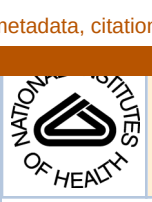

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Customized Versus Population Approach for Evaluation of Fetal Overgrowth

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Abstract

Objective—To compare the ability of customized versus normalized population fetal growth norms in identifying neonates at risk for adverse perinatal outcomes (APOs) associated with fetal overgrowth and gestational diabetes (GDM).

Study Design—Secondary analysis of a multicenter treatment trial of mild GDM. The primary outcome was a composite of neonatal outcomes associated with fetal overgrowth and GDM. Birthweight percentiles were calculated using ethnicity- & gender-specific population norms and customized norms (Gardosi).

Results—203 (9.8%) and 288 (13.8%) neonates were LGA by population (LGApop) and customized (LGAcust) norms, respectively. Both LGApop and LGAcust were associated with the primary outcome and neonatal hyperinsulinemia, while neither was associated with hypoglycemia or hyperbilirubinemia. The ability of customized and population birthweight percentiles for predicting APOs were poor (receiver operating characteristic area under the curve <0.6 for 6 out of 8 APOs).

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Conclusion—Neither customized nor normalized-population norms better identify neonates at risk of APOs related to fetal overgrowth and GDM.

Keywords

customized growth; adverse neonatal outcomes; gestational diabetes; large for gestational age

Introduction

Disturbances in fetal growth, and secondarily birthweight, are associated with adverse neonatal outcomes. Infants who are born small (SGA) or large (LGA) for gestational age are at increased risk of short- and long-term adverse health consequences. (1–6) Birthweight is determined by a combination of intrauterine genetic and environmental influences, and traditionally has been evaluated by comparison to population-based norms. (6–8) Population norms are derived from either heterogeneous or highly selected patient cohorts, and do not account for individual variability. Population norms do not differentiate between abnormal grown versus constitutionally large, or small, but otherwise healthy fetuses. They also may not identify abnormal growth in a fetus that remains within the normal range for the population. Relying on these norms can therefore lead to misclassification of fetuses and over or under diagnosis of fetal growth abnormality (9, 10)

In order to circumvent these limitations with population-based standards, a number of customized norms have been developed. A widely used customized growth model is that of Gardosi et al. (11–13) In this model, the assessment of fetal growth relies on each fetus' growth potential that would have been expected at the end of an uncomplicated pregnancy. This growth potential is calculated using maternal and fetal variables that have been previously determined to influence individual growth independent of pregnancy complications. Because of this individual approach, this method is thought to be better at detecting disturbances in fetal growth compared with a population-based approach. (9–12) The ability of this model to identify neonates at risk of adverse perinatal outcomes (APOs) related to decreased fetal growth has been demonstrated in multiple studies. (14–21) This is thought to be mostly related to the better performance of the customized norms in the setting of SGA and preterm birth, where the population-based norms derived from birthweights typically underestimate the proportion of growth restricted preterm newborns. However, the ability of the Gardosi model to identify LGA neonates at risk of adverse outcomes related to fetal overgrowth has not been studied.

Therefore, the purpose of this study is to compare the ability of the customized "Gardosi" approach (12, 13) and a population-normalized assessment (6) in identifying neonates at risk of APOs associated with fetal overgrowth and gestational diabetes (GDM) using a cohort of normal and mild gestational diabetic women at risk for fetal overgrowth. (22)

Materials & Methods

Study Design

This was a secondary analysis of women enrolled in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network multicenter randomized trial of treatment for mild GDM conducted between October 2002 and November 2007 in 16 United States centers. (22) Mild GDM was defined as abnormal oral glucose tolerance test (OGTT), but with normal fasting glucose value i.e. <95 mg per deciliter (5.3 mmol per liter). Women with mild GDM were randomized to an intervention arm consisting of formal nutritional counseling and diet therapy, self-glucose monitoring and insulin pharmacotherapy if needed (treated mild GDM group; n=438) or usual prenatal

care (untreated mild GDM group; n=414). In addition, women with normal glucose loading test (GLT) (normal group; n=395) and women with positive screening GLT test but normal OGTT (pos GLT/neg OGTT group; n=836) were identified and matched to the treatment group. Further details of the methodology of the study have been described elsewhere. (22) All women enrolled in these four groups (n=2326) were eligible for inclusion in the present secondary analysis except those women with missing information needed to determine the customized growth of their pregnancy and pregnancies complicated by major congenital malformations (n=243). Approval for the primary study was obtained from the Institutional Review Board of each participating institution. This study was deemed exempt from institutional review board review since the data and samples were de-identified before the analysis was performed.

Growth Centile Calculations

Centile birthweight was determined for each individual pregnancy using ethnicity- and gender-specific population (pop) norm, (6) and from a customized (cust) growth standard developed by Gardosi et al.(12,13) The Gardosi customized growth model generates optimal growth curves for individual pregnancies by taking into account maternal and fetal characteristics: maternal weight (kg) and height (cm) pre-pregnancy or at entry to care, ethnicity/race, parity (any birth after 20 weeks), and infant gender. (11, 12) The actual birthweight is compared to the optimal weight, and a measure of the percentage of optimal growth is calculated. [GROW (Gestation Related Optimal Weight) at www.gestation.net] (13) Large for gestational age (LGA) was defined as birthweight >90th percentile by either population (LGApop) or customized (LGAcust) method.

Outcomes

The primary outcome of the study was a composite that included perinatal mortality (stillbirth or neonatal death) in addition to outcomes related to glycemic control and fetal overgrowth (neonatal hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and birth trauma). Birth trauma included either brachial plexus palsy, clavicular, humeral or skull fracture. Neonatal hperinsulinemia was defined as cord blood C-peptide level > 95th percentile (> 1.77 ng/ml) determined from an unselected obstetrical population. Neonatal hypoglycemia was defined as blood glucose level < 35 mg/dl within 2 hours of birth and before feeding, and neonatal hyperbilirubinemia defined as serum bilirubin > 95th percentile between 16 and 36 hours of life. Details about these selected outcomes are described elsewhere. (22) A secondary analysis was also performed using the individual components of the primary outcome, except for perinatal mortality and birth trauma that were not frequent enough outcomes to warrant separate analysis.

Statistical Analysis

Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC) and R (www.r-project.org). Maternal and neonatal continuous data were reported as mean ± standard deviation and categorical data were reported in frequencies. The odds ratio (OR) with 95% confidence intervals (CIs), sensitivity and specificity for the various outcomes were calculated for LGAcust and LGApop. The concordance (or agreement) between presence or absence of LGA and presence or absence of APOs was calculated for each norm and APOs. For each APO and norm, a case was concordant when LGA by that norm and that particular APO were both present or both absent. Concordance was compared between the population and customized norms for each APO using McNemar test. (23)

Since the continuous values of the population norms were not available to us, we used the following approximation approach. After an Arc-Tan based transformation of birthweights (ArcTan((weight/1000)2)*2/π), we calculated the corresponding continuous values of the

population norms using a simple approximation method based on the linear connection of the 3rd, 10th, 50th and 90th percentiles provided by Alexander et al. (6) in the different races, infant genders and gestational age groups. The ability of the customized and generated population birthweight centiles to identify neonates at risk of APOs was then compared using the receiver operating characteristics curve (ROC) and the area under the curve (AUC, or c-statistic). For this study, since we did not assume any prior knowledge of the association, we did not specify the association direction (positive or negative) between an adverse outcome and SGA but rather used a two-sided approach. The population and customized AUC's for an individual outcome were then compared using a nonparametric statistical method for comparing AUC's. (24) Two-sided p values <0.05 were considered statistically significant and no adjustments were made for multiple comparisons.

Results

Two thousand and eighty three neonates were included in the analysis. Two hundred and three (9.8%) and 288 (13.8%) neonates were LGA by population and customized norms, respectively. (Figure 1) The baseline maternal and fetal characteristics of neonates LGApop, LGAcust and those not LGA by either method are summarized in Table 1. Of the neonates who were LGA by at least one method, 167 neonates were LGA by both methods, 36 (11.1%) were LGA by population centiles only (i.e. not LGA by customized; LGApop-only), and 121 (37.4%) were LGA by customized norms only (i.e. not LGA by population; LGAcust-only). (Figure 1) Six hundred forty two (32.1%) developed the primary outcome, and these had higher customized growth centiles compared to those who did not (59.5±29.6 vs. 50.0±29.3; p<0.0001). Of those infants who developed the primary outcome 19.3% were LGAcust and 13.2% were LGApop, and of those who did not 11.3% were LGAcust and 8.2% were LGApop (6.1% difference vs. 3.1%, P=0.03). The rates of the secondary outcomes are summarized in table 2.

The associations between LGApop and LGAcust with the composite and individual neonatal outcomes are summarized in table 2. Both LGApop and LGAcust were associated with the composite primary neonatal outcome (LGApop: OR 1.7, 95% CI 1.3–2.3 and LGAcust: OR 1.9, 95% CI 1.4–2.4) as well as hyperinsulinemia (LGApop: OR 2.3, 95% CI 1.6–3.2 and LGAcust: OR 2.5, 95% CI 1.9–3.4); however neither was associated with hypoglycemia or hyperbilirubinemia. (Table 2) Both had low sensitivity (range 10.9% – 25.5%) and high specificity (range 86.5% – 91.8%) for the various outcomes, although LGAcust had slightly higher sensitivities and lower specificities than LGApop. (Table 2)

The concordance (or agreement) between presence or absence of LGA and presence or absence of neonatal outcomes ranged between 66.4% and 82.7% (Table 3). This measures the combined proportions of concordance between LGA status and the outcome, as well as non-LGA status and the absence of the outcome. LGApop had significantly higher proportions of concordance compared with LGAcust for all outcomes except for the primary outcome for which the difference in agreement was not statistically significant (Table 3).

Table 4 summarizes the AUC (and 95 % CI) of the ROC curve for prediction of neonatal outcomes by population and customized norms. In general, the ability to predict neonatal outcomes was poor as 6 out of the 8 ROC's had AUC's less than 0.6. No significant differences between methods were noted for any of the AUCs except for hyperbilirubinemia (Table 4).

Discussion

In our cohort, neither a customized nor a normalized population-based approach to evaluate fetal growth better identifies neonates at risk for adverse perinatal outcomes related to overgrowth and GDM. The association between LGA and these adverse outcomes was not superior whether using the customized or the population-based norms.

Our study is novel in that we used two approaches in analyzing the data: first, we analyzed the association between neonates born >90th percentile and adverse outcomes, and then we approximated the continuous values of the population percentiles and compared the 2 norms using ROC curves, which has not been done in the prior validation studies. Additional strengths of our study include the use of the same cohort of patients to compare customized and population norms. This allowed us to control for differences in potential confounders when using different cohorts, such as pregnancy dating bias, which is especially important since growth modeling in poorly dated pregnancies results in artifactual flattening after 40 weeks secondary to the high rate of dating errors. (25) Another strength of our study is that the neonatal outcomes were prospectively and rigorously ascertained. (22)

This study, however, is limited by the study population which consisted of normal and mild GDM women, and by our sample size which may have limited our power to detect any differences in some of the secondary individual outcomes and which did not allow us to compare outcomes between neonates who were LGA for one but not the other norm. Moreover, it is important to note that the population norms that we used are gender and ethnicity specific, (6) which is not typical of the norms used in clinical practice or most studies. The typical population norms adjust for one or the other, but not both. By including both in the population norm we used, we made it closer to the individualized norm. This is different from prior studies that compared the customized model to the more commonly used population norm (7) that is not adjusted for gender and ethnicity. While our study was limited to short term outcomes, additional studies into the long-term consequences of overgrowth by customized potential are justified. Moreover, the inherent limitations of the growth model itself apply to this study as well. Although the model adjusts for many variables found to significantly affect birthweight (12), it does not adjust for all. The variables included in the model (maternal age, height, weight, parity, ethnicity as well as fetal gender) only account for 20–35% of birthweight variability at term. (26) Other characteristics such as maternal marital, education, and socioeconomic status, as well as gestational weight gain, altitude above sea level altitude and to a lesser extent paternal height have been shown to affect birthweight as well. (27–28)

Our findings should not be used to dismiss the Gardosi model. The benefit of using a customized approach for growth evaluation over population norms has been demonstrated in multiple studies that investigated the association between SGA babies and adverse outcomes (14–21), including a recent analysis of a database from the US which showed that SGA defined by the customized rather than population norms was associated with higher risk of stillbirth, early neonatal death, as well as other perinatal complications. (18) However, there are no prior studies that evaluated the utility of the Gardosi model in the setting of fetal overgrowth. Recently, Larkin et al (29) analyzed a large cohort database and published a customized fetal growth model that included similar variables compared with the Gardosi model. The authors then tested their model for the association of pregnancies LGA by their customized norm with adverse perinatal outcomes compared with pregnancies LGA by population standards, and similar to our study, they did not find that one was superior to the other. (29)

The role for birthweight customization has been debated. Many believe that the benefit of these models is gained solely by their incorporation of intrauterine-based reference values for gestational ages other than 280 days. (30) For any customized growth model, the optimal fetal weight at 280 days of gestation is predicted based on the maternal characteristics, then a fetal growth curve is generated to extrapolate backward fetal weights at other gestational ages using Hadlock's intrauterine standard proportionality formula. This is different from population norms that derive their reference values from actual birth weights of newborn infants. Another criticism of customized growth is that the strength of association with adverse perinatal outcomes is lost or attenuated outside of preterm deliveries. (31) Although the maternal characteristics frequently used in customized norms may be associated with fetal growth at the population level, they are not strong enough to be used for individual birthweight prediction, as each individual characteristic is not highly predictive of birthweight, and will only affect minimally individual birthweights. (30)

In summary, a customized approach for fetal growth assessment did not perform better than a normalized population approach that adjusts for ethnicity and infant gender, and neither approach was adequate in identifying neonates at risk of adverse outcomes related to LGA and GDM. Our study was based on birthweight. However, when evaluating the risk of neonatal adverse outcomes prior to birth, one has to rely on an estimate of fetal weight, most commonly by ultrasound. Future studies are needed to determine the role of customized growth evaluation, in combination with other parameters, in predicting adverse outcomes when used with ultrasound estimates of fetal size.

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Appendix

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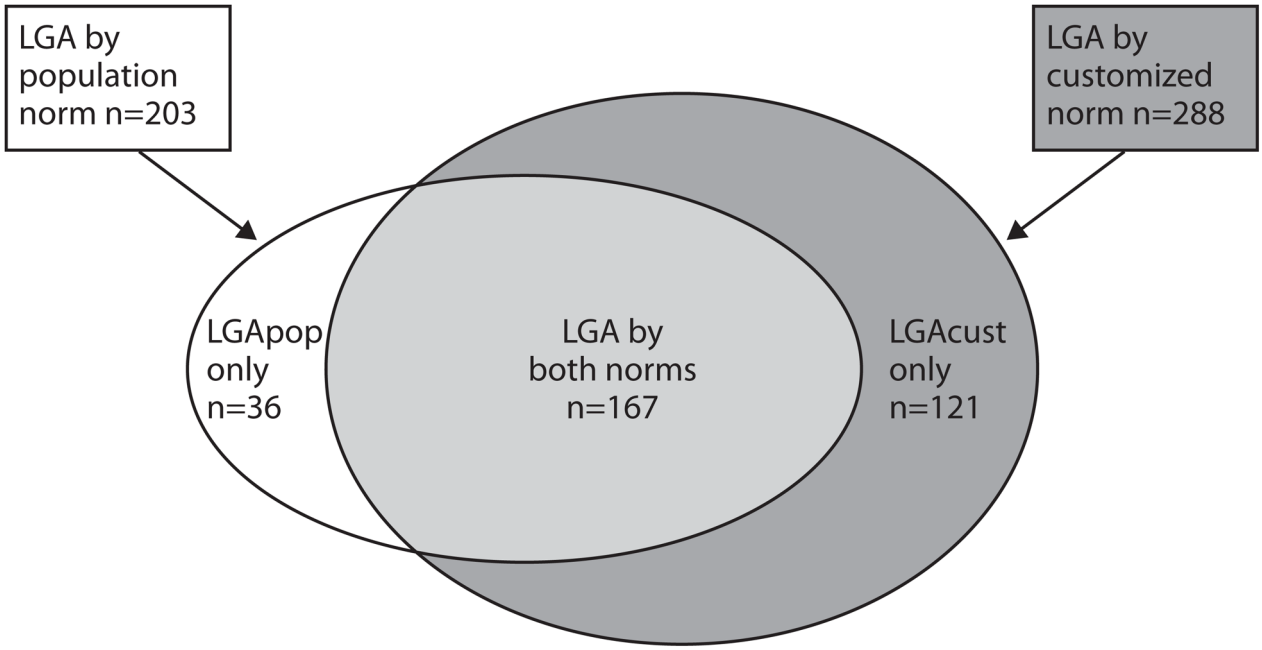

Figure 1.
distribution of neonates classified as large for gestational age (LGA) by the population (LGApop, n=203) and the customized methods (LGAcust, n=288). The diagram also shows the subgroups that are LGA by both methods (n=167) and LGA by population or customized norms only (LGApop-only, n=36 and LGAcust-only, n=121)

Table 1

Maternal and fetal characteristics of neonates LGA by population or customized standards.

Variable	LGApop (n=203)	LGAcust (n=288)	Not LGA by either method (n=1759)
Maternal age (years)	28.4 ± 5.6	27.9 ± 5.8	27.7 ± 5.7
BMI (at entry to care) (kg/m^2)	32.2 ± 5.4	30.2 ± 4.8	29.9 ± 5.3
Ethnicity			
Caucasian	54 (26.6)	73 (25.4)	511 (29.1%)
African American	23 (11.3)	24 (8.3)	235 (13.4%)
Hispanic	120 (59.1)	172 (59.7)	946 (53.8%)
Other	6 (3.0)	19 (6.6)	67 (3.8%)
Parity			
0	49 (24.1)	103 (35.8)	597 (33.9%)
≥1	154 (75.9)	185 (64.2)	1162 (66.1%)
Cesarean delivery	62 (30.5)	102 (35.4)	465 (26.4%)
GA at delivery (weeks)	39.8 ± 1.3	39.1 ± 1.5	39.1 ± 1 7
Birth weight (grams)	4191.0 ± 235.1	3954.3 ± 408.4	3235.1 ± 463.2
Estimated neonatal fat mass (grams) *	718.4 ± 130.4	639.8 ± 177.2	397.6 ± 184.3
Percent body fat ¶	17.1 ± 2.7	16.0 ± 3.6	11.8 ± 5.0

Data are reported as mean ± SD, or n (%)

LGA = large for gestational age, LGApop= LGA by population norm, LGAcust = LGA by customized norm, BMI = body mass index, GA = gestational age

* Reference 32

¶ Percent body fat = (estimated neonatal fat mass / birthweight) x 100

Table 2

Sensitivity, specificity, and odds ratio of neonatal outcomes for LGA by customized or population norms

Outcome (n, %)	Category #	Sensitivity	Specificity	PPV	NPV	OR (95% CI)
Composite neonatal outcome ¶ (n=642, 32.1%)	LGAcust (n=124)	19.3% (16.3%–22.6%)	88.7% (86.9%–90.3%)	44.6% (38.7%–50.7)	69.9% (67.7%–72.1%)	1.9 (1.4–2.4)
	LGApop (n=85)	13.2% (10.7%–16.1%)	91.8% (90.2%–93.2%)	43.2% (36.1% –50.4%)	69.1% (66.9%–71.3%)	1.7 (1.3–2.3)
Hyperinsulinemia § (n=302, 16.8%)	LGAcust (n=77)	25.5% (20.7%–30.8%)	88.0% (86.2%–89.6%)	30.0% (24.4%–36.0%)	85.4% (83.6%–87.1%)	2.5 (1.9–3.4)
	LGApop (n=53)	17.6% (13.4%–22.3%)	91.5% (89.9%–92.8%)	29.3% (22.8%–35.9%)	84.6% (82.8%–86.3%)	2.3 (1.6–3.2)
Hypoglycemia ¥ (n=265, 15.9%)	LGAcust (n=44)	16.6% (12.3%–21.6%)	87.0% (85.2%–88.7%)	19.5% (14.5%–25.2%)	84.7% (82.7%–86.5%)	1.3 (0.9–1.9)
	LGApop (n=29)	10.9% (7.5%–15.3%)	90.9% (89.3%–92.3%)	18.5% (12.7%–25.4%)	84.4% (82.5%–86.2%)	1.2 (0.8–1.9)
Hyperbilirubinemia ** (n=199, 10.3%)	LGAcust (n=34)	17.1% (12.1%–23.1%)	86.5% (84.8%–88.1%)	12.7% (9.0%–17.3%)	90.1% (88.6%–91.5%)	1.3 (0.9–2.0)
	LGApop (n=26)	13.1% (8.7%–18.6%)	90.7% (89.2%–92.0%)	13.8% (9.2%–19.6%)	90.1% (88.6%–91.5%)	1.5 (0.9–2.3)

LGApop = large for gestational age by the population norm (n=203); LGAcust = large for gestational age by the customized method (n=288). The reference group is of neonates not LGA (n=1759)

(n) represents the number of neonates who developed the outcome among the LGA category

¶ Composite neonatal outcome if any of the following: stillbirth, neonatal death, hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma.

§ Hperinsulinemia = cord c-peptide level > 95th percentile (> 1.77 ng/ml).

¥ Neonatal hypoglycemia < 35 mg/dl within 2 hours of birth and before feeding.

** Hyperbilirubinemia = Serum bilirubin > 95th percentile between 16 and 36 hours of life. Birth trauma = brachial plexus palsy, clavicular, humeral or skull fracture.

Table 3

Proportion of agreement between LGA status defined as >90th percentile and outcome

	LGApop %	LGAcust %	P *
Composite neonatal outcome ¶	66.6	66.4	0.81
Hyperinsulinemia §	79.0	77.5	0.02
Hypoglycemia ¥	78.2	75.8	0.0005
Hyperbilirubinemia **	82.7	79.4	<0.0001

LGApop = LGA by population norm; LGAcust = LGA by customized norm

* P using McNemar test for difference to test the agreement between LGApop & LGAcust for the outcome

¶ Composite neonatal outcome if any of the following: stillbirth, neonatal death, hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma.

§ Hperinsulinemia = cord c-peptide level > 95th percentile (> 1.77 ng/ml).

¥ Neonatal hypoglycemia < 35 mg/dl within 2 hours of birth and before feeding.

** Hyperbilirubinemia = Serum bilirubin > 95th percentile between 16 and 36 hours of life. Birth trauma = brachial plexus palsy, clavicular, humeral or skull fracture.

Table 4

Area under (AUC) the receiver operating characteristics (ROC) curve for prediction of neonatal outcomes by population and customized norms

	Population norm AUC # (95% CI)	Customized norm AUC (95% CI)	P *
Composite neonatal outcome ¶	0.59 (0.56–0.62)	0.59 (0.57–0.62)	0.62
Hyperinsulinemia §	0.65 (0.62–0.68)	0.67 (0.63–0.70)	0.08
Hypoglycemia ¥	0.56 (0.52–0.60)	0.57 (0.54–0.61)	0.21
Hyperbilirubinemia **	0.55 (0.50–0.59)	0.52 (0.48–0.57)	0.01

LGApop = LGA by population norm; LGAcust = LGA by customized norm

* P for pair-wise ROC comparison.

After an Arc-Tan based transformation of birth weights (ArcTan((weight/1000)2)*2/π), we calculated the corresponding continuous values of the population norms using a simple approximation method based on the linear connection of the 3rd, 10th, 50th and 90th percentiles provided by Alexander et al. (6) in the different races, infant genders and gestational age groups.

¶ Composite neonatal outcome if any of the following: stillbirth, neonatal death, hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma.

§ Hperinsulinemia = cord c-peptide level > 95th percentile (> 1.77 ng/ml).

¥ Neonatal hypoglycemia < 35 mg/dl within 2 hours of birth and before feeding.

** Hyperbilirubinemia = Serum bilirubin > 95th percentile between 16 and 36 hours of life. Birth trauma = brachial plexus palsy, clavicular, humeral or skull fracture.