# Prediction of Hypoglycemia in Large for Gestational Age Neonates by Non-Invasive Method

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**Abstract**: Macrosomic infants show increased risk for hypoglycemia. This prospective study is undertaken to determine the predictive value of ultrasonographic measurement of abdominal wall subcutaneous fat thickness (AWSFT) and neonatal anthropometric measurements in anticipating hypoglycemia in large for gestational age (LGA) neonates. Ultrasonographic measurement of AWSFT and femur length/abdominal circumference ratio (FL/AC) before delivery, neonatal serum glucose, ponderal index (PI), mid arm circumference (MAC) and skin fold thickness (SFT) at three sites (biceps, triceps and subscapular) were measured in 50 singleton, term LGA fetuses (group 1) and 20 appropriate for gestational age (AGA) fetuses as a control (group II) as detected by ultrasonographic examinations. Only 34 newborns were LGA out of fifty fetuses detected by ultrasonographic examination (group I), 14 LGA newborns (41%) developed hypoglycemia within one hour of delivery. There was a highly significant statistical difference ($P < 0.001$) as regards AWSFT and significant statistical difference ($P<0.01$) as regards PI, length and subscapular SFT between hypoglycemic and euglycemic LGA newborns. Fetal AWSFT measured by ultrasound and neonatal PI were the most sensitive (92% & 71%) and exhibited high specificity (80% & 80%) and / or efficacy (985% & 76%) in predicting hypoglycemia in LGA newborns. **Conclusion**: Fetal AWSFT measured by ultrasound and neonatal PI are simple and accurate indices that can be used to predict hypoglycemia in LGA newborns. Fetal AWSFT is a sensitive index to predict disproportionate growth in LGA newborns.
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**Key words**: Large for gestational age neonates- Fetal ultrasonography- Anthropometric measurements- Hypoglycemia.

## 1. Introduction:

Fetal macrosomia remains a considerable challenge in current obstetrics due to the fetal and maternal complications associated with this condition **(AlSammani and Ahmed, 2012).** An accurate antenatal diagnosis of macrosomia by ultrasound has been shown to offer a useful aid in the clinical management of labour and mode of delivery **(Rosati and Exacoustos, 1995).**

Hypoglycemia is one of the commonest neonatal complications that may develop in LGA newborn, the incidence of hypoglycemia in LGA may reach to 21% **(Bandika et al., 2014).**

The Pedersen (1954), hypothesis stated that neonatal hypoglycemia and fetal macrosomia in infants of diabetic mothers are related to chronic fetal hyperglycemia. Also macrosomic infants born in good general condition more frequently had hypoglycemia associated with hyper insulinemia **(Gyurkovits et al., 2011 & Akinbi and Gerdes, 1995).**

Estimation of body composition rather than size at birth is considered to be more accurate in predicting early neonatal morbidity resulting from disturbed intra-uterine nutrition. Several methods such as MAC, SFT, and assessment of the body proportionality have been used for evaluation of body composition in neonates **(Lucchini et al., 2010 & Ballard et al., 1993).**

Macrosomic infants of diabetic and non-diabetic mothers are more likely to have hyper insulinemia and increased subcutaneous fat **(Linder et al., 2014. And Hoegsberg et al., 1993).** Measurement of newborn's subcutaneous fat may be useful in the evaluation of fetal size. The majority of macrosomic infants have a subcutaneous fat thickness, measured at the anterior abdominal wall, that exceeds 10mm. Fetuses with thickness < 6 mm of subcutaneous fat rarely are macrosomic **(Arias, 1993).**

We hypothesized that these fetuses with AWSFT > 10 mm, measured by ultrasound are more likely to have hyper insulinemia and more prone to develop neonatal hypoglycemia.

## 2. Patients and Methods:

Two groups of term pregnant females admitted to the obstetric units of ALGalaa teaching hospital were included in the study. Before delivery, parental informed consent, a detailed obstetric and medical history and examination were done.

Group I included 50 females (32 diabetic and 18 non diabetic) with ultrasonographic estimated fetal weight, using the Hadlock equation, more than 4000 gm at full term. The control group (group II) included 20 non diabetic females with AGA fetuses. Complete

ultrasonographic scanning was done including fetal biometry, FL/AC ratio, biophysical profile, anterior AWSFT, and estimated fetal weight **(Hadlock et al., 1985).**

Complete neonatal examination was carried out and dubowitz scoring system was done to confirm gestational age. Plasma glucose level was estimated for each newborn soon after delivery and one hour later using the glucose oxidase method. Hypoglycemia in a term newborn is defined as a serum glucose less than 35 mg% at less than 3 hours of age and less than 40mg% from 3 to 24 hours of age. If neonatal serum glucose level fell to below 40 mg%, glucose was administered either orally or intravenously regardless the presence or absence of symptoms.

Birth weight, crown-hell length, MAC, and SFT at 3 sites (biceps, triceps and subscapular) were measured 3 times by the same investigator on the first day of life then the mean was taken.

Naked weights were obtained on an electronic digital balance, lengths were measured with the newborn held in full extension on a portable measuring board with increments in millimeters. MAC was measured using non-stretchable measuring tape graded in millimeters at the mid-point of the distance between the acromion and the olecranon with the arm parallel to the body and the hand in a prone position. SFT were measured using the Holtain skin fold caliper at 3 sites (biceps, triceps and subscapular) which were selected as representatives of limb and trunk fat stores. Biceps and triceps SFT were obtained at the mid-arm over the biceps and triceps respectively with the skin fold parallel to the long axis of the arm. Subscapular SFT was measured just below the inferior angle of the scapula on the axis of the skin crease.

For estimation of body proportionality, PI was calculated as follows:

$$PI = \frac{\text{Birth weight (gm) x100}}{\text{Length (cm)}^3}$$

Disproportionate growth was diagnosed if the PI >90$^{th}$ percentile.

**Statistical methods:**

All data were reported as mean ± standard deviation. The significance of the difference between groups was evaluated by the t-test. The accuracy of each measurement in identifying hypoglycemia and disproportionate growth in LGA neonates was evaluated by the statistical indices: sensitivity, specificity, positive and negative predictive values and efficacy.

**3. Results:**

Out of 50 fetuses diagnosed by ultrasound using the Hadlock equation to have an estimated fetal weight more than 4000 gm, only 34 (68%) newborns had a birth weight more than 4000 gm. This shows that the Hadlock equation has a good sensitivity (97.1%) but a low specificity (54.4%) to estimate fetal weight as it increases toward 4000 gm.

Plasma glucose level estimation one hour after birth in LGA newborns revealed hypoglycemia in 14 newborns (41.4%), while 20 newborns were euglycemic.

Comparing hypoglycemic and euglycemic LGA newborns (Table I), there was a highly significant statistical difference (P<0.001) as regards AWSFT, and a significant statistical difference (P<0.01) as regards PI, length and subscapular SFT. While, no significant statistical difference could be found as regards MAC, FL/AC, birth weight, biceps and triceps SFT (P>0.05).

Table II shows that fetal AWSFT measured by ultrasound, and neonatal PI were the most sensitive indices and exhibited high specificity and / or efficacy to predict hypoglycemia in LGA newborns. While MAC and SFT were with low to moderate sensitivity, specificity and efficacy in predicting hypoglycemia in LGA newborns.

Table III shows that LGA newborns with fetal AWSFT > 10 mm as measured by ultrasound had a statistically higher PI, lower plasma glucose 1 hr. after birth and shorter in length (P<0.001), and thicker SFT at the 3 sites (P<0.01) if compared to those LGA newborns with fetal AWSFT < 10 mm. while, no significant statistical difference was found as regards FL/AC, birth weight, and MAC (P> 0.05) between both groups.

LGA newborns with disproportionate growth (PI > 90$^{th}$ percentile) were more prone to develop hypoglycemia (10 out of 14 newborns i.e 71.4%) if compared to LGA newborns with proportionate growth (4 out of 20 newborns i.e 20%). 10 out of 14 LGA newborns with disproportionate growth were infants of diabetic mothers.

Table IV shows that LGA newborns with disproproportionate growth had no significant statistical difference in FL/AC and birth weight if compared to LGA newborns with proportionate growth and a highly significant difference regarding AWSFT, length, SFT at 3 sites and plasma glucose level at 1 hr. of age (P<0.001).

Also, there was a significant statistical difference in MAC between proportionate and disproportionate growth with LGA newborns (P<0.01).

Table V shows that AWSFT measurement by ultrasound was more sensitive, specific and with higher efficacy to predict disproportionate growth in LGA newborns if compared to FL/AC ratio.

Table VI shows a comparison between LGA and AGA (control) newborns. There was a highly significant statistical difference (P< 0.001) as regards all parameters measured, except for length which showed a significant statistical difference (P< 0.01).

**Table I: Comparison between hypoglycemic and euglycemic LGA newborns.**

| | Hypoglycemic n=14 | Euglycemic n=20 | P-value |
|---|---|---|---|
| * Utrasonographic AWSFT (mm) | 11.36±0.61 | 9.85±1.06 | <0.001 |
| * Birth weight (gm) | 4107±130 | 4055±40 | >0.05 |
| * Length (cm) | 50.07±1.39 | 51.23±1.45 | <0.01 |
| * Ponderal index | 3.29±0.32 | 3.01±0.28 | <0.01 |
| FL/AC (%) | 19.79±0.85 | 19.54±0.61 | >0.05 |
| * MAC (cm) | 11.39±0.71 | 11.33±0.87 | >0.05 |
| * Skin fold thickness (mm) | | | |
| A. Biceps | 5.29±1.16 | 4.6±0.73 | >0.05 |
| B. Triceps | 7.29±1.62 | 6.45±1.24 | >0.05 |
| C- Subscapular | 8.0±1.13 | 6.9±1.09 | <0.01 |

Values are means ± standard deviations. N = number P-value < 0.05 is considered significant.

**Table II: Sensitivity, specificity, predictive values and efficacy of AWSFT, PI, MAC and SFT in predicting hypoglycemia in LGA newborns.**

| | AWSFT | PI | MAC | SFT | | |
|---|---|---|---|---|---|---|
| | | | | Biceps | Triceps | Subscapular |
| * Sensitivity | 92.8% | 71.4% | 64.2% | 50% | 57.1% | 64.3% |
| * Specificity | 80% | 80% | 55% | 50% | 55.5% | 65% |
| * Positive Predictive value | 76.4% | 71.4% | 50% | 41.1% | 44.4% | 56.2% |
| * Negative predictive value | 94.1% | 80% | 68.7% | 58.8% | 62.5% | 72.2% |
| * Efficacy | 85.2% | 76.4% | 58.8% | 50% | 52.9% | 64.7% |

**Table III: Comparison between LGA newborns with AWSFT > 10 mm and those with AWSFT < 10 mm as measured by ultrasound.**

| | Newborns with AWSFT > 10mm (n=17) | Newborns with AWSFT ≤ 10 mm (n=17) | P-value |
|---|---|---|---|
| * Birth weight (gm) | 4102±110 | 4050±40 | >0.05 |
| * Length (cm) | 49.82±1.39 | 51.68±1.03 | <0.001 |
| * Ponderal index | 3.33±0.31 | 2.91±0.18 | <0.001 |
| * FL/AC | 19.76±0.80 | 19.52±0.63 | >0.05 |
| * Mid arm circumference (cm) | 11.35±0.70 | 11.35±0.90 | >0.05 |
| * Skin fold thickness (mm): | | | |
| A. Biceps | 5.35±10.03 | 4.41±0.69 | <0.01 |
| B. Triceps | 7.35±1.57 | 6.24±1.11 | <0.01 |
| C. Subscapular | 7.94±1.16 | 6.76±1.00 | <0.01 |
| * Plasma glucose level one hour after birth (mg%) | 35.41±12.71 | 60.05±9.56 | <0.001 |

**Table IV: Comparison between disproportionate and proportionate growth LGA newborns.**

| | Disproportionate growth newborns (n=14) | Proportionate growth newborns (n=2o) | P-value |
|---|---|---|---|
| *Ultrasonographic AWSFT (mm) | 11.28±1.03 | 9.9±0.89 | <0.001 |
| * Birth weight (gm) | 4114±120 | 4050±40 | >0.05 |
| * Length (cm) | 49.07±0.73 | 51.92±0.53 | <0.001 |
| * FL/AC | 19.52±0.8 | 19.72±0.66 | >0.05 |
| * MAC (cm) | 11.71±0.52 | 11.1±0.87 | <0.01 |
| * Skin fold thickness (mm): | | | |
| A. Biceps | 5.71±0.45 | 4.3±0.84 | <0.001 |
| B. Triceps | 8.14±0.74 | 5.85±1.06 | <0.001 |
| C. Subscapular | 8.57±0.62 | 6.5±0.74 | <0.001 |
| * Plasma glucose level one hour after birth (mg%) | 34.07±12.45 | 46.8±11.39 | <0.001 |

**Table V: Comparison between the predictive values of AWSFT and FL/AC in detecting disproportionate growth in LGA newborns.**

| | AWSFT > 10 mm | FL/AC < 20% |
|---|---|---|
| * Sensitivity | 85.7% | 71.4% |
| * Specificity | 75% | 40% |
| * Positive predictive value | 70.5% | 45.4% |
| * Negative predictive value | 88.2% | 66.6% |
| * Efficacy | 79.4% | 52.9% |

**Table VI: Comparison between LGA and AGA newborns.**

| | LGA newborns n=34 | AGA newborns n=20 | P-value |
|---|---|---|---|
| * Ultrasonographic AWSFT (mm) | 10.47±1.17 | 7.6±1.16 | <0.001 |
| * Length (cm) | 50.75±1.54 | 49.73±0.86 | <0.01 |
| * Ponderal index | 3.12±0.33 | 2.62±0.14 | <0.001 |
| * FL/AC (%) | 19.64±0.73 | 20.81±0.44 | <0.001 |
| * MAC (cm) | 11.35±0.81 | 10.0±0.42 | <0.001 |
| * Skin fold thickness (mm) : | | | |
| A- Biceps | 4.88±0.99 | 3.5±0.5 | <0.001 |
| B-Triceps | 6.79±1.47 | 4.35±0.48 | <0.001 |
| C- Subscapular | 7.35±1.23 | 4.32±0.46 | <0.001 |
| * Plasma glucose level 1 hr after birth (mg%) | 41.55±13.39 | 70.85±4.97 | <0.001 |

**4. Discussion:**

Neonates manifesting hypoglycemia as a consequence of disturbed intrauterine nutrition have a high risk of neurological sequels unless they are promptly diagnosed and treated. In our study 10 out of 22 LGA infants of diabetic mothers (IDM) i.e 45.4% developed hypoglycemia and 4 out of 12 LGA infants of non diabetic mothers i.e 33.3% developed hypoglycemia within 1 hour of birth. Weiss et al. (2012), Akinbi and Gerdes (1995), and Ballard et al. (1993), reported hypoglycemia in macrosomic IDM and non diabetic mothers (INDM) (68% and 20% respectively).linder et al. (2014), found that macrosomic group had higher rates of hypoglycemia (1.2% vs 0.5%, p= 0.008), also Bandika et al. (2014), reported that large for gestational age accounts for about 6.3% of admission in Kenyatta National Hospital, newborn unit and the incidence of hypoglycemia in LGA was 21%.

The use of ultrsonographic abdominal wall subcutaneous fat thickness in this study has been based on the assumption that LGA fetuses had hyper insulinemia associated with increase fat deposition as concluded by Akinbi and Gerdes (1995) and Hoegsberg et al. (1993), in their studies. Ultrasonographic AWSFT is a simple procedure and it has a good sensitivity, specificity, predictive values and efficacy not only to predict hypoglycemia in LGA neonates, but also to predict disproportionate growth in LGA neonates. While, it has s low sensitivity and efficacy to predict macrosomia (>4000 gm) as suggested by Chen et al. (2014), and Arias (1993).

Neonatal anthropometric measurements have been used for assessment of intrauterine nutrition (Gyurkovitz et al., 2011 and Gogal et al., 1991). In this study the ponderal index (PI) was the most sensitive and specific index to predict hypoglycemia in LGA neonates. Also Ballard et al. (1993), found that severe hypoglycemia was 3.9 times more common in disproportionate growth macrosomic neonates than proportionate macrosomic neonates. On the contrary, Drossou et al. (1995), considered the PI as an unreliable index to predict hypoglycemia in LGA neonates, in spite of positive correlation between the PI and the neonatal hypoglycemia.

Gyurkovits et al. (2011), found an increased skin fold thickness and shorter body length in neonates of diabetic mothers with high insulin requirement, but the authors did not attempt to relate neonatal complication to skin fold thickness. This study showed a significantly thick subscapular SFT in hypoglycemic LGA neonates if compared to euglycemic LGA neonates. Also, it had a moderate sensitivity and specificity to predict hypoglycemia in LGA neonates. While, biceps and triceps SFT had a low sensitivity and specificity to predict hypoglycemia in LGA neonates.

Bertagnon et al. (2003), and Drossou et al. (1995), found a significantly thicker biceps, triceps and sub-scapular SFT in hypoglycemic LGA neonates, but none of these parameters were adequately specific to predict hypoglycemia in LGA neonates.

This study showed that there is no significant difference in mid arm circumference between hypo

and euglycemic LGA neonates. MAC is not specific to predict hypoglycemia in LGA neonates. Also our study showed that disproportionate growth in LGA neonates represent 41%, most of them (71%) are IDM. Disproportionate growth LGA neonates are more liable to develop severe hypoglycemia (71%) than proportionate LGA neonates. This is in agreement with Gyurkovits et al. (2011), findings in their study.

This study showed that there was no significant correlation between ultrasonographic AWSFT and maternal diabetic control as estimated by maternal fasting and 2hr. post prandial blood glucose levels. While Higgins and MC Auliffe (2010), Suggested that the amount of subcutaneous fat present in IDM may be an indication of the quality of diabetic control achieved during gestation.

This study showed a low specificity of the Hadlock equation for estimated fetal weight > 4000 gm. This was also founded by Chauhan et al. (1995), and they concluded that Hadlock equation overestimates the birth weight and had a low predictive value in fetuses > 3750 gm.

**5. Conclusion:**

The results of this study suggest that the sonographic AWSFT >10mm and neonatal PI are the most sensitive and specific indices that could predict neonates at risk of developing hypoglycemia in LGA infants. These tests are non-invasive, reliable and can be performed easily in clinical practice for early prediction of hypoglycemia in LGA neonates. This is a necessity, especially in neonates that are being nursed alongside their mothers to minimize the neonatal morbidity and mortality due to development of hypoglycemia. Also, it would possibly minimize the need for laboratory tests in infants not at risk after 12 hours of birth, but should continue for 48 hours in neonates at risk of developing hypoglycemia.

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