Errors in Gestational Age: Evidence of Bleeding Early in Pregnancy

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ABSTRACT

Objectives. This study explored the extent of errors in gestational age as ascertained by last menstrual period.

Methods. More than 1.5 million birth records (covering the years 1967–1994) from the population-based Medical Birth Registry of Norway were used to study variation in gestational age within strata of birthweight.

Results. Within 100-g strata of birthweight, it was found that the observed gestational age distribution could be divided into 3 distinct underlying distributions separated by approximately 4 weeks. This pattern was present through all birthweight strata, from 200 g up to 4700 g. In addition, the apparent misclassification causing a gestational age 4 weeks too short was much more common among low-birthweight births than among heavier births.

Conclusions. The separation of the gestational age distributions by intervals of close to 4 weeks suggests that errors in gestational age measurements are caused by factors related to menstrual bleeding. Furthermore, there is evidence for a strong relation between bleeding at the time of the next menstrual period after conception and low birthweight. This conclusion should be approached with caution because of the retrospective nature of the data. (*Am J Public Health.* 1999;89:213–218)

Gestational age is one of the most studied variables in perinatal epidemiology, despite being notoriously difficult to measure. Errors in gestational age are inevitable with nearly any method of measurement, including the commonly used benchmark of the last menstrual period. The usual approach in handling this problem has been to look at the distribution of birthweight within gestational age strata.[1–7] However, a more direct look at gestational age misclassification is possible by stratifying on birthweight (which is the more accurately measured variable) and then inspecting the gestational age distribution within those securely defined strata.[8]

We used data from the Medical Birth Registry of Norway to study the gestational age distribution within birthweight strata. We attempted to summarize misclassifications in gestational age by looking for underlying distributions that might represent systematic errors in gestational age based on last menstrual period.

Methods

Data and Selection

The Medical Birth Registry of Norway, based on compulsory notification, comprises records for all births in the country since 1967 (live births, stillbirths, and reported fetal deaths with at least 16 completed weeks of gestation). In Norway, the first day of the last menstrual period is routinely recorded at the first prenatal visit and transferred to the nationally standardized registry form by the midwife at birth. Our data set contained more than 1.5 million births from the years 1967 through 1994. We excluded multiple births (2.2%), as well as births with missing birthweight (0.23%) and missing last menstrual period information (6.0%). Infants with birthweights of less than 150 g or greater than 5550 g were excluded (0.07%). The overall exclusion rate was 8.3%. Table 1 shows the number of births remaining in each birthweight stratum.

Mixture Fitting

We stratified births by rounding to the nearest 100 g. Gestational age was measured in number of days from last menstrual period to birth. To explore whether the gestational age distribution might be composed of separate underlying distributions, we fitted a mixture of 3 Gaussian distributions within each of the 54 birthweight strata using our own algorithm in S-PLUS.[9–12] Our fitting criterion was the modified chi-square distance measure.[12] For a selection of strata, the results were confirmed via the software package PeakFit.[13] To obtain a stable estimation, we assumed equal standard deviations for the 3 distributions within each stratum. In addition to the Gaussian distribution, we explored a selection of other distributions with different shapes and degrees of skewness, including the log-normal distribution. We also tried varying the number of underlying distributions. The estimated parameters from the mixture distributions consisted of the mean values of the 3 peaks (distributions), the common standard deviation, and the percentage of births in each of the peaks. Parameters were estimated for each weight stratum independently.

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To help focus on the gestational age variability due to misclassifications, we attempted to remove some of the gestational age variability due to sex and parity. Within each birthweight stratum, the gestational age distributions of the 4 sex–parity groups (male/female, zero/higher parity) were rigidly shifted so that the mean of each was set to the total mean gestational age in the stratum before correction.

Once a set of underlying distributions had been estimated for a given weight stratum, we compared these distributions, and their sum, with the observed gestational age distribution. For this purpose, the observed distributions were smoothed[14] by means of the S-PLUS function ksmooth[15] (see Figure 1). We estimated goodness of fit for the sum of the 3 distributions using chi-square statistics for the difference between observed and estimated distributions.

The mode value of gestational age was computed from the smoothed observed distribution.

Results

Peak Separations

Our estimations separated the gestational age distributions into 3 peaks. When we fitted only 2 peaks, the estimates of the 2 main peaks remained largely unchanged, but the overall fit declined somewhat. Adding a fourth peak did not improve the fit but, rather, distorted the estimates of the first 3 peaks.

The estimated values for the 3 peaks were relatively stable under different choices of underlying distributions, including skewed distributions, as long as the assumption of equal standard deviations remained in force. In the final analysis, we therefore chose a mixture of 3 Gaussian distributions.

Within representative birthweight strata, Figure 1 shows the observed gestational age distributions (smoothed), together with the 3 estimated underlying Gaussian distributions and their sum. We refer to the 3 peaks as peaks 1, 2, and 3, in order of increasing gestational age.

Inspection of Figure 1 shows a good correspondence between the observed and estimated distributions for all birthweight strata. The computed chi-square test statistics showed a reasonably good fit for birthweights below 2100 g (16 of the 19 *P* values were above .05). While the statistical goodness of fit seemed to deteriorate at higher weights, this most likely reflected the rapidly increasing sample size at heavier weights.

Table 1 lists the standard deviation and percentage of birth estimates for each peak. The presented values were computed as weighted averages of the estimates in pairs of 100-g categories.

TABLE 1—Number of Births, Estimated Percentages in Each of the 3 Peaks, and Common Estimated Standard Deviation (in Days) of the 3 Peaks, Computed Within Strata of Birthweight

Birthweight Strata, g	No. of Births	Peak 1, %	Peak 2, %	Peak 3, %	SD
200 and 300	1 703	73.8	15.4	10.9	9.2
400 and 500	1 978	76.6	14.0	9.4	8.8
600 and 700	2 005	73.3	18.0	8.6	8.8
800 and 900	2 279	67.2	23.1	9.7	8.6
1 000 and 1 100	2 449	65.3	27.3	7.4	9.2
1 200 and 1 300	2 809	65.9	26.6	7.4	10.7
1 400 and 1 500	3 159	60.8	30.2	9.0	10.5
1 600 and 1 700	4 110	63.0	30.4	6.6	11.0
1 800 and 1 900	5 392	62.6	34.0	3.5	11.8
2 000 and 2 100	8 059	56.8	39.1	4.1	11.6
2 200 and 2 300	12 468	50.8	46.5	2.7	11.2
2 400 and 2 500	22 552	41.9	56.7	1.4	11.5
2 600 and 2 700	42 469	25.3	72.1	2.6	10.7
2 800 and 2 900	80 981	11.6	86.1	2.3	10.4
3 000 and 3 100	139 407	5.5	92.1	2.3	9.8
3 200 and 3 300	197 187	3.3	94.2	2.5	9.2
3 400 and 3 500	235 226	2.2	95.3	2.5	8.8
3 600 and 3 700	233 411	1.9	95.7	2.4	8.5
3 800 and 3 900	193 543	1.7	95.9	2.4	8.2
4 000 and 4 100	137 654	1.6	95.9	2.5	7.9
4 200 and 4 300	84 486	1.5	96.3	2.1	7.8
4 400 and 4 500	46 065	1.8	96.1	2.1	7.7
4 600 and 4 700	22 433	1.8	96.1	2.0	7.6
4 800 and 4 900	10 127	3.1	94.6	2.3	7.4
5 000 and 5 100	4 327	3.7	93.3	3.0	7.2
5 200 and 5 300	1 663	5.7	89.0	5.2	7.0
5 400 and 5 500	634	14.5	72.5	13.0	6.0
Total	1 498 576	6.0	91.5	2.5	. . .

Note. Values were computed as weighted averages over the estimated values in pairs of strata.

Figure 2 summarizes the estimates across all of the birthweight strata. It provides, for each birthweight stratum, the mean for each of the 3 estimated Gaussian peaks of gestational age. In addition, the mode value for the observed gestational age distribution is shown for each birthweight stratum. Each of the 3 peaks can be traced continuously through all birthweight strata from 5500 g down to 200 g. In strata above 2600 g most of the births fell in peak 2, whereas below 2200 g the majority of births fell in peak 1.

The results were not sensitive to the prior adjustment by sex and parity. We investigated this by repeating the estimations without this adjustment. The pattern of peaks was unchanged. We looked for evidence of changes over time by repeating the estimations for the time periods 1967 to 1973 and 1988 to 1994. Although the estimated parameters showed a slight change over time, the general pattern again remained unchanged. We explored the impact of stillbirths on the observed patterns. Each weight stratum above 2000 g contained less than 5% stillbirths, and the exclusion of stillbirths had a negligible effect on the analysis of heavier births. Similarly, for the lower birthweights, the exclusion of stillbirths led only to small changes in the observed gestational age distribution, although the smaller numbers of births remaining made a precise estimation more difficult. Thus, we found no evidence that their exclusion would alter our main results.

Relation of Gestational Age Peaks to Birthweight

For each birthweight stratum, we were able to compute the estimated number of births within, for instance, peak 1 (Table 1). This produced a birthweight distribution corresponding to peak 1 (see Figure 3). The birthweight distributions corresponding to peak 2 and peak 3 were computed similarly. The 3 distributions contained 6.0%, 91.5%, and 2.5% of the total population, respectively, and 58.0%, 37.2%, and 4.8% of the low birthweight (less than 2500 g) children. Their median values were 2650 g, 3500 g, and 3450 g, respectively. Within each separate peak, the percentages of low birthweight children were 35.9%, 1.5%, and 1.7%, respectively.

Discussion

The end of a pregnancy is easily determined, but its beginnings are obscure. The

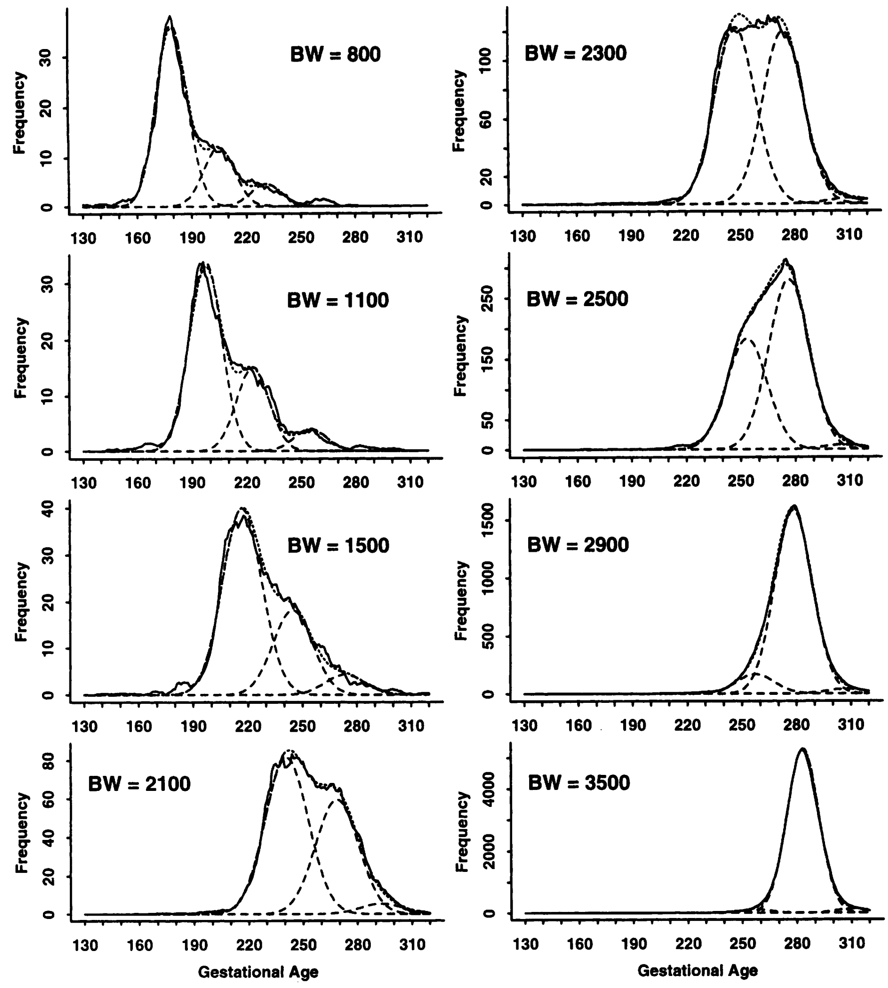

FIGURE 1—Observed gestational age frequency distributions (smoothed), peaks 1, 2, and 3 and their sum, computed within 8100-g strata of birthweight (BW) (observed: ——; peaks 1, 2, and 3: – – –; mixture: · · ·).

last menstrual period is the standard clinical benchmark for the start of gestation and the most widely available. For these reasons, last menstrual period is often the basis for estimating gestational age in epidemiologic studies. Still, gestational age based on last menstrual period is subject to frequent error.[1-7,16] Last menstrual period may be unknown (e.g., if the woman conceives a second pregnancy without an intervening menses), it may be recalled incorrectly by the woman, or it may be misinterpreted because of unusual patterns of bleeding.

Ultrasound measures of gestational age based on fetal size are not a gold standard, although they may correct some of the worst last menstrual period errors. However, ultrasound is rarely available for whole populations, and the selective nature of its use inevitably raises questions about its appropriateness for epidemiologic research. Furthermore, it is not entirely independent of the last menstrual period, since the last menstrual period is usually the basis for timing of the first ultrasound measurement. For this reason, the nature and extent of errors in gestational age based on last menstrual period remain a relevant question.

Choice of Strategy

The bivariate distribution of gestational age and birthweight offers an attractive opportunity for assessing gestational age error. Birthweight is precisely and reliably measured, while gestational age is not. The interdependence between gestational age and birthweight therefore provides a way to restrict gestational age error by controlling for birthweight. This should provide a clearer description of errors in gestational age.

How should one control for birthweight? Previous authors have approached the problem by stratifying on gestational age and inspecting the birthweight distribution. Researchers generally find it more natural to look at birthweight stratified by gestational age, because this direction of stratification is analogous to growth curves from other settings. While this approach may be useful for some purposes (e.g., defining small-for-gestational-age infants), there is no clear causal direction in the relationship between gestational age and birthweight. Thus, there is no inherent reason why gestational age cannot be stratified by birthweight rather than vice versa.

Our strategy in considering gestational age error has been to look at the distribution of gestational age within 100-g strata of weight. We fit a fairly simple and transparent model within each weight stratum, with few assumptions on the structure of the bivariate distribution. This avoided the stricter assumptions apparently required in other models.[3]

Interpreting the Peaks

Our analysis separated the distribution of gestational age based on last menstrual period into 3 Gaussian components within each weight stratum. Differences between the peaks were between 25 and 30 days for 80% of the weight strata below 4700 g. Thus, the separation of the 3 peaks turned out to be generally close to 4 weeks, even though the estimation procedures made no assumptions about the peak intervals and the estimates were calculated independently for each of these 46 weight strata.

How might these gestational age peaks be interpreted? The simplest explanation is that only 1 of the peaks represents the correct gestational age, while the other 2 represent systematic errors.

How can we say which peak is the correct one? Within the range of the most usual birthweights (say, 3000 g to 4500 g), there can be little doubt that peak 2 represents the correct gestational age distribution, since the vast majority of babies fall under the middle peak (e.g., see the distribution of gestational age at 3500 g; Figure 1 and Table 1). Figure 2 shows the positions of the 3 peaks across all birthweight strata. The peaks follow 3 nearly parallel bands from the normal-weight regions down to the low weights. The bands are reasonably smooth. The continuity of the peaks across all birthweight strata strongly suggests that peak 2 is the correct one for all weights. Any other interpretation would require an arbitrary leap from peak 2 in the upper birthweight range to peak 1 in the lower birthweight range. We thus obtained a complete separation of the entire bivariate distribution into 3 bivariate distributions separated by approximately 4 weeks in gestational age.

Moving from heavier to lighter birthweight strata, it can be seen that peak 1

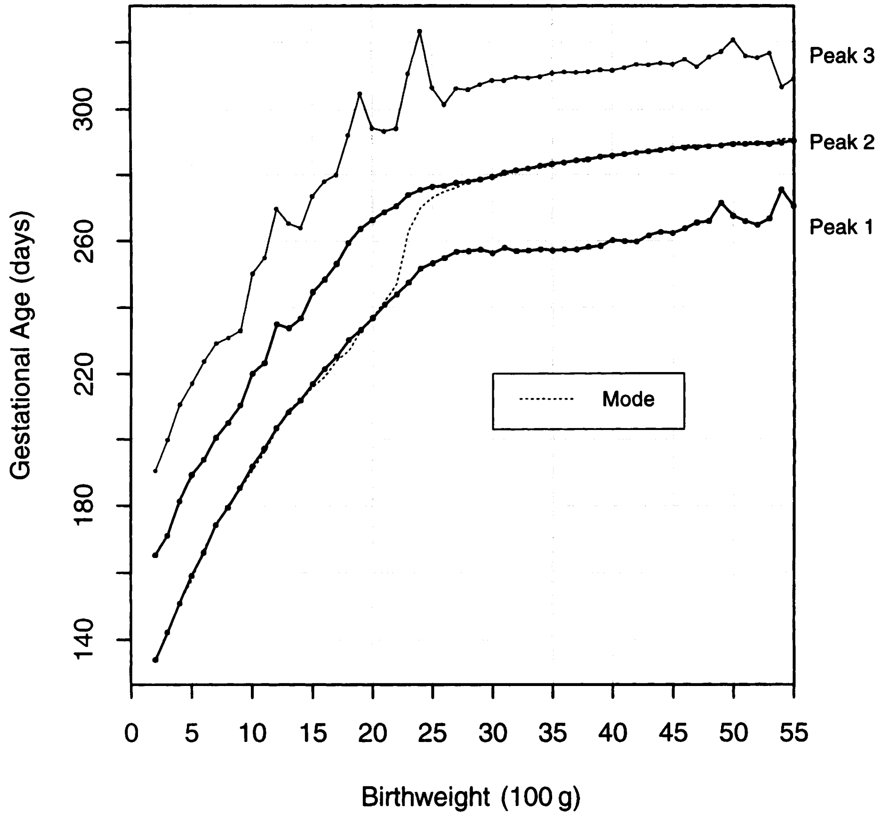

FIGURE 2—Estimated positions of the 3 Gaussian peaks, together with mode values for gestational age, computed within 100-g strata of birthweight.

becomes progressively larger. At 2900 g, there is visible asymmetry of the gestational age distribution. At 2500 g, peak 1 has attained a substantial size. By 2300 g, the distributions of births are nearly equal in peak 1 and peak 2, and at 2100 g peak 1 exceeds peak 2. At lower weights, peak 1 continues to dominate, with some increased proportion in peak 3 as well (Figure 1 and Table 1).

Figure 2 also shows the trace of the mode of the observed gestational age distributions, superimposed on the bands of peaks. The mode has an apparent discontinuity at approximately 2300 g, the weight at which peak 1 becomes larger than peak 2. Such a discontinuity seems unlikely from a biological point of view, and in our interpretation peak 2 remains the correct peak below 2300 g as well.

What error might account for peaks 1 and 3? The fact that peaks 1 and 3 are consistently separated from peak 2 by a distance of about 4 weeks suggests that the errors are related to the menstrual cycle. A gestational age that is 4 weeks too long would suggest that the woman has recalled not her most recent period but the one before. A gestational age that is 4 weeks too short would suggest that the woman experienced bleeding early in pregnancy (close to 4 weeks after the last menstrual period) that was mistaken for a period.

Consequences

If this interpretation is correct, the amount of error represented by peak 1 is highly dependent on birthweight. Babies with an erroneously short gestational age seem to be much more common among the low weights than among the heavier weights. This is consistent with the notion that bleeding early in pregnancy is associated with preterm delivery.[17]

However, the amount of misclassification suggested by these data is surprisingly large. Any estimates of actual proportions in the various peaks must be approached with caution, since such estimates depend on the assumptions of the model. Nonetheless, it appears that more than 35% of the babies in peak 1 are less than 2500 g (Figure 3). Turning this around, it appears that a large portion, perhaps even a majority, of babies weighing less than 2500 g are older than their apparent gestational age by about 4 weeks (Table 1).

If peak 1 represents gestational age errors due to bleeding during pregnancy, this would mean that bleeding in pregnancy is a very strong risk factor for low-weight births. It would also mean that the actual number of preterm births is considerably smaller than suggested by the usual last menstrual period criterion. Similarly, if peak 3 represents babies with gestational ages that are erroneously long, then the actual number of post term births may be considerably less than last menstrual period dates indicate.

Criticisms

These inferences from the analysis are unexpected, and therefore the analysis itself deserves skeptical examination. Some weaknesses in the analysis must be taken into account. First, the underlying distributions of gestational age are assumed to be Gaussian. This is convenient for modeling purposes but may not correspond to the underlying biology. However, when we experimented with other distributions, including skewed ones, we found that the general pattern remained unchanged.

A second and more critical assumption is that the standard error of the 3 distributions is the same within a given stratum. This is dubious from a biological standpoint. The errors that (presumably) produce the 4-week separations in peaks have their own variability. Therefore, the peaks produced by the errors should have larger standard deviations than the true peak. However, as a result of the relatively large overlap of the peaks, the estimation procedure for mixed distributions is not reliable when the standard deviations are allowed to vary freely among the peaks. Thus, the presumed differences in the standard deviations of the error peaks cannot be estimated by this procedure. This clearly makes any quantitative extensions of the analysis, such as the total proportion of births under peak 1, less accurate.

One notable inconsistency in the analysis occurs in the region of 2400 g to 2900 g. At these weights, the intervals between peak 1 and peak 2 are somewhat shorter than 4 weeks, and some are as short as 21 days. We have no immediate explanation for this.

How specific might the results be to the Norwegian setting? After registration at the first prenatal visit, the last menstrual period date given by the mother is supposedly left unchanged until it is transferred to the registry, regardless of whether it is in accordance with ultrasound dating and whether it is certain or not. Thus, a pattern of systematic errors may be more evident in the Norwegian material than elsewhere.

It is difficult to find empirical evidence that supports the patterns suggested in our

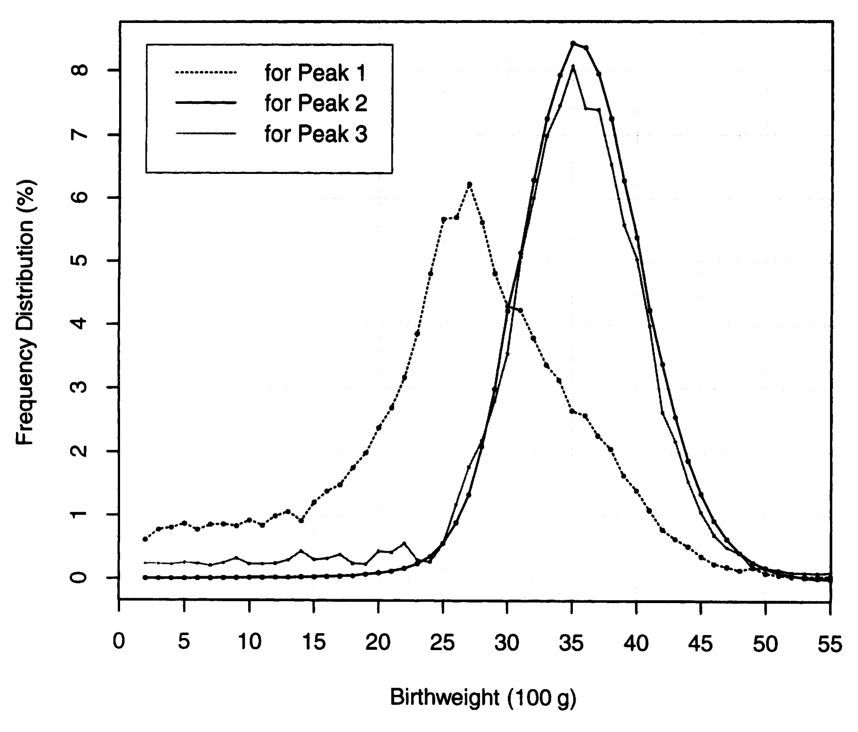

FIGURE 3—Total birthweight distributions for peaks 1, 2, and 3.

data. For example, peak 3 represents a gestational age that is too long by 4 weeks, as if the woman has recalled not her most recent period but the one before. While "missed" periods are discussed in the clinical literature, actual distributions of menstrual cycle length obtained from menstrual calendars do not show evidence of missed periods.[18] While recall of the wrong menses or systematic clerical error might occasionally occur, it is not obvious that errors would cluster at a gestational age 4 weeks too long.

The error of a gestational age 4 weeks too short is perhaps more biologically plausible. The possibility that bleeding in early pregnancy may occur around the time of the expected period has been discussed by many authors.[4,5,7,16,19] In our data, the total proportion of pregnancies affected by this error was small (6%), but among low-birthweight babies the error was frequent (58%).

We cannot find clinical evidence to support this high prevalence of misclassification of last menstrual period among small or preterm babies. Kramer et al. and other authors have compared last menstrual period and ultrasound data for large series of babies stratified by last menstrual period.[20,21] Our analysis would predict that for a large portion of preterm babies there should be major discrepancies between the last menstrual period gestational age and the ultrasound gestational age. Although the difference in Kramer's data is in the expected direction, the difference is not large enough to support the present interpretation.

Other interpretations of the gestational age distribution within strata of birthweight have also been offered. Herman et al.[8] proposed that the skewness is due to growth retardation (i.e., babies who are small for their gestational age). However, this explanation seems insufficient to account for the consistent separation of the peaks we found.

While our interpretation of the results is not immediately supported by other evidence, neither do we find apparent flaws in the analysis itself. It is possible that some unknown artifact of the bivariate distribution produced the coherent pattern in Figure 2. However, it is also possible that a previously unrecognized and substantial portion of small babies are routinely misclassified via last menstrual period.

Conclusions

The bivariate structure of birthweight and gestational age provides an opportunity to inspect the errors of gestational age that inevitably occur when last menstrual period is used as a benchmark. While this error has previously been examined in an indirect manner, by inspecting birthweight distributions within gestational age strata, we chose to assess the distribution of gestational age directly, as it occurs within securely defined strata of birthweight. Using simple curve-fitting procedures, we found that the gestational age distribution can be characterized as a mixture of 3 distributions separated by roughly 4 weeks. We interpreted this pattern as 1 distribution of true gestational age and 2 distributions of erroneous gestational age.

This pattern of the 3 gestational age distributions across the birthweight spectrum is surprisingly coherent and suggests unsuspected patterns of gestational age misclassification. In the Norwegian data, the analysis suggests a relation between low birthweight and bleeding during early pregnancy much stronger than expected. Prospective clinical studies could be designed to explore this hypothesis. Further applications of our approach on data from other countries may help to clarify these results and to elucidate the nature of gestational age error more generally. ☐

Contributors

Hakon Gjessing and Rolv Skjærven conceived the idea for the study. Hakon Gjessing also suggested the analytical strategy, did most of the analyses, and drafted and edited the paper to its final form. Rolv Skærven and Allen Wilcox contributed substantially to the discussion and interpretation of the results of the analyses. Allen Wilcox also scrutinized and revised several drafts of the paper.

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Ergonomics and the Dental Care Worker

Edited by Denise C. Murphy, DrPH, COHN

With foreword by William R. Maas, D.D.S., M.P.H., Chief Dental Officer, U.S. Public Health Service

Occupational health and adverse health consequences to dental care practitioners are issues that have been largely overlooked for decades. *Ergonomics and the Dental Care Worker* provides the reader with a timely, interesting, user-friendly, comprehensive, and practical source of information.

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