BIRTHWEIGHT BY GESTATIONAL AGE IN PRETERM BABIES ACCORDING TO A GAUSSIAN MIXTURE MODEL

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ABSTRACT

Objectives. A statistically sound criterion for identifying implausible birthweights for gestational age.

Methods. Data are from Italian 1990-94 vital statistics and concern 42 063 single 1st and 2nd liveborn preterm babies. Two-component Gaussian mixture models are used to describe the birthweight distributions stratified by gestational age. Implausibly large babies are identified through model-based probabilistic clustering.

Results. Gestational age appears underestimated of about six weeks in 12.3% of the cases. Large babies are equally present in males and females, but are more frequent in 2nd borns than in 1st borns, even when parity specific models are fitted.

Conclusions. The approach allows for quantification of the gestational age underestimate error and data correction through model-based clustering. Correct birthweight distributions and growth curves are also provided.

Key words: gestational age, birthweight, Gaussian mixture model, fetal growth.

INTRODUCTION

Preterm deliveries are one of the main causes of perinatal mortality in developed countries, and interventions aimed at improving both antenatal care and social conditions of the mothers failed to substantially decrease their incidence.[1,2] In particular, in Italy the incidence has been almost constant since the middle eighties, and in 1995 amounted to 5.6%. In the evaluation of perinatal mortality risk, distinction between smallness due to short gestation or to growth retardation may be obscured when only weight categories are considered. The role of birthweight has been generally emphasized and a value below the 10th centile of the overall birthweight distribution has been considered a main predictor of the risk. The importance of the risk assessment on the basis of the birthweight distributions by gestational age has been highlighted by several authors in so far it can provide insight into the fetal growth and support either prediction on the outcome of obstetrical choices, such as natural or cesarean deliveries, or evaluation of the advantages of a longer gestation.[3-7] Moreover, under the assumption that the growth rate of neonates prematurely born be equal to that of fetuses of the same gestational age who will eventually be born at term, ponderal growth curves based on newborn cohorts by gestation age are largely adopted as reference for fetal growth.[8-14]

At national level, birthweight distributions relative to gestational age are built with vital statistic data, where pregnancy duration is based on the last menstrual period as reported by the mother and as such may particularly suffer from dating errors. Several authors have observed asymmetry and even bimodality in birthweight distributions of preterm babies and have suggested that the unreliable weights for gestational age could be mainly attributable to erroneous reports of the last menstrual period. [4,14-21] Unreliable estimates can be ascribed to biological and/or cultural maternal factors, and have also been found associated with an increased frequency of unfavourable pregnancy outcome.[22-26] The last menstrual period may be unknown or misinterpreted because of hormonal unbalance associated with a short interval between pregnancies or of unusual bleeding after conception; or it may be incorrectly reported because of imprecision in the recall, misunderstanding in reporting the first missing instead of the actual last menses, or even voluntary date postponement to mask a pre-marriage conception.[23,26] In spite of the general recourse to adjusting gestational age by sonographic techniques, a non-negligible proportion of too large for gestational age babies have been repeatedly found even in studies based on hospital records.[15,16] In fact ultrasound measures do not necessarily provide a true dating since they presumably correct gestation length overestimates for delayed ovulation or missed spontaneous abortions, but the reliability of the correction depends on the time the measures are taken.[27-30]

In studies at population level the estimate of pregnancy duration based on last menstrual period generally remains the only available datum, and its imprecision may cause misclassification of preterm, term and post-term babies, and seriously impair the description of fetal growth and jeopardize hypothesis testing.

The excess of anomalously heavy babies has been studied by several authors who examined either the weight distributions stratified by weeks of pregnancy[4,15,18] or, conversely, the gestation week distributions stratified by birth weight[19,31]. Different approaches have been proposed to correct errors in the gestational age estimates in order to obtain reliable birth weight distributions and references for fetal growth curves. Just smoothing the raw centile curves is considered inadequate to correct the distortion introduced by the excess of implausible birthweight records for early gestational age. Various rules have been proposed to identify spurious records by means of birthweight thresholds, either empirically defined[5,20] or derived as meaningful points of deviations from the expected normality pattern.[4,14,15,18]

More interesting approaches make use of finite mixture models[21] to adequately describe the observed birthweight distributions. Our study as well is based on a Gaussian mixture model, which allows us to capture and identify the error component. Aim of the present paper is on the one hand to provide a general criterion, both population based and statistically sound, for identifying the babies that most likely got downward misclassified with respect to gestational age, and on the other hand to obtain reliable reference growth curves.

MATERIALS AND METHODS

Individual birth records routinely collected in Italy during the years 1990-1994 were acquired from ISTAT, the Italian Central Institute of Statistics. Liveborns were considered, and among them, to study the effect of birth order, single 1st and 2nd babies were selected, 1,372,707 and 960,848 respectively, who account for over 85% of the total liveborns and display the same male proportion (51.6 %).

A mixture model was applied to the birthweight distributions of 42 063 very preterm babies stratified by gestational age, whenever the observed distribution shapes suggested that data might arise from an underlying pattern of two overlapping bell-shaped distributions. Due to their paucity, the babies less than 26 weeks were pooled into one single class, labeled as 18-25 weeks.

We fitted a mixture model of two Gaussian components to the data by the maximum likelihood method, and its parameters, which include the mixing proportions and the parameters of the component distributions, were estimated. Then, the data were clustered on the basis of the posterior probabilities of group membership, which were estimated from the computed mixture model parameters.

More precisely, within each gestational age stratum we assumed that the observations arose from a distribution $G = (1- p_s)\, G_m + p_s\, G_s$, viewed as a mixture of two normal distributions G_m and G_s , in a proportion quantified by the stochastic weight p_s ($0 < p_s < 1$), and with parameters μ_m , σ_m and μ_s , σ_s respectively. Mixture models provide a useful way to identify homogeneous groups within a given population, whenever there is no a priori knowledge of any group structure on the underlying population but heterogeneity is suspected.[32] Such an approach is also commonly applied to the identification of outliers within a sample.[33] In our case, mixture models were used to identify, within early gestational age strata, the systematic error component likely originated from underestimated gestational age. As we report in the next section, we actually resorted to mixture models only before the 35th week, that is when the birthweight distribution clearly displayed an excess of too large babies and its overall shape might arise from two overlapping distributions. Maximum likelihood estimates of the mixture model parameters were derived by the expectation maximization algorithm.[34,35] Since the error component is not yet well understood, no a priori constraints were assumed for the unknown parameters. A probabilistic clustering of the observations was then obtained by allocating each observation to either group according to the corresponding posterior probability of group membership. In practice, we could estimate a weight value w that represents the threshold beyond which an observation has a higher probability of belonging from the secondary (G_s) rather than to the major (G_m) component of the distribution. Consequently, a proportion c_s of the observations, corresponding to birthweights greater than the threshold values w, was allocated to the secondary cluster, and viewed as spurious.

An estimate of the mean extent of the downward gestational age misclassification was obtained by shifting a few weeks forward the curve defined by the secondary component means over the 27-34 gestation weeks, and making it to match at best the course of the major component within the variability limits of both distributions.

RESULTS

The weight distributions stratified by week of gestational age turn out to be positively skewed before 30 weeks, and clearly bimodal between 30 and 32 weeks. Bimodality progressively disappears in later distributions, which are approximately Gaussian after the 34th week (see the four representative examples of Figure 1). The shapes of the weight distributions clearly suggest that the observations in the early gestational age classes are not really homogeneous, and are likely to arise from two groups: a major component, which may be hypothesized to account for the actual process of growth, and a secondary component, which is characterized by unacceptably large weights.

On the basis of these observations, a mixture model of two normal components was applied to adequately capture the observed patterns. The model was fitted only to the weight distributions of babies born before 35 weeks, where the secondary component is not negligible. This sub-sample amounts to a total of 42 063 babies and corresponds to 35% of all preterm (<37 gestation weeks) births. Although errors in reporting gestational age may occur within each stratum, misclassification is more evident in the earlier less numerous strata. In fact even a small percentage of misclassification around term translates in a considerable excess of large babies in early preterm groups.

In Table 1 the sample sizes and the estimated parameters of both the main and the secondary components are reported for each gestational age. The birthweight threshold values approximately correspond to the 99th centile of the main component up to the 32nd week, and to the 98th centile thereafter. The resulting proportions of the secondary cluster, corresponding to the abnormally heavy babies, are also shown: depending on the gestation week, these proportions range from ~7% to ~ 27%, with a maximum at 30 weeks; altogether, from 18 to 34 weeks, the babies identified as being too large for their gestational age amount to 12.3%.

We wondered whether the babies belonging to the spurious clusters, identified as misclassified on the basis of the threshold values of Table1, were equally distributed between sexes and between 1st and 2nd borns. While the proportion of the too heavy babies was not significantly in males and in females (12.36% vs 12.35, χ^2=0.019, 1df, P=0.89), a significant difference was found between 1st and 2nd borns (11.2% vs 14.2%, χ^2= 65.523, 1df, P<0.001), the proportion of excluded 2nd borns being always higher but in the 27th week.

In order to overcome the bias of considering as misclassified an excess of 2nd borns due to the use of a unique weight threshold for 1st and 2nd borns, we applied the mixture model to 1st and 2nd borns separately, and estimated proper threshold values for gestational age (Table 2). In spite of the fitting improvement, for almost all gestational ages the proportion of the secondary clusters was still higher in the 2nd than in the 1st borns, with a proportion of misclassified babies of 13.9% and 11.5% respectively (χ^2= 42.957, df 1, P<0.001). Not significant changes in the percentages of the secondary clusters were obtained using either unique or parity specific threshold values. On the basis of the above results, we did not consider necessary to adopt threshold values sex and/or parity specific and kept those reported in Table 1 to identify the implausible weight for gestational age.

According to the mixture model, correct ponderal growth curves were obtained from the major component, which has been assumed to model the actual pattern of growth, and were compared with those obtained using the raw data. In Figure 2a we report the 50°, 75° and 95° centiles of the observed and expected distributions. While there is a good agreement between the observed and the expected 50^{th} percentile curves, in the highest centiles the observed curves appear strongly upward distorted, noticeably between 28 and 32 weeks.

The means ± SD of both the major and the secondary model components are drawn in Figure 2b. We notice that by shifting the secondary component curve six weeks forward, its course almost matches that of the major component and is compatible with the dispersion features of both distributions. The abnormally large birth weights captured by the secondary distribution might therefore correspond to an actual fetal growth if the babies were attributed an approximately six week longer gestation.

DISCUSSION

In order to capture implausible weights due to gestational age underestimate, we applied a mixture model of two Gaussian components to the birthweight distributions stratified by gestational age before the 35^{th} week, and assumed that the major component models the actual weight distribution while the secondary component describes a systematic error in the gestational age datum. Such an error appears to be consistent with a conjecture of about six-week underestimate of the pregnancy duration (Fig.2b). With respect to the major component the secondary one has a non-negligible relative weight (Table1), so that an effective criterion for separating and removing the spurious data is in order. The weight thresholds, estimated on a probabilistic basis, provide a sound criterion for clustering appropriate for gestational age babies, and thus may be helpful in driving neonatal medical care.

Reference fetal growth curves and birthweight percentiles are often reported by sex, being males usually heavier than females.[5,14,17,19,21] Yet, as reported by previous studies, the percent difference between sexes in preterm babies is slight: it varies approximately between 7% and 5% from the 10th to the 50th centile, and diminishes to about 3% in the 90th centile.[17,21] As a matter of fact, even by using a unique non sex-specific model, we did not find any significant difference in the misclassification rate between sexes.

As to parity, a significantly higher rate of misclassification is found among the 2nd borns even when parity-specific threshold values are assumed for clustering. Thus specific investigations on the causes that make gestational age more frequently underestimated among the 2nd borns are in order.

The issue of eliminating unreliable birthweights for gestational age to define correct centile values is long dating, and smoothing procedures of the centile growth curves or cut-off rules based on the birthweight distributions have been proposed. The advantages of the present model, and of similar ones based on finite mixture of Gaussian distributions[14,21] reside in the estimate, statistically sound and independent for each gestational age, of the upper threshold for appropriate weighing babies. Moreover, the mixture model allows for a quantification both of the babies' misclassification rate and of the gestational age underestimate error. Differently from Kramer[21], we do not perform any re-sampling of the original data to separate the correct from the incorrect records, and we rather prefer a probabilistic clustering. By this strategy in defining cut-off thresholds we aim to exclude only those birthweight records that have a higher probability of belonging to the spurious than to the major group. We then obtain the growth centile curves (Fig.2a) by plotting the major component theoretical centiles, rather than using the polished data. By this choice our curves are eventually similar to Kramer's ones, obtained by making re-sampled data adhere to the major Gaussian pattern.

Although the ponderal growth curves based on newborn data are usually assumed to be representative of the fetal growth, they cannot provide normal standards, since they account for both growth restrictions and maturation anomalies, even lethal when still-borns are included in the data set, associated with a spontaneous or induced preterm delivery. Nevertheless, at population level, preterm birth data provided by national vital statistics are the only ones available to define reference curves for the fetal growth.

The high percentage of mothers of preterm babies who likely reported delayed menses thus causing a gestational age underestimate, not adjusted by early ultrasound examination, requires specific investigation on its biological and/or cultural determinants.

Since delivery is expected 40 weeks after the first day of the last menstrual period and conception generally occurs in the middle of the 28 day period, 38 weeks are expected to be the gestational age at term. Few day deviations from expected ovulation time correspond to physiological variability within 1 week, and can be reliably corrected by ultrasonografic measurements. On the other hand as generally reported[4,15], a 4-week underestimate can result from either mistaking some bleeding for menses at the time of the first missed period, or reporting the date of first instead of last missed period. In our data, the mean extent of gestational age underestimate is about 6 weeks and even more for gestations between 28 and 31 weeks (Fig.2b). A so large gap is difficult to explain and might be due to some cultural and/or biological peculiarities of the Italian mothers. Some intentional last period underreporting to mask premarital conception or low reliability in recall might be hypothesized in mothers of low socioeconomic strata[5,21], but our preliminary analyses suggested that the incidence of implausible birthweights for gestational age is independent of the maternal education and of the Italian spatial heterogeneity in socio-economic and sanitary conditions.

The excess of large for gestational age babies in the 2nd borns with respect to the 1st borns had been previously found also when implausible records had been identified by means of different procedures.[5] A more favorable pregnancy outcome, also in terms of birthweight, is expected in 2nd borns than 1st borns[36], but the higher rate of gestational age misreporting in the 2nd pregnancies might be indicative of some specific unfavourable conditions, such as a hormonal unbalance associated with a too short interval between pregnancies, or an increased probability both of bleeding and of inaccuracy in the last period date.

Preterm births are unfavourable outcomes from both a personal and a general point of view and a correct estimate of their incidence at population level is important for private and public choices of interventions in maternal and neonatal medical care. Thus errors in estimating the pregnancy length have to be quantified and appropriate birthweight distributions for gestational age must be provided, although the normal fetal growth is imprecisely represented by references based on preterm birth data sets. The proposed model adequately captures the underestimate errors frequently occurring in preterm newborn data sets, thus providing appropriate upward birthweight cutoffs. Although among preterm babies implausible birthweights have been a general finding since the sixties, their determinants are still unknown. Because of the suggested association with adverse perinatal outcomes[26,31], investigations on the issue are in order to distinguish between an unavoidable rate both of errors in last menstrual period recall or of too large babies associated to mother and/or neonate pathologies, and the interrelated factors, as maternal socioeconomic status, age at delivery and reproductive history, susceptible to public health interventions or to increased consciousness in family planning.

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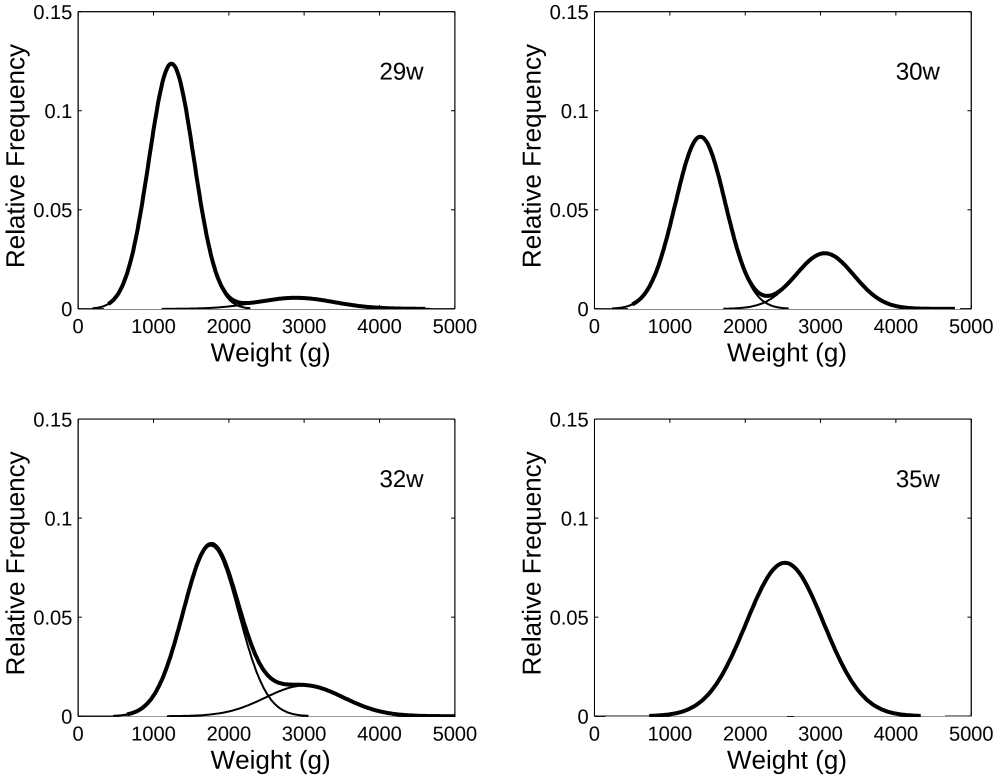

Figure 1. Birthweight distributions in liveborn babies at four representative weeks of gestation: observed (histogram), expected (solid line) and two Gaussian component (dashed line) distributions.

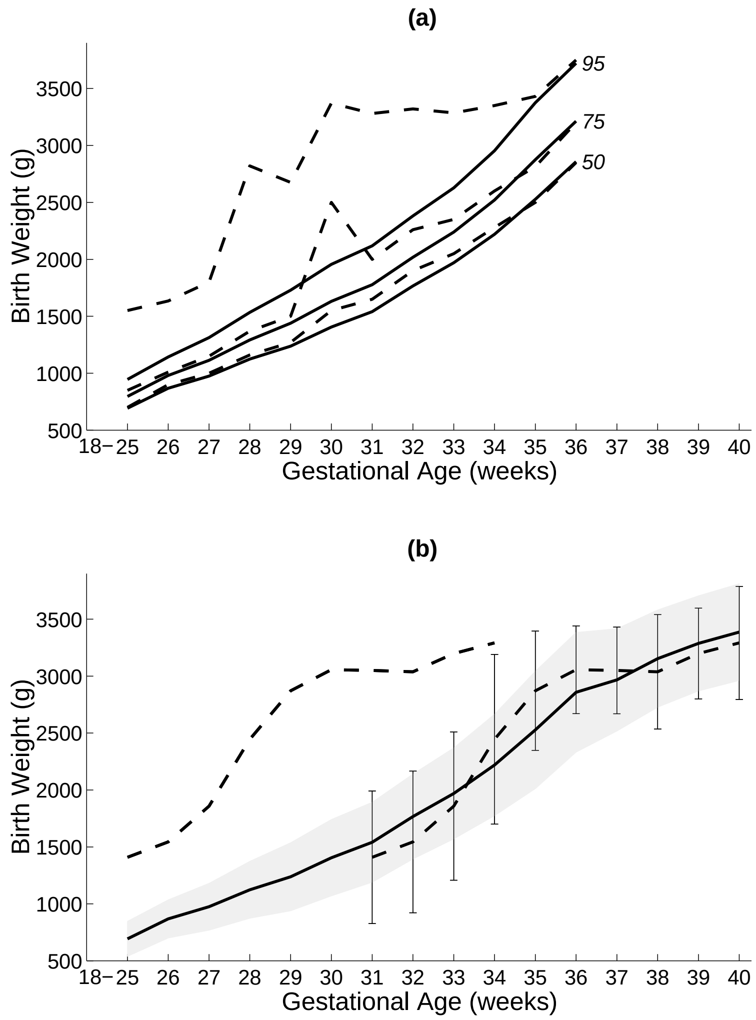

Figure 2 (**a**) Expected centile curves of fetal ponderal growth according to the major distribution (solid lines), compared with the observed ones (dashed lines); (**b)** Mean birthweight of the major component (solid line), and of the secondary component (dashed line) by gestation week. By shifting the secondary component six weeks upward, its course almost matches that of the major component, compatibly with the dispersion of both distributions (grey area and vertical bars indicates the standard deviations).

Table 1. Estimated parameters of the major (μ_m, σ_m) and secondary (μ_s, σ_s) components in the mixture model stratified by gestation week; threshold values for weight clustering (w) and proportion of the resulting secondary cluster (c_s).

gestation weeks	18-25	26	27	28	29	30	31	32	33	34
sample size	2 289	1 382	1 521	2 051	2 160	3 875	3 975	6 033	6 699	12 078
μ_m	692.8	868.1	974.8	1 124.0	1 237.7	1 405.3	1 541.0	1 766.8	1 969.8	2 219.0
σ_m	153.6	167,2	205.4	249.6	298.5	334.7	350.9	373.2	399.3	445.6
μ_s	1 409.1	1 544.0	1 858.7	2 445.0	2 871.0	3 056.0	3 049.8	3 037.8	3 198.5	3 291.6
σ_s	581.6	621.7	651.7	745.1	523.8	385.1	380.7	502.5	398.7	496.5
w	1 094.2	1 301.0	1 519.9	1 776.3	2 101.2	2 260.4	2 406.8	2 549.6	2 850.2	3 198.9
c_s (%)	9.7	8.4	7.0	11.6	6.8	26.9	17.4	17.8	10.6	7.4

Table 2. Estimated means of both the major (μ_m) and the secondary (μ_s) components of the mixture models stratified by gestation week and birth order; threshold values for weight clustering (w), and proportion of the resulting secondary cluster (c_s).

gestation weeks	18-25	26	27	28	29	30	31	32	33	34
first borns										
sample size	1,143	696	794	1,055	1,133	1,906	2,069	3,119	3,525	6,490
μ_m	689.8	863.5	956.1	1,096.9	1,213.1	1,354.9	1,494.3	1,710.9	1,932.3	2,173.0
μ_s	1,355.5	1,595.5	1,783.5	2,289.1	2,993.7	3,011.6	3,028.6	2,961.0	3,219.5	3,197.4
w	1,100.9	1,304.9	1,470.6	1,735.0	2,227.3	2,224.3	2,396.9	2,484.3	2,846.3	3,182.1
c_s(%)	8.0	8.3	9.2	10.7	5.9	25.4	15.3	17.3	9.8	6.6
second borns										
sample size	700	438	464	637	639	1,315	1,233	1,796	2,042	3,615
μ_m	692.6	876.7	992.0	1,149.8	1,257.1	1,452.4	1,591.1	1,807.3	2,011.6	2,271.0
μ_s	1,480.4	1,414.0	2,114.5	2,852.7	2,548.2	3,084.7	3,073.6	3,131.3	3,235.2	3,413.7
w	1,077.4	1,241.9	1,583.0	1,890.9	1,970.9	2,268.7	2,402.3	2,596.8	2,877.0	3,202.8
c_s(%)	11.1	10.3	4.7	10.0	8.8	30.4	20.7	19.9	11.1	7.8