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CHAPTER 10

Optimal Timing of Delivery in Small for Gestational Age Fetuses Near Term: A National Cohort Study

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ABSTRACT

Objective
Our aim was to study the competing risks of antepartum versus intrapartum/neonatal death in SGA and non-SGA fetuses.

Study design
We performed a national cohort study using all singletons delivered between 36^{+0}-42^{+6} weeks without hypertension, pre-eclampsia, diabetes, congenital anomalies or non-cephalic presentation from the Netherlands Perinatal Registry (1999-2007). The resultant cohort was divided in three groups based on birthweight by gestational age (SGA<P5 61,021 deliveries, SGA P5-10 58,902 deliveries, non-SGA group 1,168,523 deliveries). We compared the mortality risk of delivery with expectant management.

Results
Delivery was associated with more mortality than expectant management for one week from 39 weeks onward in the non-SGA group (RR1.26 95%CI1.05-1.50). For the SGA<P5 expectant management for one more week was associated with more mortality from 38 weeks onward although this only reached statistical significance from 40 weeks onwards (RR2.46 95%CI1.80-3.36).

Conclusion
At 36 and 37 weeks, delivery is associated with a higher risk of mortality in SGA<P5 fetuses than expectant management. Delivery of SGA<P5 fetuses at 38 and 39 weeks is associated with the best perinatal outcome whereas for non-SGA fetuses this is at 39-40 weeks.

INTRODUCTION

Small-for-gestational age (SGA) is most commonly defined as birthweight below the 10th percentile for a particular gestational age and thus contains around 10% of the population. The group of SGA fetuses consists of a mixture of growth restricted and constitutionally small fetuses. Up to 72% of unexplained antepartum deaths are associated with SGA [1]. The more pronounced the SGA, the higher the risk of antepartum death [2]. Moreover, neonates that are born SGA are at increased risk of adverse events in the neonatal period [3-5].

The time frame of term delivery between 37 and 42 weeks is considered physiologic for all women. However, it is not known whether this time frame is also optimal for delivery of an SGA fetus because the increased risk of antepartum death is not incorporated in this concept of normalcy.

Currently, there is little evidence to guide clinicians in their decision regarding the optimal timing of delivery in these high-risk pregnancies. Postponement may lead to an increased risk of antepartum death, whereas early delivery may lead to prematurity and its related complications. The disproportionate intrauterine growth intervention trial at term (DIGITAT) trial randomized singleton pregnancies beyond 36 weeks' gestation with suspected intra-uterine growth restriction for induction of labor or expectant management. Although the DIGITAT trial was designed to find the right timing, this study was not powered to examine the risk of antepartum death [6]. A recent study defined optimal timing of delivery for these fetuses based on the risk of stillbirth [2], however, the risk of neonatal death with delivery was not incorporated..

Our objective was to study, in isolated SGA fetuses and in non-SGA fetuses, the competing risks of antepartum death with on-going pregnancy versus neonatal death with delivery. In addition, we evaluated the optimal timing of delivery within the context of the probability of neonatal morbidity.

METHODS

Database

Data were obtained from the Netherlands Perinatal Registry (PRN) between 1999 and 2007[7].

The PRN database is obtained by a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns. [8;9] The PRN contains population-based data on pregnancies, provided care, i.e. interventions, referrals, deliveries and (re)admission of newborns of 96% of all deliveries in the Netherlands. Details on entry, linkage, aggregation, validation and verification of the data are published elsewhere [8;9]. This study used anonymous registry data so no ethical approval was needed. The Dutch perinatal registry gave permission for the use of their data (approval number 12.21).

Inclusion and Exclusion Criteria
The study population comprised all singleton deliveries between 36^{+0} and 42^{+6} weeks of gestation. Gestational age was based on ultrasound or last menstrual period. We excluded congenital anomalies, chronic or pregnancy induced hypertension, pre-eclampsia and diabetes, because timing of delivery could have been influenced by such co-morbidity. In addition we excluded non-cephalic presentation since breech position is associated with an increased risk of neonatal mortality and morbidity.

Small for Gestational Age groups
We assumed that the proportion of growth-restricted fetuses is probably higher among fetuses with severe SGA (birthweight by gestational age below the 5th percentile, P5) than among fetuses with moderate SGA (birthweight by gestational age between the 5th and 10th percentile, P5-10), as the latter group likely contains more constitutionally small fetuses. We therefore stratified our analysis into birthweight below the 5th percentile (SGA<P5 group), birthweight between the 5th and 10th percentile (SGA P5-10 group) and a group with birthweight above the 10th percentile (non-SGA group) according to Dutch reference curves for birthweight by gestational age (corrected for parity, fetal sex and ethnic background) [10].

Outcome Measures
We evaluated three outcome measures: antepartum death, intrapartum/neonatal death and neonatal morbidity. Antepartum deaths were all deaths occurring before the start of the delivery. Intrapartum/neonatal deaths were those occurring during labor or in the first 28 days of life. We grouped intrapartum and neonatal death since most intrapartum deaths are caused by events during labor and delivery [11;12]. Neonatal morbidity was a composite outcome measure, containing any of the following; meconium aspiration, necrotizing enterocolitis, respiratory distress syndrome, birth trauma, intraventricular hemorrhage or neonatal intensive care admission for at least 24 hours.

Statistical Analysis
We compared baseline characteristics among the three SGA groups with ANOVA and chi-square tests when appropriate. Post hoc multi comparison tests were performed to analyze differences in outcomes between two out of three groups with chi-square test of t test. To adjust for multiple testing a threshold of <0.01 was used to indicate statistical significance in these comparisons. Gestational age-specific risks of antepartum deaths, intrapartum/neonatal deaths and neonatal morbidity were estimated using the fetus/neonate-at-risk approach [13-15].

A moving average (death at a specific day + deaths of day before and day after divided by 3) was applied to correct for daily fluctuations in figure 2. .

Antepartum death
For a fetus to be at risk of antepartum death (AD) at 36^{+0} it is obviously necessary to be alive at 36^{+0}. Consequently, the risk of antepartum death was calculated as a proportion of the ongoing pregnancies (OP) at a particular gestation.

Risk of antepartum death at day n = $AD_n/OP_n * 1000$

Cumulative risk of antepartum death
The cumulative risk of antepartum death at day N was calculated by summing the risks of antepartum death of the previous days. Inevitably, the cumulative risk of antepartum death will increase with increasing gestation. The cumulative risk represents the risk of antepartum death in case of expectant management from 36^{+0} weeks (n0) onward (e.g antepartum deaths before 36+0 were not included).

Cumulative risk of antepartum death at day n= $(AD_{n0}/OP_{n0} * 1000)+(AD_{n1}/OP_{n1} * 1000)$ ... $(AD_{n..}/OP_{n..} 1000)$

Intrapartum/neonatal death
Similarly, the risk of intrapartum/neonatal death (IND) at any gestational age is obtained by dividing the number of intrapartum and neonatal deaths at that gestation by the number of neonates at risk of intrapartum/neonatal death at that gestation. The neonates at risk of intrapartum/neonatal death at a certain gestational age include all delivered neonates (DN) that did not die antepartum.

Risk of intrapartum/neonatal death at day n = $IND_n/DN_n * 1000$

Neonatal morbidity
The denominator used for the risk of neonatal morbidity (NM) are all alive neonates (AN) born at that gestation, since only alive neonates can suffer morbidity.

Risk of neonatal morbidity at day n = $NM_n/AN_n * 1000$

Comparison probability of death with delivery versus expectant management for one more week
We compared the probability of death in case of delivery versus expectant management. Once delivery has started, either spontaneously or by induction of labor, the probability of death is based on intrapartum/neonatal death. With expectant management the probability of death is based on the composite of intrapartum/neonatal death and the probability of antepartum death. The probability of death between delivery and expectant management per one week gestation was compared as previously proposed by Rosenstein *et al* [16]. For example, delivery at 36 weeks was compared to an expectant management at 36 weeks gestation and subsequent delivery at 37 weeks. The probability of death with delivery is defined as the risk of intrapartum/neonatal deaths in that week divided by neonates born during that week.

Probability of death with delivery at week x = $IND_x/DNx * 1000$

The probability of death with one week expectant management was defined as the risk of antepartum death during that week plus the risk of intrapartum/neonatal death with delivery in the subsequent week. The confidence interval of this composite outcome was calculated using the sum of the variances plus twice the covariance of the estimates of antepartum death and intrapartum/neonatal death.

Probability of death with one week expectant management at week x = ($AD_x/OP_x + IN_{x+1}/DN_{x+1}$) *1000.

We compared for each week separately the probability of death in case of delivery versus expectant management for one week.

A number needed to deliver to prevent one death was calculated by taking the reciprocal of the absolute risk difference between delivery and expectant management for one week. Data analyses were conducted with SAS (SAS institute Inc, Cary, NC, USA version 9.2).

RESULTS

From January 1, 1999 until December 31, 2007 a total of 1,491,534 singleton deliveries from 36^{+0} weeks onwards without congenital anomalies were identified in the PRN database. We excluded hypertensive complications or maternal diabetes (125,865) and non-cephalic or unknown presentation (77,223). After application of our inclusion and exclusion criteria 1,288,446 deliveries made up our study population: 61,021 deliveries in the SGA<P5 group (4.7%), 58,902 in the SGA P5-10 group (4.6%) and 1,168,523 in the non-SGA group (90.7%).

Maternal and neonatal baseline characteristics of the cohort are shown in table 1. Women with SGA<P5 or SGAP5-10 are more often non-Caucasian than women without SGA (23.6%, 23.1%, and 15.9% respectively; P<0.001). The same was true for low socioeconomic status (33.0%, 31.0% and 24.4% respectively P<0.0001). Induced delivery was more common in the SGA<P5 group than in the SGA P5-10 and non-SGA group (35.5%, 29.2% and 29.9%; P<0.0001). Mean gestational age at delivery was the same in the SGA<P5 and non-SGA group (40+0 weeks) but was a slightly longer in the SGA P5-10 group (40+2 weeks) (P-value <0.0001).

Antepartum death occurred more often in the SGA<P5 group (8.0‰) and in the SGA P5-10 group (2.6‰), compared to the non-SGA group (1.2 ‰) (both p<0.0001). In addition, intrapartum/neonatal death was more prevalent in the SGA<P5 group (5.9‰) and the SGA P5-10 group (2.1‰) than in the non-SGA group (0.6‰) (both p<0.0001). Finally, neonatal morbidity was more common in the SGA<P5 group (11.1‰) and the SGA P5-10 group (5.8‰) than in the non-SGA group (4.3 ‰) (both p<0.0001) (table 2).

Table 2 presents the gestational age specific risks of antepartum death, intrapartum/neonatal death and neonatal morbidity per 1000 births for the three different SGA groups. For readability reasons we displayed the risks per week (risks per day are available upon request).

In addition, the absolute number of women as well as the percentiles and cumulative percentiles of total births are shown. Remarkably, although the number of induced deliveries was higher in the SGA<P5 group (table 1), the number of early deliveries before 38 weeks of gestation was higher in the non-SGA group (Table 2: 6.7% versus. 7.2% p<0.0001, respectively).

Table 1 | Cohort characteristics of the different SGA groups

	Non-SGA (N=1,168,523)	**SGA P5-10 (N=58,902)**	**SGA<P5 (N=61,021)**	***p*-value**
Maternal characteristics				
Maternal age, (mean. SD)	30.4 (4.8)	29.9 (5.2)	29.9 (5.3)	<0.0001
Low SES, %	24.4	31.0	33.0	<0.0001
Non-Caucasian, %	15.9	23.1	23.6	<0.0001
Nulliparous, %	43.5	43.0	44.3	<0.0001
Gestational age at delivery, weeks, median	40+0 (39+1-41+0)	40+2 (39+2-41+1)	40+0 (39+0-41+1)	<0.0001
Induction of labor, %	29.9	27.1	32.5	<0.0001
Caesarean section, %	9.2	7.7	11.6	<0.0001
Elective Caesarean section, %	3.0	2.2	3.1	<0.0001
Emergency Caesarean section (fetal distress, non progression)	6.2	5.5	8.5	<0.0001
Neonatal characteristics				
Male, %	51.3	51.6	50.7	0.004
Birth weight, (gram) mean (SD)	3600 (446)	2915 (295)	2637 (225)	<0.0001

Table 2 | Gestational age specific risks of antepartum death, intrapartum/neonatal death and neonatal morbidity for different SGA groups.

		Gestational age							
		36^0 - 36^6	**37^0 - 37^6**	**38^0 - 38^6**	**39^0 - 39^6**	**40^0 - 40^6**	**41^0 - 41^6**	**42^0 - 42^6**	**Total**
Total births, N	Non-SGA	24,452	59,305	153,450	280,392	352,140	232,183	66,601	1,168,523
	SGA P5-10	829	2,445	7,136	14,382	18,239	12,231	3,640	58,902
	SGA<P5	1,019	3,082	7,744	14,701	18,254	12,481	3,740	61,021
Total births, %	Non-SGA	2.09	5.08	13.13	24.00	30.14	19.87	5.70	100
	SGA P5-10	1.41	4.15	12.12	24.42	30.96	20.76	6.18	100
	SGA<P5	1.67	5.05	12.69	24.09	29.91	20.45	6.13	100
Total births, cumulative %	Non-SGA	2.09	7.17	20.30	44.30	74.43	94.30	100.00	NA
	SGA P5-10	1.41	5.56	17.67	42.09	73.06	93.82	100.00	NA
	SGA<P5	1.67	6.72	19.41	43.50	73.42	93.87	100.00	NA
Ongoing pregnancies, N	Non-SGA	1,168,523	1.144.071	1,084,766	931316	650,924	298,784	66,601	NA
	SGA P5-10	58,902	58,073	55,628	48,492	34,110	15,871	3,640	NA
	SGA<P5	61,021	60,002	56,920	49,176	34,475	16,221	3,740	NA
Antepartum deaths, N	Non-SGA	203	208	265	266	258	188	52	1,440
	SGA P5-10	13	28	29	22	35	20	3	150
	SGA<P5	54	74	103	93	91	55	15	485
Probability antepartum death/1000	Non-SGA	0.17	0.18	0.24	0.29	0.40	0.63	0.78	1,23
	SGA P5-10	0.22	0.48	0.52	0.45	1.03	1.26	0.82	2,55
	SGA<P5	0.88	1.23	1.81	1.89	2.64	3.39	4.01	7,95
Cumulative probability antepartum death/1000	Non-SGA	0.17	0.36	0.60	0.89	1.28	1.91	2.69	NA
	SGA P5-10	0.22	0.70	1.22	1.68	2.70	3.96	4.79	NA
	SGA<P5	0.88	2.12	3.93	5.82	8.46	11.85	15.86	NA

Table 2 | Continued

		Gestational age							
		36^0 - 36^6	37^0 - 37^6	38^0 - 38^6	39^0 - 39^6	40^0 - 40^6	41^0 - 41^6	42^0 - 42^6	Total
Intrapartum/neonatal deaths, N	Non-SGA	81	105	193	236	272	261	84	740
	SGA P5-10	8	11	13	28	28	23	12	123
	SGA<P5	22	41	47	75	70	85	17	357
Probability intrapartum/neonatal deaths/1000	Non-SGA	3.34	1.78	1.26	0.84	0.77	1.13	1.26	0.63
	SGA P5-10	9.80	4.55	1.83	1.95	1.54	1.88	3.30	2.10
	SGA<P5	22.80	13.63	6.15	5.13	3.85	6.84	4.56	5.90
Composite morbidity, N	Non-SGA	434	489	649	854	1,179	1,047	400	5,052
	SGA P5-10	23	27	55	52	69	80	31	337
	SGA<P5	55	51	86	119	144	164	47	666
Probability composite morbidity /1000	Non-SGA	17.96	8.29	4.24	3.05	3.35	4.52	6.02	4.33
	SGA P5-10	28.47	11.22	7.75	3.63	3.80	6.56	8.55	5.75
	SGA<P5	58.32	17.19	11.32	8.19	7.96	13.29	12.68	11.07

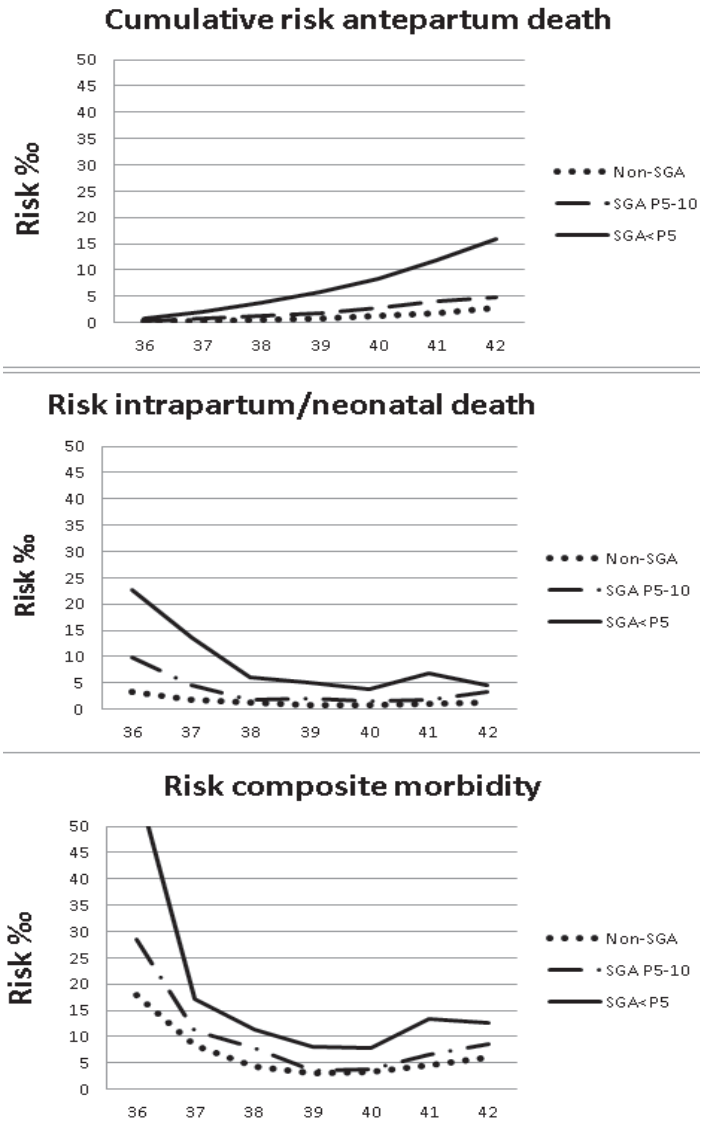

Figure 1 | Risk of death and morbidity in the different SGA groups.

The risks of antepartum death, intrapartum/neonatal death and neonatal morbidity per 1000 births are plotted in figure 1 for each week of gestation. All risks are highest for the SGA<P5 group, followed by the SGA P5-10 group. The risk differences between the groups are most pronounced at the beginning and the end of the term period (i.e. 36-37 weeks of gestation for the risks of intrapartum/ neonatal death and neonatal morbidity and 41-42 weeks for the risk of antepartum death). For all groups neonatal morbidity is lowest at 39 and 40 weeks. In addition, the probability of neonatal morbidity is higher at 37 weeks than at 42 weeks

Figure 2 displays the antepartum, intrapartum/neonatal death, and neonatal morbidity per day for the three SGA groups. For the non-SGA group, the lines representing the risk of intrapartum/neonatal death overlap the line representing the cumulative risk of antepartum death between 39+0 and 39+6. For the SGA P5-10 group, the lines representing the risk of intrapartum/neonatal death overlap the line representing the cumulative risk of antepartum death at 38+3 until 40+0 weeks. The intersection in the SGA<P5 group is at 39+3.

The probability of death with delivery in a certain week versus the probability of death with one week expectant management are represented in table 3. Table 4 provides the relative risks and the absolute risk differences including a number needed to deliver at that gestational age to prevent a single excess death. The probabilities of death of both delivery and expectant management for one more week are relatively low in the non-SGA group compared to the SGA groups. At 36 weeks, expectant management is associated with significantly less mortality than delivery (1.95 vs 3.34 per 1000, RR 0.58 95%CI 0.45-0.75). At 37 and 38 weeks expectant management for one more week is associated with less mortality than delivery although the confidence intervals of the probability of death overlap (1.44 vs 1.78 per 1000, RR 0.81 95%CI 0.64-1.02 at 37 weeks, 1.09 95%CI 0.89-1.28 per 1000 vs 1.26 95%CI 1.24-1.28 per 1000 at 38 weeks). From 39 weeks of gestation onwards, delivery is associated with significantly less mortality than expectant management for one week (1.06 vs 0.84 per 1000, RR 1.26 95%CI 1.05-1.50). The probability of neonatal morbidity is significantly lower at 39 weeks compared to 38 weeks (3.05 vs 4.24‰, p<0.0001). The numbers needed to deliver to prevent one death vary from 4,627 at 39 weeks to 1,303 at 41 weeks (table 4).

For the SGA P5-10 group, there is a trend towards less mortality at 36 and 37 weeks gestation with expectant management for one more week but the confidence intervals overlap (4.77 vs 9.80 per 1000 at 36 weeks and 2.31 vs 4.55 per 1000 at 37 weeks). From 38 weeks onwards, delivery is associated with less mortality than expectant management for one more week but the confidence intervals overlap. Only from 40 weeks onwards, the differences are statistically significant (2.91 vs 1.54 per 1000, RR 1.89 95%CI 1.15-3.11). The numbers needed to deliver to prevent one death are 1,558 at 38 weeks and 373 at 41 weeks.

For the SGA<P5 group, expectant management for one more week is only favorable at 36 weeks (14.5 vs 22.8 per 1000, RR 0.64 95%CI 0.39-1.04) and 37 weeks (7.38 vs 13.6 per 1000, RR 0.54 95%CI 0.37-0.79). The mortality risks of delivery are lower from 38 weeks onwards although the confidence intervals overlap at 38 and 39 weeks. The probability of neonatal morbidity is also lower at 38 weeks compared to 37 weeks (11.32 vs 17.19‰, p=0.02, table 2). From 40 weeks onwards delivery is statistically better (9.48 vs 3.85 per 1000, RR 2.46 95%CI 1.80-3.36). The numbers needed to deliver to prevent one death are 1,262 at 38 weeks and 898 at 41 weeks.

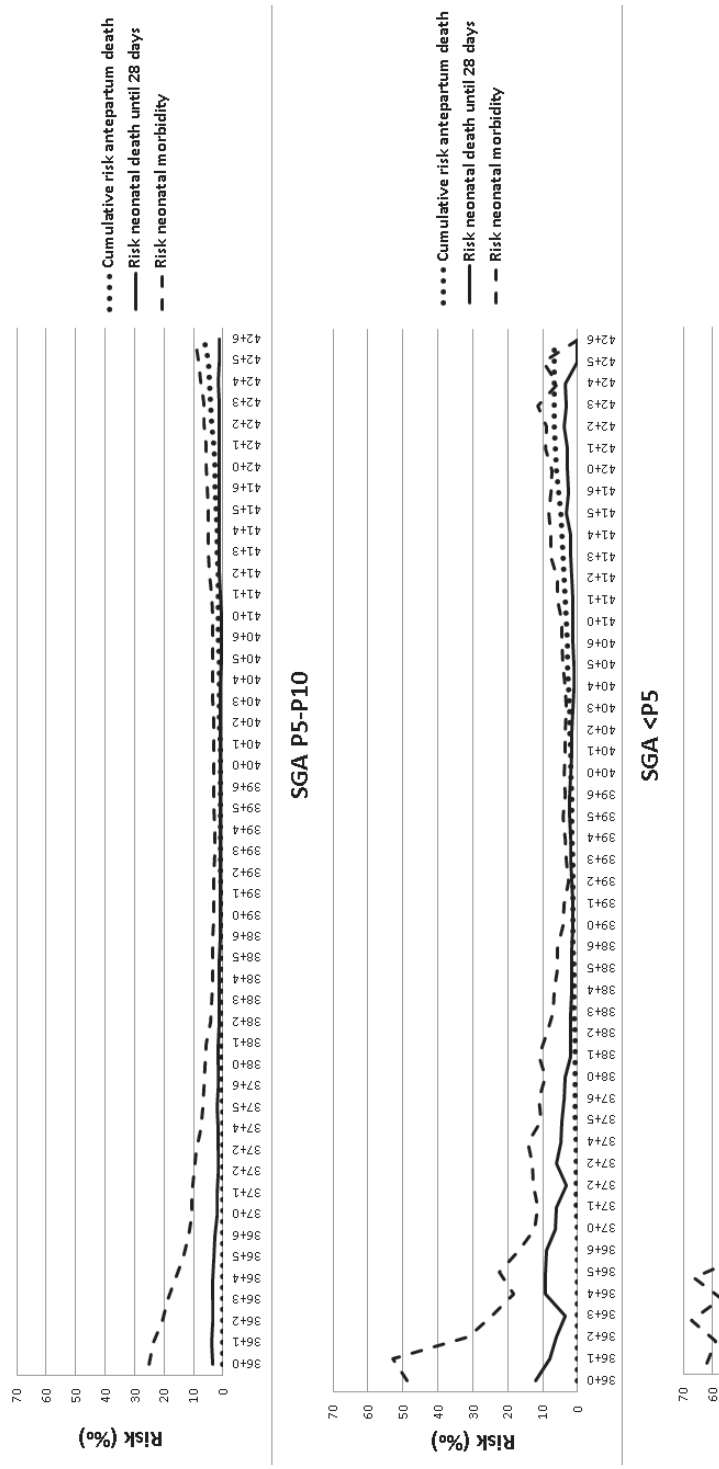

Figure 2 | Balance between antepartum death, intrapartum/neonatal death and neonatal morbidity in the different SGA groups.

Table 3 | Probability of death per 1000 with delivery or expectant management for one week.

Probability of death per 1000 (95% confidence interval)	**Week 36** **36+0 to 36+6**	**Week 37** **(37+0 to 37+6)**	**Week 38** **(38+0 to 38+6)**	**Week 39** **(39+0 to 39+6)**	**Week 40** **(40+0 to 40+6)**	**Week 41** **(41+0 to 41+6)**
Non-SGA; delivery in week	3.34 (3.28-3.40)	1.78 (1.75-1.81)	1.26 (1.24-1.28)	**0.84 (0.83-0.85)**	**0.77 (0.77-0.78)**	**1.13 (1.11-1.14)**
Non-SGA; one week expectant	**1.95 (1.22-2.69)**	1.44 (1.09-1.80)	1.09 (0.89-1.28)	1.06 (0.92-1.20)	1.52 (1.37-1.67)	1.89 (1.66-2.12)
SGA P5-10; delivery in week	9.80 (9.68-9.88)	4.55 (4.35-4.75)	1.83 (1.74-1.92)	1.95 (1.89-2.02)	**1.54 (1.49-1.59)**	**1.88 (1.82-1.95)**
SGA P5-10; one week expectant	4.77 (-2.03-11.6)	2.31 (-0.43-5.05)	2.47 (1.32-3.62)	1.99 (1.1-2.89)	2.91 (1.98-3.84)	4.56 (3.10-6.02)
SGA<P5; delivery in week	22.8 (20.3-25.6)	13.6 (12.5-14.9)	6.15 (6.04-6.26)	5.13 (5.05-5.22)	**3.85 (3.78-3.93)**	6.81 (6.73-6.89)
SGA<P5; one week expectant	14.5 (5.00-24.0)	**7.38 (3.12-11.6)**	6.94 (4.94-8.95)	5.75 (4.27-7.22)	9.48 (7.91-11.05)	7.95 (5.71-10.2)

Bold numbers are statistically significant better strategies when comparing delivery in the particular week to expectant management for one more week

Table 4 | Relative risks and absolute risks of expectant management for one more week compared with delivery in a certain week.

	Non-SGA				**SGA P5-10**				**SGA<P5**			
	Relative risk	**95%CI**	**Absolute risk difference**	**Number needed to deliver**	**Relative risk**	**95%CI**	**Absolute risk difference**	**Number needed to deliver**	**Relative risk**	**95%CI**	**Absolute risk difference**	**Number needed to deliver**
36	0.58	(0.45-0.75)	-1.41	x	0.49	(0.20-1.17)	-5.03	x	0.64	(0.39-1.04)	-8.28	x
37	0.81	(0.64-1.02)	-0.34	x	0.51	(0.25-1.02)	-2.24	x	0.54	(0.37-0.79)	-6.25	x
38	0.86	(0.72-1.04)	-0.17	x	1.35	(0.70-2.60)	0.64	1,558	1.13	(0.89-1.59)	0.79	1,262
39	1.26	(1.05-1.50)	0.22	4,627	1.02	(0.58-1.78)	0.04	23,840	1.12	(0.83-1.52)	0.61	1,637
40	1.97	(1.66-2.33)	0.75	1,335	1.89	(1.15-3.11)	1.37	729	2.46	(1.80-3.36)	5.63	178
41	1.68	(1.39-2.03)	0.77	1,303	2.42	(1.33-4.41)	2.67	373	1.16	(0.83-1.63)	1.11	898

DISCUSSION

Our data suggest that the optimal timing of delivery according to mortality risk in SGA<P5 is at 38 to 39 weeks, as well as for non-SGA pregnancies.. For the SGAP5-10 there is a less clear defined interval. Delivering a SGA<P5 fetus outside this window is associated with an increased probability of antepartum death, neonatal death and morbidity compared with non-SGA fetuses.

The strength of this study is the size of the cohort (1,294,547), including patients over a long and recent period (1999-2007), with data derived from a reliable and validated linked population-based database [8;9]. The registry includes almost all deliveries in the country (96%) and is therefore a good reflection of our population. In addition, we were able to exclude congenital anomalies and comorbidities, creating a cohort with isolated SGA.

Moreover, this study incorporates the risk of antepartum death with ongoing pregnancy as well as the risk of intrapartum /neonatal death with delivery. Most other studies investigating the timing of delivery in SGA only take the risk of stillbirth into account [2;17].

Ideally, this study should be done in a population without any medical interference to study the natural course of pregnancy. We chose to include both women in whom labor was induced as well as those who had a spontaneous onset of labor. In the Netherlands, most antepartum deaths are induced. Analyzing only spontaneous deliveries would therefore introduce selection bias because doing so would exclude the majority of antepartum deaths. The fact that we included induced deliveries, implicated that we introduced a medical decision factor that could have influenced our outcomes. In view of the fact that induction was clinically applied and probably based on factors indicating a poor outcome, we hypothesize that the effects would even have been stronger when the natural course would have been followed. Indeed, more women in the SGA group < P5 had labor induced.

One of our study limitations was the use of birthweight instead of estimated fetal weight. We base our decisions to intervene in a pregnancy on estimated fetal weight. Because of the use of registry data instead of original patient records, we do not know which fetuses were suspected to be SGA or growth restricted, although this was probably a minority [18]. As a result, we could not extrapolate which pregnancies had interventions because of the suspected growth restriction. Based on clinical practice, we assumed that pregnancies with abnormal Dopplers or fetal distress were more likely to be delivered earlier than other pregnancies (worst first).

Difficulty with studying antepartum death is that the exact time of the death is mostly not known. The antepartum death could have occurred days before the diagnosis. Women have weekly antenatal checkups after 36 weeks, so diagnosis of stillbirth could not have been delayed by more than a week in most cases. As a result, the risks at earlier gestational age are probably higher than currently displayed. This would shift the line representing the risk of antepartum death to the left, possibly leading to an earlier optimal timing of delivery. In addition, intrauterine fetal weight gain or loss after antepartum death could have led to misclassification of birthweight percentile in individual cases.

A further point of discussion is the gestational age estimation. Our database does not contain information about pregnancy dating. Although in our study period ultrasound increasingly replaced last menstrual period for dating, no data are available on how pregnancy was dated in individual cases.

Our findings are supported by a secondary analysis of the DIGITAT trial. In the DIGITAT trial, women with suspected growth restriction between 36^{+0} and 41^{+0} were randomized for induction of labor or expectant management for one more week[6]. The goal of the secondary analysis was to assess the neonatal morbidity of both groups in more detail. That analysis showed that the incidence of neonatal morbidity in IUGR at term is comparable and relatively mild either after induction or after expectant management. However, neonatal admissions are lower after 38 weeks of pregnancy. They concluded that if induction to prevent possible stillbirth is considered, it is reasonable to delay until 38 weeks, provided watchful monitoring [19]. Another study looked at the risk of stillbirth in the SGA group near term and reported that the risk of stillbirth becomes steeper from 39 weeks onwards [2].

Our conclusion differs from a recent study which advocates a policy of delivery at 37-38 weeks of SGA fetuses based on the 5-fold increased risk of stillbirth [17]. Notably, the risk of neonatal death was not taken into account. Although our study underlines the fivefold increased risk of stillbirth/antepartum death at and over 37 weeks, our conclusion about the optimal timing of delivery is different because we incorporated both antepartum as well as intrapartum/neonatal risk of death.

Notably, the results of this study also indicate that for women without SGA, delivery at 39 weeks is associated with the lowest risk of death. Currently a randomized trial is running in the United States randomizing nulliparous women for induction of labor at 39 weeks of gestation versus expectant management and induction at 42 weeks (NCT01076062)[20], which is powered (N=200) on caesarean delivery as primary endpoint. In the future, we need larger studies to address the impact of induction of labor on perinatal mortality and long term neonatal development.

Our results are important since many clinicians induce suspected SGA fetuses at 36 or 37 weeks of gestation to prevent antepartum death. Our results show that for SGA<P5 infants at 37 weeks expectant management for one more week leads to less mortality then delivery. This suggests that by inducing SGA infants at 37 weeks in the absence of other indications for delivery, infants might (unintentionally) be harmed.

We think that with the current knowledge, one should consider delaying delivery of isolated SGA infants until 38 weeks without other indications for delivery and watchful monitoring. It is important to realize that the earlier mentioned DIGITAT study indicated that, based on randomized data, there was no harm observed from induction of labor in terms of an increased Caesarean section rate or poor neonatal outcome rate, and that financial costs were comparable [6].

Obviously, maternal preferences and maternal and fetal condition should be taken into account in the ultimate decision, but our data suggest that in pregnancies with suspected SGA, induction of labor should be considered from 38 weeks onwards.

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