When is the optimal time to deliver late preterm IUGR fetuses with abnormal umbilical artery Dopplers?

Vanessa R. Lee¹, Rachel A. Pilloyd², Antonio E. Frias¹, Juha P. Rasanen¹, Brian L. Shaffer¹, and Aaron B. Caughey¹

¹Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA and ²Department of Obstetrics and Gynecology, Brigham and Women’s Hospital and Massachusetts General Hospital, Boston, MA, USA

Abstract

Objective: To determine the optimal timing of delivery in late preterm intrauterine growth restriction (IUGR) fetuses with abnormal umbilical artery Doppler (UAD) indices.

Methods: A decision-analytic model was built to determine the optimal gestational age (GA) of delivery in a theoretic cohort of 10,000 IUGR fetuses with elevated UAD systolic/diastolic ratios diagnosed at 34 weeks. All inputs were derived from the literature. Strategies involving expectant management accounted for the probabilities of stillbirth, spontaneous delivery and induction of labor for UAD absent or reversed end-diastolic flow (AREDF) at each successive week. Outcomes included short- and long-term neonatal morbidity and mortality with quality-adjusted life years (QALYs) generated based on these outcomes. Base case, sensitivity analyses and a Monte Carlo simulation were performed.

Results: The optimal GA for delivery is 35 weeks, which minimized perinatal deaths and maximized total QALYs. Earlier delivery became optimal once the risk of stillbirth was threefold our baseline assumption; our model was also robust until the risk of AREDF at 35 weeks was half our baseline assumption, after which delivery at 36 weeks was preferred. Delivery at 35 weeks was the optimal strategy in 77% of trials in Monte Carlo multivariable sensitivity analysis.

Conclusions: Weighing the risks of iatrogenic prematurity against the poor outcomes associated with AREDF, the ideal GA to deliver late preterm IUGR fetuses with elevated UAD indices is 35 weeks.

Keywords

Decision analysis, delivery timing, Doppler assessment, intrauterine growth restriction

Introduction

Intrauterine growth restriction (IUGR) represents a pathological fetal growth pattern and is associated with increased risks of stillbirth, neonatal death, neonatal morbidities and long-term sequelae [1,2]. The management of suspected IUGR (i.e. estimated fetal weight <10th centile) remains a challenge with respect to fetal surveillance and timing of delivery. Among high-risk pregnancies, including those with suspected IUGR, the use of Doppler ultrasound has been shown to reduce the risk of perinatal death [3]. Interrogation of several fetal vessels has been described, but current Society for Maternal–Fetal Medicine guidelines recommend umbilical artery Doppler (UAD) velocimetry as the initial assessment tool for monitoring cases of suspected IUGR [4].

UAD assessment examines the fetoplacental impedance to blood flow. Arteriolar destruction in the placental tertiary stem villi leads to a progressive decrease in end-diastolic flow until diastolic flow becomes absent or reversed in the umbilical artery waveform [5]. Commonly used indices of UAD assessment are the peak systolic to end-diastolic frequency shift ratio (S/D ratio) and the pulsatility index (PI), which can be used in lieu of the S/D ratio when end-diastolic flow is absent [6]. Progression to absent or reversed end-diastolic flow (AREDF) indicates significant placental insufficiency and is an ominous finding associated with increased risks of stillbirth, perinatal death and severe neonatal morbidities [7–11].

While numerous studies recommend UAD as the first-line assessment in the IUGR fetus, evidence-based protocols for managing pregnancies with abnormal UADs remain absent. Determining the timing of delivery in such cases is of particular concern: an obstetrician must balance the in utero risks of progression to more severe UAD abnormalities and stillbirth against the neonatal risks associated with iatrogenic prematurity. In an effort to better quantify the tradeoffs of early delivery versus continued fetal development, the goal of our study was to determine the optimal timing of delivery in a late preterm IUGR fetus with elevated UAD indices.
Methods

A decision-analytic model was created using TreeAge Pro 2013 software (TreeAge Software Inc, Williamstown, MA) to simulate a cohort of 10,000 IUGR fetuses with elevated UAD S/D ratios diagnosed at 34 weeks gestation (Figure 1). The population of interest was fetuses with suspected IUGR secondary to placental insufficiency; multiple gestations, chromosomal abnormalities or congenital anomalies were not considered in this model. As no human subjects were involved in creating this model, this study was exempted from institutional review board approval. Model options ranged from delivery at 34 weeks to expectant management until 35, 36, 37 or 38 weeks. Strategies involving expectant management until a later gestational age accounted for the probabilities of stillbirth, spontaneous labor and progression of UAD indices to AREDF at each successive week of gestation. The model was built to incorporate weekly antenatal UAD assessment; if a fetus progressed to AREDF, induction of labor was performed at that gestational age. Neonatal outcomes in the model included neonatal death and cerebral palsy. All model inputs were derived from the literature (Table 1).

Probabilities

The probabilities of stillbirth and spontaneous delivery were derived from literature describing rates of these events in SGA fetuses ≤ 10th centile based on the United States National Center for Health Statistics database [12] (Table 1). To estimate the risk of stillbirth in IUGR fetuses with elevated UADs compared to IUGR fetuses with normal UADs, data
from four small cohort studies were aggregated to calculate a relative risk of 3.929 (95% confidence interval (CI) 1.201–12.857), which was then applied to the baseline probabilities [10,13–15]. In each of the above studies, the criteria for elevated UADs was defined as a S/D ratio ≥ 95th percentile or a PI > 2 standard deviations above normal. The probabilities of progressing from an elevated UAD S/D ratio to AREDF at 35, 36 and 37 weeks’ gestation were estimated from a 2008 study characterizing the progression of UAD abnormalities in a cohort of IUGR fetuses [16].

The risks of neonatal death at each gestational age were taken from a 2013 study describing United States National Center for Health Statistics data [17]. To estimate the effect of IUGR on these outcomes, baseline probabilities were multiplied by relative risks of neonatal death and cerebral palsy in SGA infants taken from a registry-based cohort study of singleton births in Norway [18]. Then, to further estimate the risk of neonatal death in fetuses with AREDF compared to fetuses with elevated S/D ratios, data were aggregated from the same four previously mentioned cohort studies to give a relative risk of 3.7077 (95% CI 2.021–6.831) [10,13–15].

The probabilities of developing cerebral palsy were stratified by gestational age and derived from the literature [19]. Aggregate data from the four cohort studies did not find a significantly increased risk of cerebral palsy in fetuses with AREDF, so the probability of cerebral palsy in fetuses with AREDF was only modified with sensitivity analyses in the model.

Utilities

Utilities were included from the maternal and neonatal perspectives and were derived from the literature (Table 1). In decision analyses, utilities are a measure of the well-being derived from various health states and are applied to life expectancies to generate quality-adjusted life years (QALYs). Although only neonatal outcomes were investigated in this model, both maternal and neonatal QALYs were calculated in order to accurately reflect the health states of adverse perinatal outcomes on both the mother and the infant. The utility of a stillbirth or neonatal death from the maternal perspective was set to 0.92 based on the published utility for a procedure-related miscarriage [20]. The utility of a stillbirth or neonatal death from the neonatal perspective was by definition 0. The utilities of cerebral palsy were reported from prior studies to be 0.733 from the maternal perspective and 0.612 from the neonatal perspective [21,22]. Utilities were applied over the course of the remaining maternal life.
expectancy (56.9 years, assuming delivery at 25 years) and neonatal life expectancy (78.7 years) at a discount rate of 3% to calculate total QALYs associated with each strategy [23].

Analysis

Analysis consisted first of comparing rates of clinical outcomes that would occur with delivery at 34, 35, 36, 37 and 38 weeks using baseline values in our model. Next, we calculated total QALYs for each strategy to determine the optimal timing of delivery from a societal perspective.

Sensitivity analysis is a statistical tool that allows an estimation of how changes in parameters, such as the probabilities of stillbirth, worsening Doppler indices or neonatal death could affect results. To test the robustness of the model, univariate sensitivity analyses were performed on every input in order to determine the threshold value beyond which the results of the model would change.

In order to incorporate uncertainty into the baseline model, a Monte Carlo microsimulation was performed using 10,000 trials to simultaneously vary all model inputs. One trial represents a fetus getting delivered at 34, 35, 36, 37 or 38 weeks, and its probabilities are randomly chosen from pre-specified distributions. All probability inputs were given a beta distribution, and relative risk inputs were assigned a triangular distribution with means and standard deviations derived from the literature. This simulation is repeated with a different set of randomly chosen values within the input distribution and the aggregate represents a theoretical cohort of IUGR fetuses.

Results

In our theoretic population of 10,000 women with fetuses with an EFW of <10th percentile and elevated UAD S/D ratios, delivery at 35 weeks’ gestation was the optimal management strategy, which maximized total QALYs (Table 2). Delivery at 35 weeks conferred the fewest combined fetal and neonatal deaths, while expectant management until 38 weeks would minimize cases of cerebral palsy. In our theoretic cohort, there were 31.6 stillbirths in the 35-week group versus 84.9 stillbirths in the expectant management until 38-week group. There would be 94.4 neonatal deaths at 35 weeks as compared to 144.7 neonatal deaths with immediate delivery at 34 weeks and 175.5 neonatal deaths with expectant management until 38 weeks. The incidence of cerebral palsy in our cohort declined with increasing gestational age in our model; delivery at 38 weeks minimized the risk of cerebral palsy at 72.1/10,000 fetuses.

Table 2. Simulated outcomes per 10,000 gestations.

| Planned gestational age at delivery (weeks) | Stillbirth/10,000 | Neonatal death/10,000 | Cerebral palsy/10,000 | Total QALYs |
|--------------------------------------------|------------------|----------------------|----------------------|-------------|
| 34                                         | –                | 144.69               | 220.36               | 56.308259   |
| 35                                         | 31.63            | 94.4                | 129.65               | 56.547873   |
| 36                                         | 57.98            | 117.57              | 86.34                | 56.473800   |
| 37                                         | 76.79            | 151.91              | 78.29                | 56.381230   |
| 38                                         | 84.89            | 175.47              | 72.12                | 56.228404   |

QALYs, quality-adjusted life years.

Discussion

Our decision-analytic model showed that for late preterm IUGR fetuses with abnormal S/D measurement of the UADs, expectant management until delivery at 35 weeks would minimize stillbirths and neonatal deaths while maximizing QALYs. Delivery at 35 weeks is the optimal strategy in 77% of scenarios and delivery at either 35 or 36 weeks’ gestation accounts for more than 95% of the optimal strategies.

With regard to health effectiveness, delivery at 35 weeks conferred 565,478 total QALYs per 10,000 women. The next most effective strategy, delivery at 36 weeks, resulted in 564,738 QALYs per 10,000 women. Delivery at 35 weeks results in an incremental gain of 740 QALYs for this theoretical cohort of 10,000 women over waiting until 36 weeks’ gestation.

Sensitivity analysis

The model remained robust across reasonable ranges for all of the variables with a few exceptions. Delivery at 35 weeks remained the optimal strategy until the relative risk of stillbirth in IUGR fetuses with elevated S/D ratios was 13.3, more than threefold of our baseline assumption of 3.9 (Supplementary Figure S1).

Due to the paucity of data on the risk of UAD indices progressing from elevated S/D ratios to AREDF stratified by gestational age, one-way sensitivity analyses were conducted varying the probability of progressing to AREDF at 35, 36 and 37 weeks gestation. Delivery at 35 weeks remained the optimal strategy until the probability of developing AREDF at 35 weeks fell from our baseline assumption of 17.4–9.2%, which led to the optimal strategy being expectant management until 36 weeks gestation. Varying the probability of worsening UAD indices at 36 or 37 weeks did not affect the robustness of our model.

Similarly, few large-scale studies have characterized the risk of neonatal death in IUGR fetuses with AREDF relative to IUGR fetuses with those with elevated S/D ratios. One of the key and potentially controversial assumptions in the model is that fetuses with AREDF have an increased risk of neonatal death compared to fetuses with preserved forward flow; our baseline assumption used a relative risk of 3.7 calculated from four small cohort studies. To fully appreciate the impact of this assumption on model outcomes, sensitivity analysis was performed varying the relative risk along a range from 0.25 to 10.0. Our model was robust until the relative risk of neonatal death in AREDF fetuses fell below 2.3, after which delivery at 36 weeks became the optimal strategy. Additionally, there are scarce data on the risk of neurodevelopmental disability in IUGR fetuses with AREDF, but sensitivity analysis found that our model was robust regardless of the relative risk of cerebral palsy in the AREDF group, suggesting that the risk of cerebral palsy was not a significant driver of our model.

A Monte Carlo probabilistic sensitivity analysis of 10,000 iterations was performed. In this analysis, all model inputs were simultaneously randomly varied. Based on these simulations, delivery at 35 weeks was the optimal strategy in 77.0% of trials, with 22.6% of optimal trials pointing towards 36 weeks gestation (Supplementary Figure S2).
suggesting that one of these two strategies, in all probability, would be the optimal strategy for a population of women with suspected IUGR fetuses with elevated S/D ratios.

While the incidence of neonatal death generally decreases with increasing gestational age, our model estimated a U-shaped curve for this outcome, with a nadir of deaths at 35 weeks gestation. This drives the optimal timing of delivery to 35 weeks in our model, and is primarily due to the elevated risks of stillbirth and neonatal death associated with developing AREDF. Our results underscoring the significance of AREDF are generally concurrent with existing literature. In the largest study examining this issue, Karsdorp and colleagues assessed outcomes of 459 high-risk pregnancies and found that compared to fetuses with forward flow, the odds ratios for perinatal mortality in pregnancies with AREDF were 4.0 and 10.6, respectively, even after adjusting for gestational age [24]. More recent studies in the IUGR population have supported these findings, leading to our pooled estimated odds ratio of neonatal death in AREDF of 3.7 compared to fetuses with preserved forward flow [10,13–15]. According to our sensitivity analysis, delivery at 35 weeks would remain the optimal management strategy until the risk of neonatal death in AREDF fell below a relative risk of 2.3, illustrating the robustness of our model.

An additional factor driving our results is the probability of UADs deteriorating from elevated S/D ratios to AREDF. Although, the pattern of progression of UAD abnormalities has been well described, no studies to date have reported these rates stratified by gestational age [8,25,26]. Furthermore, the rate of deterioration can vary depending on the etiology and onset of IUGR. We estimated these probabilities based on Turan and colleagues’ study describing the median progression intervals and intervals to delivery in a cohort of 104 IUGR fetuses; however, the fetuses in that study had a lower mean gestational age at enrollment than specified in our model and exhibited a wide array of deterioration patterns [16]. Despite the limitations of these baseline inputs, our sensitivity analyses varying the probability of progression to AREDF confirmed the robustness of our model in that the true probability of progression to AREDF at 35 weeks would need to be half of our baseline assumption in order to affect the optimal management strategy.

Gestational age remained the primary driver of cerebral palsy in our model, with expectant management until 38 weeks minimizing the incidence of cerebral palsy in our theoretical cohort. This result is consistent with a number of studies that have failed to show a significant association between AREDF and cerebral palsy [27,28]. Sensitivity analyses further reinforced that varying the risk of cerebral palsy in fetuses with AREDF does not change the optimal timing of delivery. Gestational age was also the primary driver of stillbirth rates, with our model estimating more stillbirths with increasing gestational age.

No decision-analytic model can fully capture the complexity of a clinical situation or integrate all the factors a physician can consider when managing late preterm IUGR pregnancies. Although, we attempted to approximate a reasonable clinical scenario, we did not include every possible piece of diagnostic information. For example, our baseline model utilized <10th centile for suspected IUGR as this is what is commonly utilized by the majority of clinical practices and in the published literature. However, lower thresholds such as <5th centile or <3rd centile appear to have greater risks and might lead to an even earlier gestational age for delivery [12]. Unfortunately, there was such limited data on these even lower thresholds and the Doppler outcomes that we could not create such a model. An additional model simplification was that we incorporated weekly antenatal Doppler monitoring into the model, but clinicians may manage IUGR pregnancies with different frequencies of monitoring, multiple testing modalities or perform Doppler velocimetry on other fetal vessels. We chose to only examine the UA because UA abnormalities are typically the first to manifest in the IUGR setting, and the lack of randomized trials interrogating other vessels has precluded their recommended routine usage in clinical practice [4]. Further, there would be much additional complexity in the model from the interaction between antenatal testing, such as NSTs or BPPs in addition to Doppler with exactly what practice would evolve with discordant tests. That being said, such testing would only lead to earlier deliveries and given that our optimal outcome was 35 weeks’ gestation, it would likely only strengthen that finding.

We did not include every possible neonatal outcome in our model, and instead chose to only include the more severe outcomes of stillbirth, neonatal death and cerebral palsy that may be impacted by advancing gestational age. Additionally, because the sequelae of an IUGR pregnancy predominantly lie with the fetus, our model only examined neonatal outcomes and did not consider mode of delivery or adverse maternal outcomes. While such outcomes would impact maternal utilities, they would do so much less than the adverse neonatal outcomes included, thus were excluded from the model. Again, given that the risk of cesarean delivery would only increase as the rate of AREDF increased, earlier induction of labor prior to development of AREDF would likely have improved such maternal outcomes as well.

We used existing literature to obtain point estimates of the probabilities and utilities to populate the model, and the studies included may have been underpowered, older and thus not reflective of advancing technology, conducted in different populations or susceptible to bias. However, through sensitivity analysis and Monte Carlo simulation, we were able to examine the impact of uncertainty by considering a wide distribution of values around our point estimates and confirmed that our model remained robust. Nonetheless, additional data are needed to better characterize the relationships between gestational age, the likelihood of worsening UAD indices and rates of neonatal morbidities in IUGR fetuses with abnormal UADs. Large cohort studies, or even randomized trials of different clinical strategies, will help us to better refine the management of these complicated patients.

The strength of this model is that it is the first to address an issue with much clinical uncertainty. The timing of delivery of a late preterm IUGR fetus with abnormal Doppler indices poses a dilemma for the obstetrician: early delivery may place the fetus at risk for prematurity-related complications, whereas delaying delivery will increase the risk of a deteriorating uterine environment resulting in stillbirth or significant hypoxia at the time of delivery. Most of the
literature on Doppler assessment in the IUGR fetus is comprised of small, retrospective studies that have not directly examined timing of delivery. Two randomized trials, the Growth Restriction Intervention Trial (GRIT) and Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE), have incorporated Doppler assessment in their study of management and delivery timing in IUGR pregnancies; however, the median gestational age at entry in those trials was 32 and 29 weeks, respectively, and as such high-quality data on late preterm IUGR fetuses are still lacking [29,30].

Decision analyses can aid evidence-based decision-making in that they integrate epidemiologic uncertainty, gaps in evidence and tradeoffs between competing strategies. Weighing the risks of iatrogenic prematurity against the risks of stillbirth and outcomes of AREDF, we have demonstrated that the optimal management strategy for IUGR fetuses with elevated UAD S/D ratios diagnosed at 34 weeks is expectant management until delivery at 35 weeks. Given these results, economic analyses are needed to determine whether this strategy is cost-effective from a societal standpoint. More research is also needed to guide the timing of delivery in cases IUGR with UAD abnormalities diagnosed at earlier gestational ages. Finally, additional randomized trials should be conducted to ascertain how best to manage these complicated pregnancies.

Declaration of interest

The authors report no conflicts of interest.

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Supplementary material available online
Supplementary Figures S1 and S2