Published in final edited form as:

*J Matern Fetal Neonatal Med*. 2019 February ; 32(3): 442–447. doi:10.1080/14767058.2017.1381904.

# The growth-restricted fetus: risk of mortality by each additional week of expectant management

**Rachel A. Pilliod**[a], **Jessica M. Page**[b], **Teresa N. Sparks**[c,d], and **Aaron B. Caughey**[a]

[a]Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA

[b]Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT, USA

[c]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco, San Francisco, CA, USA

[d]Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA

## Abstract

**Objective—**To compare fetal/infant mortality risk associated with each additional week of expectant management with the infant mortality risk of immediate delivery in growth-restricted pregnancies.

**Methods—**A retrospective cohort study was conducted of singleton, nonanomalous pregnancies from the 2005–2008 California Birth Registry comparing pregnancies affected and unaffected by growth restriction, defined using birth weights as a proxy for fetal growth restriction (FGR). Birth weights were subdivided as greater than the 90th percentile, between the 10th percentile and 90th percentile, and less than the 10th percentile. Cases greater than the 90th percentile were excluded from analysis. Cases less than the 10th percentile were considered to have FGR and were further subcategorized into <10th percentile, <5th percentile, and <3rd percentile. We compared the risk of infant death at each gestational age week against a composite risk representing the mortality risk of one additional week of expectant management.

**Results—**We identified 1,641,000 births, of which 110,748 (6.7%) were less than 10th percentile. The risk of stillbirth increased with gestational age with the risk of stillbirth at each week of gestation inversely proportional to growth percentile. The risks of fetal and infant mortality with expectant management outweighed the risk of infant death for all FGR categories analyzed beginning at 38 weeks. However, the absolute risks differed by growth percentiles, with the highest risks of infant death and stillbirth in the <3rd percentile cohort. At 39 weeks, absolute risks were low, although the number needed to deliver to prevent 1 death ranged from 413 for <3rd percentile to 2667 in unaffected pregnancies.

**CONTACT** Rachel A. Pilliod, pilliodr@ohsu.edu, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, Oregon, USA.

Supplemental data for this article can be accessed here.

**Disclosure statement**

None of the authors have a conflict of interest or financial disclosures.

**Conclusion—**At 38 weeks, the mortality risk of expectant management for one additional week exceeds the risk of delivery across all growth-restricted cohorts, despite variation in absolute risk by degree of growth restriction.

**Keywords**

Fetal growth restriction; stillbirth; timing of delivery; ultrasound

## Introduction

Pregnancies diagnosed as having fetal growth restriction (FGR) are those in which the estimated fetal weight by ultrasound is less than the 10th percentile and have been associated with multiple adverse outcomes [1,2]. Several studies have shown an association between FGR fetuses and stillbirth, with the risk of stillbirth inversely proportional to the degree of growth restriction [3–5]. Further, the rate of stillbirth has been estimated in multiple studies to increase most significantly starting in the late preterm period and extending through post-term [3,4]. Given this risk, there is an increasing focus on determining the optimal timing of delivery in these pregnancies.

The only available randomized clinical trial data are limited to the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT), which evaluated pregnancies at 36 weeks or greater with FGR and randomized to delivery versus expectant management. Though morbidity was comparable between the groups, the study was not powered to evaluate stillbirth [6]. More recently, an observational cohort study evaluating stillbirth rate alone by gestational age in FGR pregnancies recommended delivery between 37 0/7 and 38 0/7 weeks' gestational age. However, this recommendation did not take neonatal death or morbidity into account [4]. To address neonatal death, a Dutch prospective cohort study recently found overall mortality to be reduced in pregnancies affected by FGR at less than the 5th percentile when delivered between 38 0/7 and 39 0/7 weeks, although with less conclusive cutoffs for pregnancies in the 5th–10th percentile [7]. Based on available data and expert opinion, a strategy for delivery between 38 0/7 and 39 0/6 weeks' gestational age in cases of isolated FGR and late preterm delivery (34 0/7 weeks and 37 0/6 weeks) in cases of FGR with additional risk factors for adverse outcomes was proposed by a joint conference of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the Society for Maternal-Fetal Medicine (SMFM), and the American College of Obstetricians & Gynecologists (ACOG) in 2011 [8,9].

Given the limited data available and the need for more evidence to inform practice, the aim of this study was to further evaluate the overall risk of perinatal mortality by each gestational age week and to estimate the optimal timing of delivery among FGR subgroups of <10th percentile, <5th percentile, and <3rd percentile.

## Materials and methods

We conducted a retrospective cohort study of singleton, nonanomalous pregnancies utilizing the California Birth Registry from 2005 to 2008. We utilized stillbirth data at each gestational age week and infant death data following live births at each gestational age week between 24 weeks' and 42 weeks' gestational age. As sonographic estimates of fetal weight were not available for analysis in this data set, birth certificate recorded birth weights were analyzed and served as a proxy for FGR. Birth weights were subdivided as greater than the 90th percentile, between the 10th percentile and 90th percentile, and less than the 10th percentile as defined by published birth weight derived and sex-specific intrauterine growth curves [10].

Cases greater than the 90th percentile were excluded from analysis. Cases between the 10th percentile and 90th percentile served as the reference group. Cases at or below the 10th percentile were considered to have FGR and were further subcategorized into <10th percentile, <5th percentile, and <3rd percentile.

Maternal characteristics including demographics, socioeconomic factors, and available high-risk conditions (hypertensive disorders and diabetes) were analyzed for comparison of our study populations. Pregnancy dating was determined using the last menstrual period with an allowance of the correction of gestational age if the estimated age based on the last menstrual period is significantly different from that estimated by ultrasound [11]. In cases where gestational age was missing, the record was excluded. Approval for this study was granted by the Oregon Health & Science University Institutional Review Board and the state of California.

The risk of stillbirth encountered at each gestational age was calculated using a pregnancy at-risk life table method, which accounts for all ongoing pregnancies in the denominator and uses the half-week correction described by Smith [12]. This calculation includes the number of stillbirths during a given gestational age week in the numerator divided by the total number of ongoing pregnancies minus half of the deliveries that occurred during the gestational age week in question, accounting for the fact that stillbirths occur throughout the week of gestation. Risk of infant death was calculated as the number of live infants born during each week of gestation who died within the first year of life divided by the total number of live births at that gestational age. The stillbirth and infant death risks were expressed as a rate per 10,000 pregnancies.

Composite fetal and infant mortality was then calculated for each gestational age week as the sum of the risk of stillbirth during each gestational age week plus the risk of infant death with delivery during the subsequent week [13]. This composite mortality risk represented the risk of expectant management for one additional week. The value in this estimated composite risk is to compare it directly to the risk of infant death which would be associated with the risk of delivery. When the composite risk surpasses the risk of infant death, delivery is indicated.

The relative risk of expectant management versus delivery was then calculated for each week gestational age. Finally, number needed to treat (NNT) analyses were performed to determine the number needed to either deliver or manage expectantly to prevent one excess fetal/infant death. NNT was calculated as the inverse of the risk difference between the mortality associated with delivery and that with expectant management followed by delivery the subsequent week. The NNT reflected a number needed to deliver to avoid one additional death if the risk difference at that gestational age was a positive value and the number needed to manage expectantly rather than deliver to avoid one additional death if the risk difference was a negative value.

Stata (version 11.0, StataCorp, College Station, TX) and Microsoft Excel were utilized for statistical analyses. The chi-square test compared proportions and Wilcoxon's rank sum test examined nonparametric continuous variables. *p*-values of less than .05 and 95% confidence intervals that did not overlap 1.0 were considered statistically significant.

## Results

We identified 1,644,184 pregnancies, of which 110,748 (6.7%) met criteria for FGR. In the time period observed, there were 1487 (1.3%) stillbirths in the FGR cohort and 2573 (0.2%) in the reference group ($p < .001$). The demographics for the FGR subgroup compared to the reference population are included as supplemental materials. Mothers with FGR pregnancies were more often younger, had less educational attainment, were more likely to be publicly insured, and more frequently had fewer than five prenatal visits ($p < .001$). Maternal racial/ethnic differences were also observed in the cohort. Affected pregnancies were also more often associated with chronic hypertension and preexisting diabetes mellitus ($p < .001$), but not gestational diabetes mellitus ($p = .09$). When adjusted for maternal age, educational status, insurance status, prenatal visits, race, chronic hypertension, and diabetes, the presence of FGR <10th percentile remained associated with an increased odds of stillbirth in nonanomalous singleton pregnancies, with an adjusted odds ratio of 7.1 (95%CI 6.3–8.1).

As expected, the risk of stillbirth increased with advancing gestational age across all pregnancies, with the risk of stillbirth at each week gestation inversely proportional to growth percentile (Figure 1). By 37 weeks, the rate of stillbirth/10,000 ongoing pregnancies was 1.6 (95%CI 1.4–1.8) for pregnancies without FGR compared to 10.2 (95%CI 8.3–12.2), 18.1 (95%CI 14.0–22.2), and 26.3 (95%CI 19.7–32.8) for pregnancies <10th percentile, <5th percentile, and <3rd percentile, respectively. This rate continued to increase for each FGR subgroup through 41 weeks.

In terms of infant death, rates were highest among all FGR subcategories at the earliest gestational ages examined, with rates as high as 5686/10,000 live births (95%CI 5679–5694) at 24 weeks for unaffected pregnancies and 8360/10,000 live births (95%CI 8338–8382) for FGR <10th percentile. A steady reduction in rates of infant death was observed with each advancing week of gestational age until reaching a nadir at 40 weeks (Figure 1). For every week examined, pregnancies unaffected by FGR had lower rates of infant death compared with affected pregnancies. Among FGR pregnancies, the rates of infant death at each gestational age were inversely proportional to the degree of growth restriction.

Rates of stillbirth, infant death, and composite risk of mortality associated with expectant management were included in the supplemental materials. The composite risk of fetal and infant mortality with expectant management for one additional week was calculated as the sum of the risk of stillbirth during a given week plus the risk of infant death with delivery the following week. Composite risk of combined fetal and infant death with expectant management decreased with advancing gestational age with the nadir for all cohorts at term. Unaffected pregnancies demonstrated a nadir of 11.0 deaths/10,000 pregnancies (95%CI 10.4–11.6) when managed expectantly through 38 weeks and delivered at 39 weeks, while FGR pregnancies demonstrated the following nadirs by subgroup with expectant management during week 39 and delivery at 40 weeks: 29.6 deaths/10,000 pregnancies (95%CI 25.9–33.3), 49.8 deaths/10,000 pregnancies (95%CI 42.2–57.4), and 67.6 deaths/10,000 pregnancies (95%CI 55.8–79.4) for <10th percentile, <5th percentile, and <3rd percentile, respectively. After 39 weeks, composite risk increased for all FGR subgroups.

To ease comparison, this was plotted graphically. For the <10th percentile cohort, there was overlap at 36 weeks, but this was not sustained until 38 weeks when the composite risk crosses and remains greater than the risk of infant death. For the cohorts less than 5th percentile and <3rd percentile, a similar trend is observed with composite risk exceeding infant death at 38 weeks after a transient increase in composite risk at 36 weeks (Figure 2). Though the trends are similar in growth-restricted cohorts, the absolute risks differed with the greatest mortality risks occurring in the <3rd percentile cohort.

The relative risk of expectant management compared with delivery was then calculated. Between 34–40 weeks' gestation, the relative risk became <1 starting at 38 weeks, favoring expectant management prior to 37 weeks and delivery at 38 weeks onward in all cohorts. Though the relative risk is small, the 95% confidence interval excludes unity in the majority of weeks and cohorts examined, suggesting that there is a small, but statistically significant difference in mortality between delivery and expectant management in these gestational ages (Table 1).

To further evaluate this difference, risk difference and NNT calculations were performed. At 34 and 35 weeks for all cohorts and the reference population, expectant management was favored. Similar to the trends illustrated in Figure 2, FGR pregnancies demonstrated very small risk differences at 36 weeks with delivery favored over expectant management. However, at 37 weeks, expectant management was again favored with a resultant decrease in NNT among FGR pregnancies (Table 2). The unaffected pregnancies did not demonstrate this discrepancy between 36 and 37 weeks and favored expectant management at every gestational age through 37 weeks.

At 38 weeks onward, mortality is consistently reduced by delivery. At 38 weeks, the risk difference is less pronounced and thus the NNT is greater among all cohorts. The NNT continues to fall for each cohort with advancing gestation beyond 38 weeks, with the greatest reduction in mortality through delivery in the most growth-restricted pregnancies: 201 deliveries required in the <3rd percentile cohort to avoid one excess death at 40 weeks compared to 462 deliveries in the <10th percentile cohort and 2456 in unaffected pregnancies.

## Discussion

We observed an association between decreased perinatal mortality in patients who underwent delivery starting at 38 weeks rather than expectant management in all FGR cohorts examined. This was underscored by the observation that the relationship between FGR and stillbirth was observed at every week gestation and was more pronounced with advancing gestation at term. This risk was inversely proportional to the degree of growth restriction. Infant death rates, on the other hand, decreased with advancing gestational age in all cohorts as well as the reference population until reaching a nadir at 40 weeks. As with stillbirth rates, increased rates of infant death were again inversely associated at each gestational age with degree of growth restriction. This is comparable to other studies examining mortality in growth-restricted pregnancies [1–4,7].

We further noted that a transient risk difference at 36 weeks in FGR pregnancies favored delivery to reduce perinatal mortality, with a statistically significant risk reduction in the <5th percentile and <3rd percentile cohorts. This suggests that late preterm delivery of some of the most growth-restricted infants may be warranted, but that a universal approach to this delivery strategy will not necessarily reduce overall mortality, even in the most growth-restricted cohort as demonstrated. It is likely that in such higher risk FGR pregnancies additional testing, for example with Doppler interrogation, may be useful to further delineate those fetuses at higher risk that should be delivered earlier [14]. These findings are in agreement with a similarly designed national Dutch study examining mortality in the cohorts less than 10th and 5th percentiles, and support the expert opinion endorsed by the NICHD, SMFM and ACOG in 2011, which recommends delivery of suspected FGR pregnancies between 38 0/7 and 39 6/7 weeks in the absence of evidence of further compromise [8,9].

The strength of this study is in the large, diverse patient population examined and the ability to explore clinically relevant cutoffs including pregnancies with the greatest degree of growth restriction. Importantly however, this study lacks insight into any prenatal diagnosis of FGR or other high-risk conditions when considering what, if any, antenatal management may have differed between the study population and the reference group. It is reasonable to assume that given the expert recommendation for late preterm or early-term delivery in cases of suspected growth restriction with additional risk factors, an unknown proportion of our population was consequently delivered during this time frame. This would result in an overrepresentation of infant mortality and an underrepresentation of fetal mortality, which would bias our findings toward a strategy of delivery at a later gestational age. However, our observation that mortality is reduced among all cohorts as well as the reference population with a strategy of delivery between 38 0/7 and 38 6/7 weeks' gestation despite significant differences in absolute mortality risks suggests that the true association may be blunted, but is not completely masked. This study also relies on administrative data, which are subject to a limitation in the number of available variables and to possible underreporting or misclassification of these variables. Additionally, the use of birth certificate recorded gestational age is subject to error, particularly in pregnancies with limited or late presentation to prenatal care; however, recent work assessing the accuracy of birth certificate recorded estimated due date and gestational age found the birth certificate recorded dating to be highly accurate compared to best obstetric estimate [15]. This study contributes information related only to infant and fetal mortality. We acknowledge the absence of other serious maternal and neonatal morbidities which may have considerable impact in clinicians' decisions regarding timing of delivery. Finally, this study relies on birth weights rather than estimated fetal weight and while there is evidence to suggest the accuracy of birth weights as recorded in birth certificate data sets, there is known inaccuracy in sonographic estimates of fetal weight compared with eventual birth weight [10]. This limitation, however, is reflected in clinical practice in that intrauterine growth curves are based on cross-sectional birth data and are the standard for assessing both the risk and growth of preterm and term infants and to estimate growth restriction *in utero*.

Despite these limitations, we believe this study demonstrates that in a large, diverse patient population, a strategy of expectant management until 38 0/7 weeks' gestation reduces infant and neonatal mortality even among the most growth-restricted cohort examined. When taken in conjunction with the limitations, these findings suggest a policy of antenatal surveillance with possible late preterm or early-term delivery in the setting of additional risk factors for stillbirth is warranted, but that recommendations for universal late preterm or early-term delivery for even the most growth-restricted pregnancies without other clinical findings do not necessarily reduce perinatal mortality. Future studies should seek to define which additional risk factors are of greatest significance in terms of affecting morbidity and mortality and to improve the accuracy of identifying FGR.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We would like to acknowledge Jonathan Snowden, PhD and Yvonne Cheng MD, PhD for their contributions to the development of this work. This was presented as an Oral Presentation (abstract # 110) on 6 February 2016 at the Annual Meeting of the Society for Maternal Fetal Medicine in Atlanta, GA.

## References

1. Stoknes M, Andersen GL, Dahlseng MO, et al. Cerebral palsy and neonatal death in term singletons born small for gestational age. Pediatrics. 2012; 130(6):e1629–e1635. [PubMed: 23166338]
2. McIntire DD, Bloom SL, Casey BM, et al. Birth weight in relation to morbidity and mortality among new-born infants. N Engl J Med. 1999; 340(16):1234–1238. [PubMed: 10210706]
3. Pilliod RA, Cheng YW, Snowden JM, et al. The risk of intrauterine fetal death in the small-for-gestational-age fetus. Am J Obstet Gynecol. 2012; 207(4):318.e1–318.e6. [PubMed: 23021697]
4. Trudell AS, Cahill AG, Tuuli MG, et al. Risk of stillbirth after 37 weeks in pregnancies complicated by small-for-gestational-age fetuses. Am J Obstet Gynecol. 2013; 208(5):376.e1–376.e7. [PubMed: 23523099]
5. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet. 2011; 377(9774):1331–1340. [PubMed: 21496916]
6. Boers KE, Vijgen SM, Bijlenga D, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ. 2010; 341:c7087. [PubMed: 21177352]
7. Kazemier BM, Voskamp BJ, Ravelli AC, et al. Optimal timing of delivery in small for gestational age fetuses near term: a national cohort study. Am J Perinatol. 2015; 30(2):177–186. [PubMed: 24915557]
8. Spong CY, Mercer BM, D'Alton M, et al. Timing of indicated late-preterm and early-term birth. Obstet Gynecol. 2011; 118:323–333. [PubMed: 21775849]
9. ACOG. ACOG Practice bulletin no. 134: Fetal growth restriction. Obstet Gynecol. 2013; 121(5): 1122–1133. [PubMed: 23635765]

10. Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. Pediatrics. 2010; 125(2):e214–e224. [PubMed: 20100760]
11. Guide to completing the facility worksheets for the certificate of live birth and report of fetal death 2003 revision. Hyattsville (MD): Centers for Disease Control; 2016.
12. Smith GC. Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies. Am J Obstet Gynecol. 2001; 184(3):489–496. [PubMed: 11228508]
13. Rosenstein MG, Cheng YW, Snowden JM, et al. Risk of stillbirth and infant death stratified by gestational age. Obstet Gynecol. 2012; 120(1):76–82. [PubMed: 22914394]
14. Lee VR, Pilliod RA, Frias AE, et al. When is the optimal time to deliver late preterm IUGR fetuses with abnormal umbilical artery Dopplers? J Matern Fetal Neonatal Med. 2016; 29(5):690–695. [PubMed: 25754212]
15. Dietz PM, Bombard JM, Hutchings YL, et al. Validation of obstetric estimate of gestational age on US birth certificates. Am J Obstet Gynecol. 2014; 210(4):335.e1–335.e5. [PubMed: 24184397]

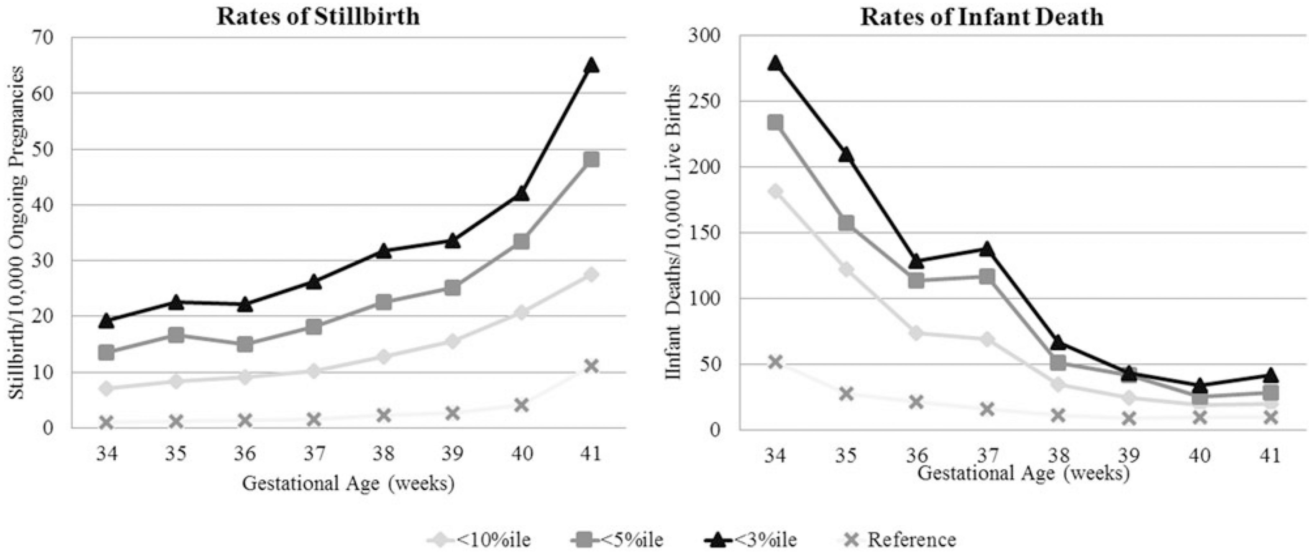


**Figure 1.**
Rates of stillbirth and infant death by growth percentile.

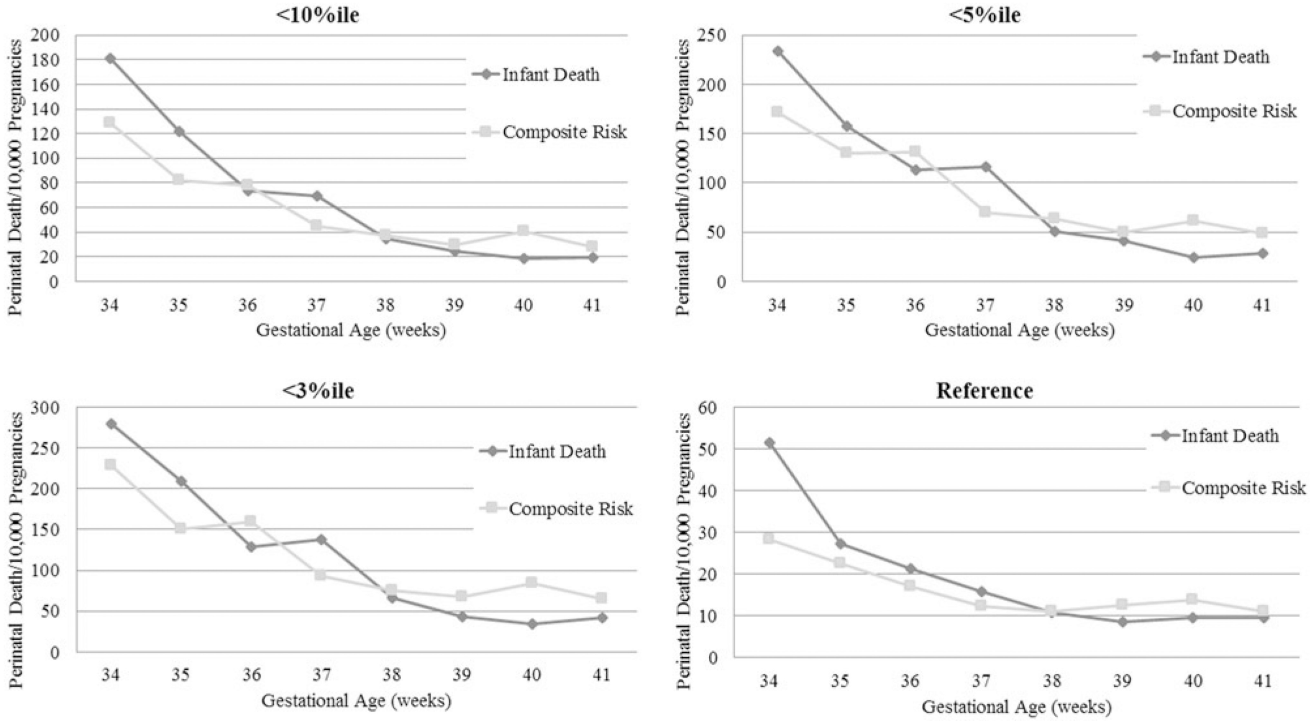


**Figure 2.**
Fetal and infant mortality with expectant management compared to delivery.

## Table 1

Adjusted relative risk of delivery compared with expectant management.

| GA (weeks) | <10th percentile Relative risk (95%CI) | <5th percentile Relative risk (95%CI) | <3rd percentile Relative risk (95%CI) | Reference group Relative risk (95%CI) |
|---|---|---|---|---|
| 34 | 1.41 (1.34–1.48) | 1.37 (1.26–1.48) | 1.22 (1.09–1.36) | 1.83 (1.81–1.85) |
| 35 | 1.49 (1.42–1.57) | 1.21 (1.11–0.132) | 1.39 (1.24–1.54) | 1.21 (1.20–1.23) |
| 36 | 0.94 (0.88–1.00) | 0.86 (0.77–0.95) | 0.80 (0.69–0.92) | 1.24 (1.22–1.25) |
| 37 | 1.56 (1.48–1.63) | 1.68 (1.55–1.81) | 1.48 (1.33–1.64) | 1.28 (1.26–1.29) |
| 38 | 0.92 (0.60–0.98) | 0.80 (0.71–0.89) | 0.88 (0.76–1.01) | 0.98 (0.98–0.99) |
| 39 | 0.82 (0.76–0.88) | 0.83 (0.73–0.92) | 0.64 (0.53–0.76) | 0.70 (0.68–0.72) |
| 40 | 0.46 (0.41–0.52) | 0.40 (0.32–0.49) | 0.40 (0.29–0.52) | 0.71 (0.68–0.73) |

CI: confidence interval; GA: gestational age.

## Table 2

Number needed to treat to avoid one excess death.

| GA | <10th percentile | | <5th percentile | | <3rd percentile | | Reference | |
|---|---|---|---|---|---|---|---|---|
| | Risk difference per 10,000 | NNT | Risk difference per 10,000 | NNT | Risk difference per 10,000 | NNT | Risk difference per 10,000 | NNT |
| 34 | −52.5 | 191[a] | −62.8 | 159[a] | −50.7 | 197[a] | −23.1 | 422[a] |
| 35 | −40.2 | 249[a] | −27.5 | 364[a] | −58.5 | 171[a] | −4.7 | 2120[a] |
| 36 | 4.7 | 2108[b] | 18.0 | 556[b] | 0.003 | 320[b] | −4.0 | 2505[a] |
| 37 | −24.5 | 408[a] | −47.0 | 213[a] | −44.7 | 224[a] | −3.4 | 2916[a] |
| 38 | 2.8 | 3556[b] | 12.6 | 792[b] | 8.9 | 1125[b] | 0.2 | 50997[b] |
| 39 | 5.3 | 1880[b] | 8.7 | 1154[b] | 24.2 | 413[b] | 3.7 | 2667[b] |
| 40 | 21.6 | 462[b] | 36.9 | 271[b] | 49.7 | 201[b] | 4.1 | 2456[b] |

NNT: number needed to treat; GA: gestational age.

[a]Favors expectant management.

[b]Favors delivery.