Survival and neonatal morbidity among extremely preterm born infants in relation to gestational age based on the last menstrual period or ultrasonographic examination

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Abstract

Objectives: The aim of this study was to investigate the potential impact of gestational age (GA) estimation on the basis of the last menstrual period (LMP) in comparison with GA based on ultrasound examination on rates of survival and neonatal morbidity among extremely preterm infants.

Methods: The Swedish national registry of infants born extremely preterm (Extremely Preterm Infants in Sweden Study), including infants born before 27 weeks of gestation, was used to identify 645 infants with available information. Incidences of stillbirth, survival, small for GA (SGA), and major neonatal morbidity were calculated in relationship to the GA estimated by each of the approaches.

Results: Pregnancies, in general, appeared to be longer when GA was estimated by LMP than by ultrasound (17.2% of the pregnancies were longer than 27 weeks). The incidences of stillbirth, neonatal death, and major neonatal morbidity in relationship to GA were similar for both groups. The risks for SGA were elevated when GA according to ultrasound examination was at least 7 days shorter than GA based on the LMP.

Conclusions: In our cohort of infants born extremely preterm, estimation of GA on the basis of LMP indicated a longer pregnancy than estimated by ultrasound but did not influence the incidences of neonatal survival and morbidity.

Keywords: Extremely preterm infants; gestational age estimation; pregnancy; pregnancy dating; ultrasound.

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Introduction

Clinical decision making and perinatal management of infants born extremely preterm are routinely based on the estimated gestational age (GA), which is strongly associated with neonatal mortality and morbidity in such cases [7, 8]. Today, it is generally accepted that estimation of GA by ultrasound (US) in early pregnancy is more precise and reliable than dating based on the last menstrual period (LMP) [9, 14, 18, 30], and US fetometry has become the exclusive means of pregnancy dating in Sweden during the past decades [13]. Consequently, if the estimated date of delivery according to the LMP (GA-LMP) and according to US examination (GA-US) differs, obstetricians rely entirely on the latter [1].

Several authors have described an elevated risk for fetal growth restriction, preterm delivery, low birth weight, and fetal death when the GA determined by US was substantially shorter than that estimated by LMP [17, 20, 24, 25]. Indeed, a recent Swedish study confirmed that such a discrepancy reflects early intrauterine growth restriction (IUGR), a phenomenon associated with enhanced risk for small for GA (SGA) birth weight, preterm delivery, and preeclampsia [30].

The morbidity and mortality among infants born extremely preterm, i.e., prior to 27 weeks of gestation, in a recent large Swedish national study (Extremely Preterm Infants in Sweden Study [EXPRESS]) were lower than what have been reported for other population-based studies [7, 5, 19, 21, 31]. Because neonatal morbidity and mortality are strongly correlated to GA, the method employed to estimate GA should be considered when comparing the results between studies.

Accordingly, the aim of the present investigation was to compare the potential impact of GA-LMP or GA-US with respect to neonatal morbidity and mortality among infants born extremely preterm.

Materials and methods

Data from the EXPRESS registry were used for this analysis. The EXPRESS registry is population based and national wide and contains information on all infants born alive prior to 27 weeks of gestation and all stillborn infants born at 22+0–26+6 between April 1, 2004, and March 31, 2007, in Sweden.

In Sweden, all pregnant women are offered free antenatal care. At their first visit, usually 10–12 weeks after the LMP, obstetric history, smoking status and alcohol consumption, height and weight, general state of health, family situation, and the first day of LMP are recorded. Most of pregnant women undergo a routine US examination by specially trained midwives at 16–18 weeks of gestation, in order to detect multiple pregnancies and fetal malformations and to calculate the date of delivery. In this context, the estimated GA is recorded in medical charts and used for subsequent clinical management [1, 13]. The most commonly used formula for estimation of GA in Sweden is that by Persson and Weldner based on the ultrasonically measured fetal biparietal diameter (BPD) and femur length [13, 27]. A standardized quality control of the US procedure is performed regularly [13]. The information from mothers' antenatal and delivery records and the data on infants from neonatal records were collected and transferred to the EXPRESS database. Data collection, validation, and organization of the EXPRESS registry, as well as the characteristics of the mothers included in this study, are described elsewhere [7]. In the study population, 78% received antenatal therapy with corticosteroids and 50% of infants were born by cesarean section [7].

In total, 860 women (95%) in the EXPRESS registry underwent US pregnancy examination during the study period [7]. For our present purposes, we initially included 650 singleton pregnancies for which information on GA-LMP and GA-US was available from the EXPRESS registry. Of these, we subsequently excluded five pregnancies with a discrepancy between GA-US and GA-LMP of >30 days apparently due to erroneous measurement. The remaining 645 infants were divided into live-born and stillbirths in accordance with the World Health Organization definitions [35].

Newborns whose birth weight was more than 2 standard deviations (SDs) less than expected for their GA according to the Swedish standards were considered to be SGA [22]. Major neonatal morbidity was defined as the presence of one or more of the following: retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (cPVL), persistent ductus arteriosus, bronchopulmonary dysplasia, and/or necrotizing enterocolitis (NEC). Severe ROP was defined as ROP ≥stage 3; severe IVH/cPVL, as ≥grade 3; and severe bronchopulmonary dysplasia, as requiring administration of at least 30% oxygen at age corresponding to 36 weeks of gestation [15, 16, 26]. NEC was defined according to Bell et al. [3].

Initially, we correlated the GA-LMP and GA-US to the incidence of stillbirth for each individual week of gestation. Thereafter, we correlated the incidence of stillbirth, neonatal death, and major neonatal morbidity to the GA-LMP and GA-US for the entire cohort. For the final survival analyses, we excluded infants whose GA-LMP was at least 7 days shorter than the GA-US if the GA-LMP specific birth weight was more than 2 SDs above the expected weight.

Discrepancy between GA-US and GA-LMP was expressed in days, with a negative difference indicating that the length of pregnancy (GA) based on US was shorter than that based on the LMP.

Three groups depending on the discrepancy were formed: group 1 included pregnancies with a GA-US minus GA-LMP of ≥–7 days; group 2, with a corresponding difference of –6 to +6 days; and group 3, with a difference of ≥+7 days. The incidences of stillbirth, neonatal death, and morbidity were calculated for each group and compared.

Statistical analyses

The difference between GA-US and GA-LMP was evaluated using Wilcoxon signed rank test. The Spearman ρ was computed to estimate the correlation between GA-US and GA-LMP. The associations between a discrepancy between GA-US and GA-LMP of ≤–7 days (compared with a discrepancy of ≤+/–6 days) and various dichotomized perinatal and neonatal outcomes (listed above) were investigated using simple logistic regression analysis. Overall survival by GA-US and by GA-LMP was determined by standard Kaplan-Meier survival analysis. The statistical analyses were performed using Gauss (Gauss, Aptech Systems Inc., Maple Valley, WA, USA; http://www.aptech.com).

Results

In our study database of 645 singleton infants born extremely preterm, 440 (68.2%) were born alive, and of these, 321 (72.9%) survived to 1 year of age (Table 1).

The distribution of GA at birth, as presented in Figure 1, differed significantly depending on the method used for estimation of GA ($P<10^{-6}$). The mean GA-US was 24.7 weeks [95% confidence interval (CI), 24.6–24.8], whereas the mean GA-LMP was 25.3 (95% CI, 25.2–25.4). The GA-US was significantly lower than the GA-LMP ($P<10^{-6}$). The Spearman ρ for correlation between GA-LMP and GA-US was 0.79 (95% CI, 0.77–0.82).

Although all pregnancies were reported in agreement with criteria for inclusion in the EXPRESS to be shorter than 27 weeks of gestation, the GA-LMP indicated a higher GA in 111 cases (17%). In total, 207 (34%) pregnancies were longer by at least 7 days when GA was calculated according to the LMP than according to US; i.e., the difference between GA-US and GA-LMP was ≥–7 days (Table 2). According to GA-US, 154 pregnancies were at 26+0–26+6, but 75 (49%) of them were longer than 27+0 according to GA-LMP (Table 2).

Twenty-eight fetuses were older than expected at the time of US examination; i.e., the difference between GA-US and GA-LMP was ≥+7 days. In 14 (50%) of these,

Table 1 Availability of information on GA for infants born extremely preterm, both as determined on the basis of the LMP (GA-LMP) and of US examination (GA-US).

	Stillbirths (n=253)	Postnatal deaths (0–364 days) (n=149)	Survived (n=400)	Total (n=802)
	n (%)	n (%)	n (%)	n (%)
GA-LMP missing	42 (16.6)	20 (13.4)	65 (16.2)	127 (15.8)
GA-US missing	6 (2.4)	8(5.4)	11 (2.8)	25 (3.1)
Difference GA-US–GA-LMP ≥+/–30 days	0 (0.0)	2 (1.3)	3 (0.8)	5 (0.6)
GA-LMP and GA-US available	205 (81.0)	119 (79.9)	321 (80.2)	645 (80.4)

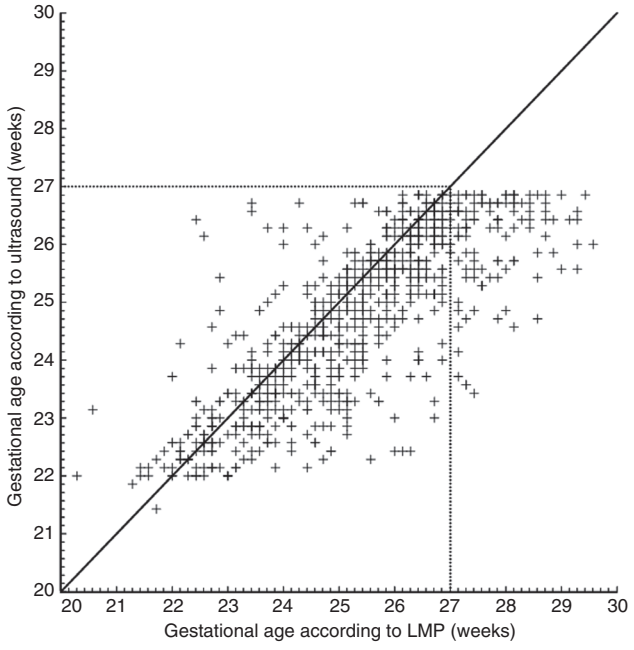

Figure 1 Plot diagram of the relationship between the individual GAs of infants born extremely preterm based on the LMP and on US examination.

did the infants with a GA-LMP of <27 weeks (P for survival<0.01 and P for any morbidity=0.01). Restricting the the birth weight was more than 2 SDs above the expected weight on the basis of GA-LMP. This indicates that for these cases, the LMP recorded was probably erroneous. Therefore, these 14 pregnancies were excluded from the analyses of survival.

The relationship between survival and GA, as determined by the two procedures, is illustrated in Figure 2. For the estimated GA, the survival rates for 23–26 weeks of gestation were similar for both methods. According to the graph, the survival rate of the infants with a GA-LMP longer than 27 weeks seemed to be somewhat lower than that of infants born at a GA of 25 and 26 weeks, but a logistic regression analysis did not reveal any significant difference. The odds ratio (OR) for survival, GA-LMP ≥27 weeks vs. GA-US 25–26 weeks with GA-LMP <27 weeks, was 0.70 (95% CI, 0.42–1.15; P=0.14).

Infants with a GA-US of 24 weeks with corresponding GA-LMP were less likely to suffer stillbirth than were infants with a GA-US of 24 weeks with a different GA-LMP (P=0.024). For the other GA groups, no significant differences were seen. Thus, the incidence of stillbirth demonstrated a similar distribution according both GA-LMP and GA-US (Table 3).

Children with a GA-LMP of ≥27 weeks had significantly higher survival and lower neonatal morbidity than

Table 2 Relationship between the GA of infants born extremely preterm based on LMP or on US examination.

GA based on LMP (weeks)	GA based on US (weeks)						
	<22 (n=2) n (%)	22 (n=76) n (%)	23 (n=120) n (%)	24 (n=129) n (%)	25 (n=164) n (%)	26 (n=154) n (%)	Total <27 (n=645) n (%)
<22	1 (50.0)	6 (7.9)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.2)
22	1 (50.0)	31 (40.8)	8 (6.7)	3 (2.3)	1 (0.6)	2 (1.3)	46 (7.1)
23	0 (0.0)	23 (30.3)	47 (39.2)	6 (4.7)	2 (1.2)	3 (1.9)	81 (12.6)
24	0 (0.0)	11 (14.5)	37 (30.8)	57 (44.2)	11 (6.7)	6 (3.9)	122 (18.9)
25	0 (0.0)	2 (2.6)	18 (15.0)	43 (33.3)	74 (45.1)	5 (3.2)	142 (22.0)
26	0 (0.0)	3 (3.9)	5 (4.2)	11 (8.5)	53 (32.3)	63 (40.9)	135 (20.9)
≥27	0 (0.0)	0 (0.0)	4 (3.3)	9 (7.0)	23 (14.0)	75 (48.7)	111 (17.2)

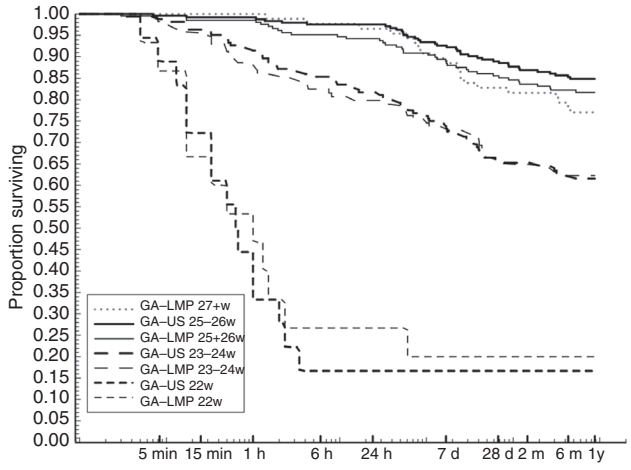

Figure 2 Survival among infants born extremely preterm according to the GA at birth and method of GA estimation. w=weeks.

cohort to infants with a GA-LMP of <27 weeks would be expected to lower the survival rates and to increase the morbidity rates. As demonstrated in Table 4, the percentages of stillbirth, neonatal death, and morbidity in the cohort with a GA-LMP of <27 weeks and the corresponding percentages in the cohort with a GA-US of <27 weeks were quite similar.

Table 5 compares the risk for stillbirth, SGA, postnatal death (0–364 days), and morbidity for pregnancies where the GA-US was at least 7 days shorter than the GA-LMP (GA-US minus GA-LMP ≤–7 days). Infants who were smaller than expected at the routine US examination exhibited an increased risk for SGA or stillbirth, but there was no difference with respect to major neonatal morbidity.

Among the 28 pregnancies where GA-US minus GA-LMP was ≥+7 days, five of the infants demonstrated severe IVH/cPVL; this morbidity remained elevated even after adjustment for possible confounders (data not shown). There was no elevated risk for other neonatal morbidity or mortality in this group.

Table 3 Incidence of stillbirths among infants born extremely preterm in relation to GA based on US examination or on LMP.

GA (weeks)	GA based on US	GA based on LMP
	n/N (%)	n/N (%)
<22	1/2 (50.0)	4/8 (50.0)
22	58/76 (76.3)	27/46 (58.7)
23	48/120 (40.0)	37/81 (45.7)
24	33/129 (25.6)	44/122 (36.1)
25	33/164 (20.1)	31/142 (21.8)
26	32/154 (20.8)	38/135 (28.1)
≥27	–	24/111 (21.6)

Table 4 Incidence of stillbirths, postnatal death (0–364 days), major neonatal morbidity among infants with a GA of <27 weeks based on LMP or US examination.

	GA <27 weeks based on US	GA <27 weeks based on LMP
	n/N (%)	n/N (%)
Stillbirth	205/645 (31.8)	181/534 (33.9)
Death 0–364 days	119/440 (27.0)	99/353 (28.0)
SGA[a]	73/440 (16.6)	44/353 (12.5)
Severe ROP[b]	115/321 (35.8)	99/254 (39.0)
Severe IVH/cPVL[c]	47/318 (14.8)	45/254 (17.7)
Severe BPD	70/293 (23.9)	54/232 (23.3)
NEC	16/321 (5.0)	8/254 (3.1)
No major morbidity[d]	172/321 (53.6)	145/254 (57.1)

BPD=bronchopulmonary dysplasia.
[a]Birth weight more than 2 SDs below the Swedish standard mean [15].
[b]ROP stage >2.
[c]IVH stage >2.
[d]Survival without any major neonatal morbidities (severe ROP, severe IVH/cPVL, severe BPD, and NEC).

Discussion

In the present study, our findings confirm that when GA is determined on the basis of the LMP, pregnancies appear to be longer than when US is employed to calculate GA. However, among the studied infants born extremely preterm, the incidences of stillbirth, early neonatal death, SGA, and major neonatal morbidity were similar for the two dating approaches.

The above results might seem contradictory because the incidence of mortality and neonatal morbidity is reduced with increasing GA [7]. The probable explanation for this finding is that the fetuses that were smaller than expected at the time of US scan, i.e., those who appeared to be older on the basis of LMP, actually experienced IUGR and were at a higher risk for an adverse neonatal outcome [6, 12]. Clinical management of imminent preterm births, as well as the treatment of and prognosis for infants born extremely preterm, is strongly influenced not only by GA but also by a timely and reliable antenatal diagnosis of IUGR [10, 33]. In the current practice, estimation of GA by US is considered to be the most accurate, without taking the possible fetal growth restriction into consideration. This could lead to erroneous diagnosis of a preterm rather than growth-restricted infant and thereby result in a suboptimal clinical management.

Internationally, estimation of GA is most often based on US fetometry, but quite frequently on the records of LMP as well. In reports on several large European studies, the method for estimation of GA has not been described in

Table 5 Perinatal outcome among infants born extremely preterm in relationship to the discrepancy between GA-US and GA-LMP.

		Difference between GA-US and GA-LMP (days)				
	All	≥−7	≥−6–≤+6	OR for GA US–GA LMP ≥−7 compared with reference		≥+7
	N	n (%)	n (%)	OR	95% CI	n (%)
All births	605	207 (34.2)	410 (67.8)			28 (4.6)
Stillbirth	205	79 (38.5)	119 (58.0)	1.51	1.06–2.15	7 (3.4)
Born alive	440	128 (29.1)	291 (66.1)	1.00	Reference	21 (4.8)
Death 0–364 days	119	41 (34.5)	72 (60.5)	1.43	0.91–2.26	6 (5.0)
Survived 1 year	321	87 (27.1)	219 (68.2)	1.00	Reference	15 (4.7)
Growth in infants born alive						
SGA[a]	73	31 (42.5)	40 (54.8)	2.00	1.19–3.39	2 (2.7)
AGA+LGA	367	97 (26.4)	251 (68.4)	1.00	Reference	19 (5.2)
Neonatal outcome in infants surviving 1 year						
ROP 3+	115	34 (29.6)	75 (65.2)	1.23	0.73–2.06	6 (5.2)
ROP 0–2	206	53 (25.7)	144 (69.9)	1.00	Reference	9 (4.4)
IVH 3+/cPVL	47	8 (17.0)	34 (72.3)	0.56	0.25–1.27	5 (10.6)
IVH 0–2	281	79 (28.1)	192 (68.3)	1.00	Reference	10 (3.6)
Severe BPD	70	19 (27.1)	48 (68.6)	1.04	0.57–1.92	3 (4.3)
No or mild BPD	230	59 (25.7)	158 (68.7)	1.00	Reference	13 (5.7)
NEC	16	8 (50.0)	8 (50.0)	2.70	0.97–7.41	0 (0.0)
No NEC	305	79 (25.9)	211 (69.2)	1.00	Reference	15 (4.9)
Any major morbidity[b]	172	46 (26.7)	117 (68.0)	0.96	0.56–1.64	9 (5.2)
No major morbidity[b]	149	41 (27.5)	102 (68.5)	1.00	Reference	6 (4.0)

The table displays ORs for stillbirth, neonatal mortality and morbidity (vs. the reference groups indicated in the table), difference between GA-US and GA-LMP ≥−7 days, compared with a corresponding difference of +/−6 days. The ORs were obtained using logistic regression analysis. AGA=appropriate for gestational age, LGA=large for gestational age, BPD=bronchopulmonary dysplasia.

[a]Birth weight more than 2 SDs below the Swedish standard mean [20].

[b]Major neonatal morbidity: severe ROP, severe IVH/cPVL, severe BPD, and/or NEC.

detail [5, 19, 31]. In order to include infants with correct GA in their study, Wood et al. [34] recalculated GA by using the date of LMP and excluded infants with a discrepancy of at least 14 days between GA-US and GA-LMP. In that study, as in many other reports, the outcome was presented for the whole cohort independent of the method of GA estimation; possibly, in an unknown proportion of cases, the duration of pregnancies was estimated by LMP [5, 19, 31, 34]. The American College of Obstetricians and Gynecologists emphasized that the estimation of GA by US is more accurate when performed in the first trimester, i.e., when GA is based on measurements of crown-rump length [2]. Thus, variation in the method used for GA determination, the time of US examination, as well as the measurement procedure, equipment, and dating formula employed might all influence the estimation of GA [29]. In cases of infants born extremely preterm, in whom determination of GA is central to classification and diagnosis, such variation can significantly influence the research findings and public health reports. The results of the EXPRESS, where GA was mainly (in 95%) based on US examination, indicate comparatively lower neonatal mortality and morbidity rates [7]. Nevertheless, in the present investigation, similarly to the findings described by Markestad et al. [21], the incidence of neonatal morbidity and mortality in relation to GA-LMP was similar to those reported previously in the EXPRESS [7]. Thereby, our findings justify comparisons with the results reported from other population-based studies, even if the estimation of GA was based on LMP.

Estimation of GA by ultrasonographic biometry is recognized as being more reliable than GA-LMP [9, 18, 30] mostly because estimation based on the LMP assumes that conception occurs on day 14 of the cycle, whereas the time point of ovulation during the menstrual cycle varies greatly. Indeed, several studies have shown that estimation of GA based on LMP, even when the recall is certain, is unreliable [4, 11, 28, 32]. Moreover, there is evidence that a discrepancy between GA-US and GA-LMP is correlated with an enhanced probability of fetal growth restriction, fetal death, and preterm delivery [17, 20, 24, 25]. In agreement with previous reports, we demonstrated here that the risk for SGA was higher among fetuses that were smaller

than expected at the time of the US scan, i.e., fetuses for whom GA-US minus GA-LMP was ≤–7 days [23]. However, these infants exhibited nearly the same incidence of major neonatal morbidity compared with those for whom GA-US and GA-LMP were in agreement, even after adjusting the OR for GA, maternal age, parity, smoking, and body mass index. Thus, the discrepancy between the two procedures for estimation of GA was not associated with any alteration in major neonatal morbidity.

The OR was increased only for grade 3 IVH in the group of fetuses larger than expected upon US examination. Most likely, these infants had a larger BPD and were therefore estimated as being older. Fetuses with a larger BPD than expected have been reported to be at increased risk for macrosomia and preterm birth, but to our knowledge, there is no evidence of any relationship between enlarged BPD and IVH during the neonatal period [23].

The EXPRESS registry contains information on all infants born prior to 27 weeks of gestation during a 3-year period, and this database can therefore be considered to be representative for the entire extremely preterm population of Sweden. There was no selection regarding socioeconomic status, ethnicity, or geographical location and all pregnancies were included, even those conceived with assisted reproduction techniques. The information required for the present analyses was available for 80.4% of pregnancies, indicating that the study material was large enough to allow the results to be applicable to corresponding populations in other industrialized countries.

In summary, the present study shows that in connection with extremely preterm births, GA differs depending on the method employed for pregnancy dating. It illustrates also the complexity of GA estimation and the difficulties associated with interpretation of biometrical US measurements. Despite the differences in the estimated GA, the incidence of neonatal mortality and morbidity in relation to GA was similar with both methods. Furthermore, our findings seem to allow comparisons with other reports on outcome of preterm births in various populations when estimation of GA is based on BPD and femur length (FL) measurements.

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