age 29-365 days of life) per 10,000 perinatal deaths than in the neonatal period. Infant mortality has also been shown to vary with gestational age at term and share many of the same risk factors as stillbirth. Thus, infant death was examined because of its significant magnitude and persistent association with gestational age at delivery. The incidence of stillbirth at a given gestational age was calculated as the number of stillbirths at that gestational age per 10,000 ongoing pregnancies. Infant mortality at each gestational age was calculated as the number of infants born at this gestational age who die within 1 year of life per 10,000 live births at that same gestational age. The composite risk of expectant management for 1 week represents the sum of the probabilities of stillbirth during a given week of gestation plus the probability of infant death when birth occurs the following week. This composite risk of expectant management was then compared to the risk of infant death in the prior week of gestation to compare risk of delivery vs expectant management.

Our calculations rely on the following assumptions:

1) The risk of infant death has a uniform distribution throughout the week of gestation.
2) When estimating the risk of delivering at a particular gestational age, the fetus is not at risk for stillbirth beyond that gestational age, therefore mortality risk in that week is equal only to the risk of infant death.
3) The composite risk associated with expectant management is the sum of the risk of stillbirth during the week of gestation plus the risk of infant death in the following week of gestation.

Statistical calculations were performed with Excel (version 14.1.4; Microsoft Corporation, Redmond, WA).
RESULTS

Our dataset included 4,190,953 nonanomalous deliveries from gestational ages of 36-42 weeks, including 193,028 deliveries to women with GDM. Women with GDM were more likely to be older, be Latina or Asian rather than white or African American, and carry a diagnosis of chronic hypertension. There was a slight decrease in gestational age at delivery (38.8 vs 39.1 weeks) and a slight increase in birthweight at delivery (3475 vs 3415 g) (Table 1).

The risk of stillbirth increased continuously with gestational age in women with and without GDM, rising to its highest level at 42 weeks of gestation. The risk of neonatal and infant death displayed a U-shaped curve, highest at 36 weeks and decreasing to a nadir at 39-40 weeks in both the women with and without GDM before increasing again at 41 and 42 weeks (Table 2 and Figure 1).

The overall risk of stillbirth from 36-42 weeks was higher in women with GDM when compared with women without diabetes (17.1 vs 12.7/10,000 deliveries; RR, 1.34; 95% CI, 1.2–1.5). Stillbirth rates were also examined at each gestational age, and from 36-39 weeks, women with GDM had a statistically significant elevated RR of stillbirth compared with women without GDM, ranging from RR, 1.43 (95% CI, 1.1–1.9) at 38 weeks to RR, 1.84 (95% CI, 1.5–2.3) at 37 weeks. Although the risk was also higher for women with GDM at 40 and 41 weeks, this did not reach statistical significance (Table 3). At 42 weeks, the point estimate of stillbirth was lower for women with GDM compared with women without, although due to the low numbers of women with GDM at this gestational age the CI were very wide and this result was not statistically significant in women with GDM (9.5/10,000 ongoing pregnancies; 95% CI, 3.5–20.7/10,000) vs women without GDM (11.5/10,000 ongoing pregnancies; 95% CI, 10.0–13.3/10,000).

There was no statistically significant difference in the risk of infant death when stratified by gestational age (Table 3), although the total risk of infant mortality at gestational ages 36-42 weeks was lower for babies born to women with GDM compared to those born to women without GDM (10.7 vs 12.9/10,000 live births; RR, 0.83; 95% CI, 0.72–0.95).

When the risk of planned delivery (as quantified by the risk of infant death at a given gestational age) is compared with the risk of expectant management for 1 week (calculated as the sum of the risk of stillbirth at that given gestational age plus the risk of infant death in those born the following week) in women with GDM, the risk of delivery is higher than expectant management at 36 weeks. The risks of expectant management and delivery were similar at 37 weeks; however, the risk of expectant management exceeded that of delivery at ≥38 weeks (Figure 2). This risk difference is statistically significant at 39 and 40 weeks (RR, 1.8 at 39 and 40 weeks; P < .05). The absolute risk difference can also be calculated and the reciprocal of that risk difference is the “number needed to deliver” (analogous to the number needed to treat): the number of pregnant women who would have to be delivered at 39 or 40 weeks to prevent 1 excess death. At 39 weeks this would be 1518 women with GDM, while at 40 weeks it would be 1311 (Table 4).

COMMENT

GDM is a condition specific to pregnancy with known short- and long-term risks to mother and fetus. In this analysis, contrary to other recent studies, we showed that women with GDM were more likely than women without dia-

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### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women with GDM (N = 193,028)</th>
<th>Women without GDM (N = 3,997,925)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y), mean, SD</td>
<td>31.4 5.8</td>
<td>27.7 6.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>White</td>
<td>52,488 27.2</td>
<td>1,504,878 37.7</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>7548 3.9</td>
<td>217,883 5.5</td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>94,682 49.1</td>
<td>1,766,579 44.2</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>35,295 18.3</td>
<td>443,980 11.1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2877 1.5</td>
<td>59,816 1.5</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>7827 4.1</td>
<td>84,588 2.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>4574 2.4</td>
<td>22,325 0.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>GA at delivery (wk), mean, SD</td>
<td>38.8 1.4</td>
<td>39.1 1.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Birthweight (g), mean, SD</td>
<td>3475 541</td>
<td>3415 475</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Education ≥12 y</td>
<td>71,014 43.5</td>
<td>1,496,734 42.6</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

GA, gestational age; GDM, gestational diabetes mellitus.
to experience a stillbirth >35 weeks.
This increased risk persisted at all gestational ages except at 42 weeks, likely because few women with GDM receiving prenatal care in California remained undelivered at 42 weeks’ gestational age. This study is the first to examine the incidence rate of stillbirth by gestational age in women diagnosed with GDM, and such stratification by gestational age may explain the difference in our findings from other recent studies. Since many women with GDM are delivered by 39 weeks, the overall magnitude of difference in the incidence rate of stillbirth between women with and without GDM may be diminished or even reversed because of prevention of stillbirths that are overall more likely to occur at 40 and 41 weeks’ gestation. Another important difference between this study and others in the literature with different findings is the baseline characteristics of the study population. Due to the rarity of the adverse events of stillbirth and infant death, it is difficult to design and power a study to show a difference compared with non-diabetic control subjects or with women receiving treatment compared with those poorly controlled. Our findings could be explained by the increased prevalence of GDM in our population as well as the possibility of more severe or undertreated disease. The prevalence of GDM is much higher in our dataset (4.6%) than in Sweden or Italy (0.8% and 0.9%, respectively). Also, the Israeli study included only women with diet-controlled GDM while this study did not differentiate between those who were only diet controlled and those who required medical therapy; thus, it is likely that our study population could have more severe disease, representing a population at higher risk of stillbirth.

Although we know that infants born to mothers with GDM are more likely to be macrosomic, experience shoulder dystocia, and have short-term metabolic derangements such as hypoglycemia, hyperbilirubinemia, and polycythemia, our analysis does not demonstrate that these morbidities contribute to an excess risk of infant or neonatal mortality. In fact, in this analysis, it appears that these
infants overall are at a lower risk of infant death when compared with babies born to women without GDM. An explanation for this finding may be that more women with GDM were delivered by 40 weeks such that there were fewer babies born to mothers with GDM who were born at 41 and 42 weeks, when infant mortality rates are higher. \(^{14,16}\) It may also be that because the infants born to mothers with known GDM are at higher risk of the short-term morbidities listed above, these babies are more likely to undergo more screening and treatment compared to the general population that may experience unexpected neonatal morbidities. However, this analysis was restricted to mortality comparisons only and thus can only hypothesize about the effects on neonatal morbidity seen in these populations.

We cannot exclude the fact that confounding may play a role in the elevated risk estimates for stillbirth seen in the women with GDM. From our dataset, we are only able to examine maternal age and race, which have been previously demonstrated to be associated with GDM as well as increased stillbirth risk. \(^{3,14,17}\) As expected, women with GDM are more likely to be older and of Latino or Asian descent. Also as expected, the highest rate of stillbirth was seen in the African American population, which is less likely to have GDM compared with other ethnic groups (data not shown). Due to the limitations of the dataset and the rarity of the outcomes, we are unable to quantify the magnitude of these potential confounders, which should be a focus of future research.

There is substantial controversy in the literature and in clinical practice regarding the optimal time to deliver a woman with GDM to minimize the risks to her fetus. The American Diabetes Association recommends delivery at 38 weeks while the American College of Obstetricians and Gynecologists does not recommend routine delivery <40 weeks. \(^{3,18}\) Multiple observational studies and a single randomized controlled trial did show decreased macrosomia and shoulder dystocia with delivery at 38 weeks, but none of these studies were powered to examine stillbirth or infant death. \(^{19,20}\)

There has been increasing concern about the excess morbidities seen in neonates delivered electively <39 weeks. \(^{21,22}\) and these results have been extrapolated to include women with GDM. The limitation of the studies that focus on neonatal morbidities by gestational age at delivery is that they do not take into consideration the risks faced by the fetus while still in utero. However, at least 1 recent study has suggested that the policy of limiting nonindicated labor induction <39 weeks was associated with an increased rate of stillbirth at 37 and 38 weeks of gestation. \(^{23}\) Our methodology, which compares expectant management with planned delivery, is useful as it more closely approximates the decision faced by a woman with GDM and her pro-

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Relative risks of stillbirth and infant death comparing women with and without gestational diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk</td>
<td>RR of stillbirth (95% CI)</td>
</tr>
<tr>
<td>36</td>
<td>1.57 (1.2–2.0)</td>
</tr>
<tr>
<td>37</td>
<td>1.84 (1.5–2.3)</td>
</tr>
<tr>
<td>38</td>
<td>1.45 (1.1–1.9)</td>
</tr>
<tr>
<td>39</td>
<td>1.56 (1.2–2.0)</td>
</tr>
<tr>
<td>40</td>
<td>1.29 (0.92–1.8)</td>
</tr>
<tr>
<td>41</td>
<td>1.35 (0.85–2.13)</td>
</tr>
<tr>
<td>42</td>
<td>0.83 (0.37–1.9)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.34 (1.2–1.5)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.


| FIGURE 2 | Mortality risk of expectant management compared with delivery in women with gestational diabetes mellitus |

Comparing risk of expectant management for 1 week (calculated as risk of stillbirth this week plus risk of infant death at subsequent week) with risk of delivery (calculated as risk of infant death at that gestational week) at each gestational age (GA) from 36-41 weeks.

one of our study limitations is that we do not have access to the medical records of these women and thus cannot comment on the degree to which poor glycemic control due to late diagnosis or suboptimal treatment contributes to these risk estimates, or the extent to which other comorbidities are present and may play a role. As previous research has demonstrated that perinatal mortality rates decrease with improved glycemic control, perhaps the optimal time for delivery for women with poor glycemic control is actually earlier, while those with excellent control could be managed expectantly >39 weeks of gestation.24,25 We also cannot rule out significant selection bias where the women who had more severe GDM were also those most likely to have early iatrogenic deliveries, avoiding stillbirth as an outcome but inflating the infant death rate due to prematurity. This may play a role in the elevated infant death risk seen in the population of infants delivered at 36 weeks who may have had more severe comorbidities that necessitated a late preterm delivery. We note, however, that the infant death rates at all gestational ages are higher in the nondiabetic group compared with the gestational diabetics and that the stillbirth rate increases with gestational age in both groups. This suggests that early delivery does not account for a substantial decrease in the stillbirth rate and that these women not been delivered earlier, the difference in mortality at later gestational ages might be even more pronounced.

Another limitation is that our dataset determines gestational age by LMP alone. Studies show that pregnancies that are dated based on LMP alone rather than clinical judgment or ultrasound have less accurate gestational age assignments, and these pregnancies are more likely to be classified as “post-term.”26-29 Women with GDM are more likely to be obese and to be of lower socioeconomic status, factors associated with incorrectly recalled LMPs and more specifically, of cycles >28 days.30 This bias, while more prevalent in the GDM group compared with the non-GDM group, should otherwise be distributed evenly among the stillbirth and infant death populations. This misclassification would bias the result toward the null since many “term” infants (at 37-40 weeks) would be classified instead as “postterm” (41 and 42 weeks) making the pregnancies at these different gestational ages seem more similar than they actually are. Thus, if such misclassification was occurring, our threshold designation of the gestational age at which the GDM patients were having higher risk of the combined fetal and infant death outcome would only be earlier.

Our study suggests that there exists a mortality benefit in delivering women with GDM at 39 weeks instead of continuing with expectant management. We are cautious when making clinical rec-

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**TABLE 4**

<table>
<thead>
<tr>
<th>GA</th>
<th>Mortality risk of delivery (risk of infant death/10,000 live births at this GA) (95% CI)</th>
<th>Mortality of expectant management/10,000 (risk of stillbirth at this GA + risk of infant death at GA + 1) (95% CI)</th>
<th>RR of expectant management compared with delivery (95% CI)</th>
<th>Absolute risk difference between delivery and expectant management/10,000</th>
<th>No. needed to deliver at this GA to prevent single excess death</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>19.3 (11.8–29.8)</td>
<td>17.4 (11.9–22.8)</td>
<td>0.89 (0.52–1.5)</td>
<td>2.127</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>14.0 (9.5–19.9)</td>
<td>14.7 (11.1–18.2)</td>
<td>1.0 (0.68–1.6)</td>
<td>0.567</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>10.6 (7.8–14.1)</td>
<td>12.9 (10.0–15.9)</td>
<td>1.2 (0.84–1.8)</td>
<td>2.255</td>
<td>4435</td>
</tr>
<tr>
<td>39</td>
<td>8.7 (6.5–13.2)</td>
<td>15.2 (11.3–19.1)</td>
<td>1.8 (1.2–2.6)</td>
<td>6.588</td>
<td>1518</td>
</tr>
<tr>
<td>40</td>
<td>9.5 (6.7–13.2)</td>
<td>17.1 (10.7–23.6)</td>
<td>1.8 (1.1–3.0)</td>
<td>7.626</td>
<td>1311</td>
</tr>
<tr>
<td>41</td>
<td>11.5 (6.8–18.1)</td>
<td>18.2 (7.6–28.7)</td>
<td>1.5 (0.7–3.2)</td>
<td>6.019</td>
<td>1661</td>
</tr>
</tbody>
</table>

CI, confidence interval; GA, gestational age; RR, relative risk.

* P < .05 using $\chi^2$ test.

ommendations from these types of observational data alone, and we acknowledge the absence of neonatal and maternal morbidity in these calculations. We cannot comment on the impact on short-term neonatal outcomes, cesarean delivery rate, maternal complications, and cost to the health care system that a policy of inducing women with GDM at 39 weeks compared with 40 weeks would incur and further research should explore these potential repercussions. Because the absolute risks of stillbirth and infant death are so low, an increase in short-term neonatal morbidities such as neonatal intensive care unit admissions associated with a policy of early delivery may have a public health ramification that overshadows any small mortality benefit. Specifically, randomized clinical trials need to be considered to determine the best management of term pregnancy for women with GDM that considers both morbidity and mortality as outcomes. Until prospective studies can be performed, this type of risk assessment demonstrated in our study may prove to be very useful in helping women with GDM and their care providers determine the optimal gestational age for delivery.

REFERENCES


