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Birthweight percentiles by gestational age in Georgia

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ABSTRACT

Background: Development of country specific birthweight percentile by gestational age chart has been suggested to identify small for gestational age (SGA) or large for gestational age (LGA) babies who are at a risk of perinatal and neonatal mortality and morbidity.

Objectives: The objective of this study was to construct sex-specific standard birthweight by gestational age chart for Georgia.

Methodology: A cross-sectional study was conducted using the Georgia Birth Registry (GBR) for the period of May 2016 to February 2017. All singleton births with complete gestational weeks from 23 to 44 was included in the study. Gestational age were assessed by last menstrual period or ultrasound examination. For constructing the standard chart for newborn only those pregnant women and the newborn who meet the standard eligibility criteria were selected. Altogether,14,230 livebirths were included after exclusion and removal of outliers for analysis. Data from the GBR were analysed using R 3.2.5 software. Birthweight percentiles by gestational age were computed for each completed gestational age week and sex. Generalised Additive Model for Location Scale and Shape **(**GAMLSS) was used for smoothening of birthweight percentile curves.

Results: The mean birthweight was 3276 g and the mean gestational age at birth was 38.76 weeks. 95% of the babies had a birthweight ranging from 2500 g to 4499 g and most of the babies (94.6%) were born during the gestational age 37 to 41 (term week). Generally, males were heavier than females at all gestational ages except at 24 and 29 weeks of gestation. The 3rd, 10th, 50th, 90th and 97th percentile curves were created according to gestational age and sex. The 10th and 90th percentile values of birthweight were higher for males at most of the gestational ages except for few weeks.

Conclusion: This is the first study constructing sex-specific standard birthweight percentile chart and curve by gestational age for Georgia. Comparison of the birthweight percentile chart with other countries showed that the 10th and 90th percentile values of Georgia was higher in preterm weeks compared to Norway and Australia. However, the cut-off values for SGA and LGA in term weeks were higher for Georgia compared to WHO, Brazil, Ukraine and Turkey.

Key words: birthweight, gestational age, small for gestational age, large for gestational age

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LIST OF ABBREVIATIONS

AGA	Appropriate for Gestational Age
BCT	Box-cox Transformation
BMI	Body Mass Index
DHS	Department of Health Service
ELBW	Extremely Low Birthweight
GAMLSS	Generalised Additive Model for Location Scale and Shape
GBR	Georgia Birth Registry
HBW	High Birthweight
IQR	Interquartile Range
LMP	Last Menstrual Period
LBW	Low Birthweight
LGA	Large for Gestational Age
MoLHSA	Ministry of Labour, Health and Social Affair
MUAC	Mid-Upper Arm Circumference
NCDC	National Centre for Disease Control
SD	Standard Deviation
SGA	Small for Gestational Age
VLBW	Very Low Birth Weight
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Introduction

Birthweight by gestational age has been recognized by World Health Organization (WHO) as one of the strongest indicators to assess the health of infant at birth (1). The importance of classifying babies as small for gestational age (SGA), appropriate for gestational age (AGA) or large for gestational age (LGA) has been highlighted in many studies (2-11). Infants born smaller than their peers of similar gestational age are at increased risk of perinatal and neonatal mortality and other adverse health outcome (12). Similarly, infants born large for their gestational age also have related health problems (12). Available estimates for the prevalence and mortality of SGA babies indicate that their assessment is a major priority for public health (8). Birthweight percentile charts (standard or of reference) which include weight and gestational age of newborns at birth, have been regarded as an important tool for the identification of such babies (2-11). However, the absence of such charts have been a major limitation for estimates of SGA or LGA babies (8).Development of a country specific birth weight percentile standard chart is thus essential, to enable accurate identification of small or large for gestational age babies. This identification provides an indication of a risk of perinatal and neonatal mortality and morbidity (3, 8, 13, 14).

1.2 Measuring size at birth

Size at birth is an important indicator of health and should be measured as accurately as possible. A number of anthropometric measurements are used to evaluate newborn size at birth they include birthweight, birth length, head circumference, chest circumference, mid-upper arm circumference (MUAC) and abdominal circumference. Among the above-mentioned, birthweight, length and head circumference are most commonly used globally and chest circumference, MUAC and abdominal circumference are used ordinarily as an alternate measurement, if weight scale or length board are not available (5, 15).

1.2.1 Birthweight

Birthweight is measured with a baby scale where the newborn is lying down in the weighing pan. Scales used in different countries are either electronic or mechanical and should provide reasonably valid and precise reading. A measurement can be performed by one person, since baby can lie freely in the weighing pan (16).

1.3 Terms and definitions related to size at birth

Most commonly used measurements are based on birthweight and there are concepts related to weight only or taking gestational age in consideration.

1.3.1 Low birthweight

To assess the risk associated with size at birth, in 1950, a WHO expert group on prematurity, endorsed the use of term "Low birthweight" (LBW). LBW is defined as birthweight less than 2500 g. Very low birthweight (VLBW) is defined as birthweight less than 1500 g and extremely low birthweight (ELBW) as less than 1000 g (17, 18) .

1.3.2 High birthweight

High birthweight (HBW) is defined as birth weight above 4000 g and above 4500 g as exceptionally high birthweight (18).

1.3.3 Gestational age

Gestational age at birth is the time between the first day of the woman's last menstrual period (LMP) and the day of the delivery. Gestational age at birth is expressed in complete weeks.

For instance, a newborn born at 39 weeks and four days of gestation is expressed as being born at 39 weeks of gestation (19). Gestational age at birth is calculated from Naegele's rule in which 280 days or (nine months and seven days) is added to the women's LMP date (20) .Another method of estimating gestational age at birth is through ultrasound examination ideally conducted at eight to 13 weeks of gestation. The ultrasound examination has upgraded the accuracy of estimation of gestational age. In this regard, there is a unanimous agreement that the best estimation of gestational age at birth is obtained from the combination of reported LMP and ultrasound examination.(3, 21).

Until 1967, the term gestational age was not combined with birthweight. However, with the growing evidence of the dominant effect of gestational age on survival and long-term impairment, there has been a shift from measuring birthweight alone to focusing on gestational age. This shift has argued that it will be incomplete to define the terms related to birth weight without the terms SGA, AGA, and LGA (22).

1.3.4 Small for gestational age

SGA refers to a statistical definition, which is based on an auxological cross-sectional evaluation (prenatal or neonatal). It indicates neonates whose weight are below a given threshold value of the newborn population having the same gestational age. SGA is defined as a birthweight lower than the 10th percentile for the given gestational age. It includes infants who have not achieved their own growth potential, because of maternal, uterine, placental and fetal factors, as well as small but otherwise healthy infants. SGA children may be preterm, term or post-term and also etiology of growth restriction differs (3).

1.3.5 Large for gestational age

LGA also refers to the statistical definition, based on an auxological cross-sectional evaluation (prenatal or neonatal). It denotes neonates whose weight are higher than a given threshold value of the newborn population of same gestational age. LGA is defined as a birth weight higher than 90th percentile for the given gestational age. Most of the LGA babies are born at term (37 to 41 weeks of pregnancy), while a few premature babies may also be LGA (3). Some babies are large because their parents are large as genetics also play a part. Birthweight can also be related to the amount of weight a mother gains during her pregnancy. Excessive weight gain can translate to increased fetal weight (23).

Yehuda Malul's image (Figure 1) illustrates different terms and definitions related to birth weight (24).

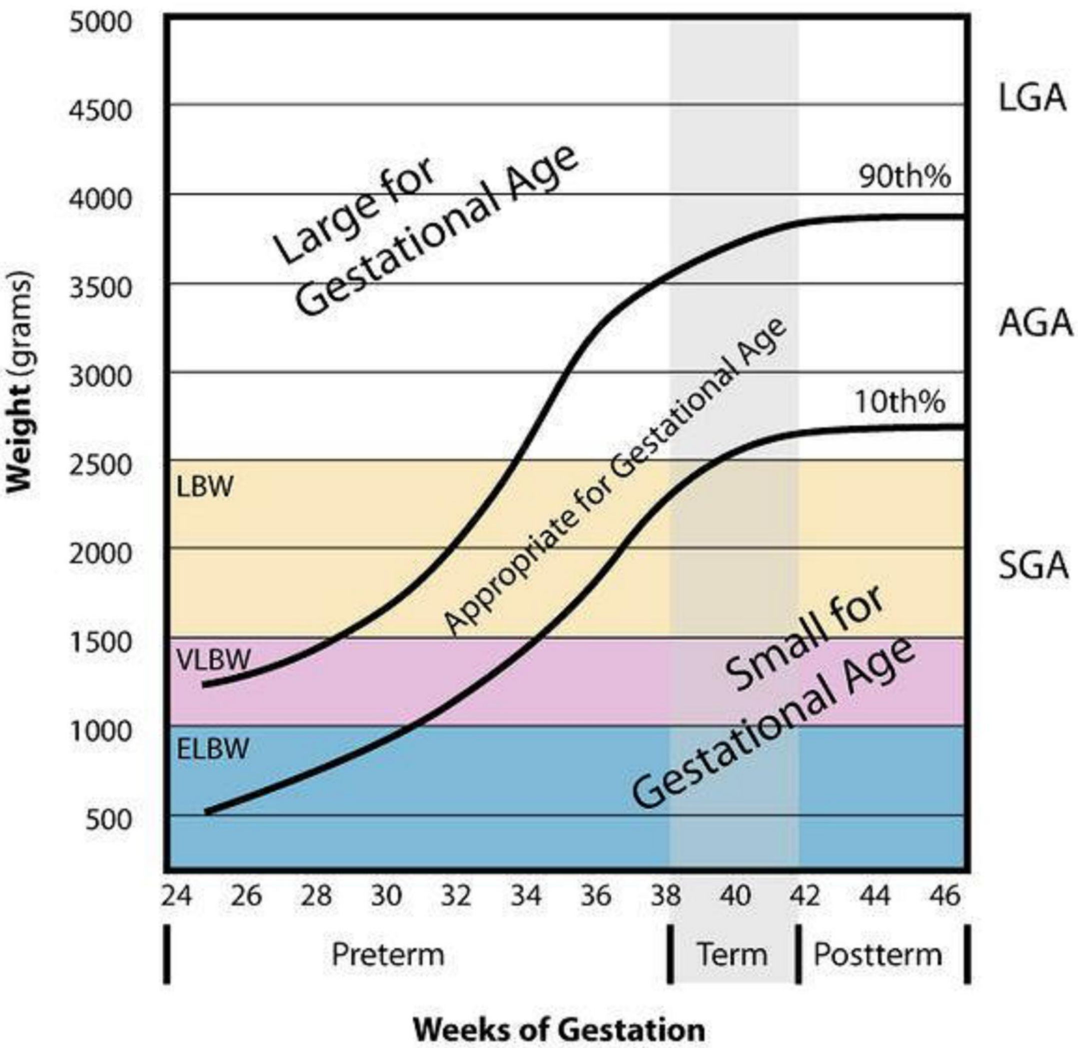

Figure 1: Terms and definitions related to birth weight

The above figure shows that the terms, LBW, VLBW and ELBW are used, when birthweight is lower than set limit irregardless of gestational age. When definitions of SGA, AGA and LGA are used gestational age is taken into consideration. Different definitions can overlap; for example LBW infants can be at the same time also defined as AGA or LGA or normal weight infant can be defined as SGA (25). In the figure, SGA, AGA and LGA newborn are classified based on percentiles, but also standard deviations (SD) can be used; for example AGA can be classified also as -2SD to +2SD for weight (26).

1.4 Types of birthweight chart

There are two main types of birthweight chart, defined either as a reference chart or as a standard chart. A newborn is classified as SGA, AGA or LGA according to the threshold values that are derived from the percentile distribution of birthweight for gestational age in a population of newborns considered either as reference or as standard. A standard is based on highly restrictive criteria intended to exclude all newborns exposed to any risk factor for fetal growth, thus describing "how growth should be." In the absence of exclusion criteria, a chart is considered a reference, which describes "how growth actually is" (3, 27). At present, the large majority of growth charts in use are essentially references (6, 27) .

1.5 Trends in birthweight

According to WHO, the global prevalence of LBW is 15.5%, which amounts to about 20 million LBW infants born each year and 96.5% of them are in developing countries (4). One third of babies born with LBW are also SGA (28). The prevalence of SGA births are approximately double the prevalence of low-birthweight births (using the common indicator of <2500 g birthweight) globally and in the world's regions (29). The perinatal mortality rate is higher at any gestational age in SGA children compared with normal weight children. A study from 2006 that included more than 18 million singleton births showed that, at 26 weeks of gestation, infants born with birthweight at the 10th percentile or below experienced a 3-fold risk of dying within the first 28 days of life relative to children born with birthweight between the 45th and 55th percentiles. At 40 weeks, the ratio was 1.13 with the use of data from the same population. (30).

1.5.1 Trends in developing countries

A study on global prevalence of SGA estimated that in 2010, 32.4 million babies were born SGA in low- and middle-income countries, constituting 27% of all live births. The estimated prevalence of SGA is highest in South Asia and in Africa (29). From developing countries, data on birth weight is not available from over long period of time. In Iran, the birth weight has decreased from 3222 g to 3152 g from 1970 to 2000. In Vietnam there was a significant increase of birth weight from 1980 to 2000. According to longitudinal data on birthweight from 20 countries, prevalence of LBW has remained more or less constant from 1990 to 2000 (24% and 23%) (15).

1.5.2 Trends in developed countries

There is considerable variation in the prevalence of infants born SGA (4.6–15.3% across Europe) and LGA (5–20% in developed countries) (31).In developed countries, the size at birth seems to have turned in the opposite direction during the past few decades (15, 31). Decline in average birthweight has recently been observed in some countries, such as France and USA (31).However, over the last three to four decades, there has been an increase in birthweight reported in Australia and Canada. For example, among term infants in Canada, the proportion of babies born SGA decreased from 11.1% to 7.2%, while LGA births increased from 8.0 to 11.5% over an 18-year period (1978–1996) (31). An even bigger increase of LGA by 23 percent was seen in Sweden from 1992 to 2001 (32).

The reasons underpinning the observed variations over time are uncertain, but temporal increases in birthweight are said to reflect the increasing maternal adiposity and nutritional excess in utero as maternal factors directly affect fetal growth (31).

1.6 Trend of birthweight charts in the world

The first chart showing the distribution of birthweight at each gestational age was created by Lubencho et al. in 1963 (10). Over the years, many birthweight by gestational age charts have been created for populations throughout the world and at present these, are the cornerstone of screening for SGA and LGA babies (7, 11, 25, 33-42). According to a WHO report, there are more than 104 birthweight percentile chart published since 1990 (8).These charts have different characteristics in terms of source of data and methodology. Moreover, more than 80% of the available charts are reference charts (6).

While there are a growing number of country specific reference chart, the international standard chart is also important for clinical practice and essential to estimate accurately the prevalence of SGA and LGA babies worldwide (3, 8). In this regard, WHO has constructed the international standards for newborn weight, length, and head circumference by gestational age and sex: The INTERGROWTH-21st PROJECT. This chart is based on a multicentre, multinational and multi-ethnic population. This chart was developed considering a "one size fits all" approach and is the prescriptive standard chart that was developed recently (8).

1.7 Georgia country profile

Georgia is defined as a developing, upper-middle-income country with a population of 3.7 million (43).

Table 1: Relevant demographic information for Georgia from 2015 (44, 45)

Population	**3,720,000**
Birth rate (per 1000 population)	15.9
Infant mortality (per 1000 live birth)	8.6
Neonatal mortality rate (per 1000 live birth)	5.8
Early neonatal mortality rate (per 1000 live birth)	3.6
Perinatal mortality rate (per 1000 live birth)	13.4
Under 5 mortality rate (1000 live birth)	10.2
Stillbirth (1000 birth)	9.8
Term deliveries (%)	82.1
Birth registration coverage (%)	≈100

After the collapse of the Soviet Union in 1991, there was a catastrophic drop in public health expenditures and in the quality of medical services in Georgia. In the year 2000, the Georgian National Health Policy was developed with the aim of improving equity, accessibility and affordability of health services. A new direction was set in 2003 that aimed at liberalizing the healthcare policy and in 2007 Georgia moved to an insurance-based healthcare model. In 2013, a Universal Health Coverage (UHC) system was implemented for the entire population who do not have a private health insurance. The expenditures in the maternal and perinatal system is also covered by the UHC system. There are some other state programs providing services related to mother and child care this include Mother and Child Care Program. This program covers antenatal care, antenatal genetic screening, newborn screening and management of complication during pregnancy, labor and delivery and is free for all pregnant women (46). All of these programs aims to reduce the perinatal and neonatal mortality and morbidity in the country (46).

1.8 Statement of problem

In Georgia, the neonatal mortality rate was 5.8 per 1000 live births and the perinatal mortality rate was 13.4 per 1000 lives births in 2015. It is noteworthy that infants born small or large for gestational age are at an increased risk of perinatal and neonatal mortality and morbidity (31). In addition, infants born SGA are at an increased risk of adverse health consequences including childhood malnutrition, neurodevelopmental problems, adult-onset cardiovascular disease and metabolic alteration. LGA babies are also at the risk of perinatal adverse outcomes such as, obesity, and metabolic syndrome later in life (12).

Therefore, the first step to reduce perinatal or neonatal mortality and morbidity rate is the correct identification of babies at risk. Birthweight percentile charts allows the detection of newborn at high risk and assists in the assessment of the need for further care of these babies. These charts are needed for both clinical and epidemiological purposes. At clinical level, it helps to identify babies who are SGA or LGA so that their immediate health care need can be addressed. Similarly, at population level, the statistical reviews of the birthweight percentile chart are informative for the monitoring of epidemiological outcomes and public health care policies. (37).

Although, Georgia has national guidelines for management of SGA babies, they lack a national chart for estimation of such babies and uses WHO international standard for classifying babies as SGA or LGA (47). However, it has been argued that each country should develop its own specific chart since the evaluation of SGA or LGA babies based on chart from other countries can possibly lead to misdiagnosis of such babies (3, 14). While many countries have developed their own standard or reference birthweight percentile chart acknowledging its importance, no such chart has been developed in Georgia till date.

Hence, this study will provide the first national standard birthweight percentile by gestational age chart for Georgia.

1.9 Objectives of the study

The objectives of this study were described as general objective and specific objectives.

1.9.1 General objective

The general objective of this study was to develop a birthweight percentile by gestational age chart for Georgia. In addition, the objective was to perform a quality control on the variables that are used for this study.

1.9.2 Specific objectives

The specific objectives of this study were:

i. To construct sex-specific standard birthweight percentile by gestational age chart for Georgia.

ii. To provide the cut-off values for SGA, AGA and LGA in Georgia.

iii. To compare the cut-off values for SGA and LGA of Georgia with WHO international standard chart and with the chart of other countries.

iv. To use the findings for providing recommendation to GBR for future data collection and studies.

1.10 Research Question

i. What are the cut-off values for SGA, AGA, and LGA for newborns at each gestational age?

ii. Is there any difference in the birth weight of males and females at each gestational age?

iii. What is the quality of the recently established GBR data?

CHAPTER 2: MATERIALS AND METHODS

2.1 Study design

This study was a cross-sectional study.

2.2 Data source description

The data for this study has been taken from the medical birth registry of Georgia. On January 1st 2016, Georgia launched a nation-wide medical birth registry (GBR) that aimed to provide steady and reliable information about pregnant women and newborns in Georgia (48, 49).

GBR ensures registration of the entire pregnancy and information on the newborn. The purpose of the GBR is to help to provide health care and health management information to Ministry of Labour, Health and Social Affair (MoLHSA) without violating privacy, so that health care can be given in a proper and efficient manner. Through research and statistics, the GBR aims to contribute with information and knowledge on population health conditions, causes of impaired health and development of disease management, quality assurance, planning and management (48, 49).

The system is digital and fully integrated into the national e-health platform. All delivery departments or clinics that might receive a woman during pregnancy for consultations are required to enter her information online onto a secure website. All information entered is further processed and refined at the birth registry office at the National Centre for Disease Control (NCDC) (48).

2.3 Study variables

Predictors: Gestational age (in complete weeks), sex.

Outcome: Birthweight (in gram)

2.4 Predictor and outcome measurement

Gestational age was estimated using the LMP date of the pregnant women. In case of missing or uncertain LMP, a clinician's estimate of gestation at birth based on an ultrasound examination was used. Gestational age at birth was reported in completed weeks.

Birthweight measurement was performed by trained midwives or doctors, within two hours of birth, in maternity homes. The birthweight was measured using a regularly calibrated digital scale.

2.5 Preliminary Analysis

Step 1: Data cleaning

The data from GBR was the first set of data exported from the registration database to Excel for analysis purpose. Altogether four separate files were received from the registry: Visits, Pregnancy, Newborn and Hospitalization.

Among the four datasets within the GBR database, the Visits, Pregnancies and Newborns sheet were used for analysis. Visits comprised information about pregnant women each time they attended antenatal care. There were more than one record for the same pregnant woman. Hence, 191,308 records on the Visits that contained more than one recorded information of the same pregnant woman were removed. From Pregnancies, 2,414 records belonging to Non-Georgian nationality were removed.

Step 2: Establishment of inclusion and exclusion criteria

For constructing the standard birthweight percentile chart, this study used the same exclusion criteria that was used by WHO for the Intergrowth 21st Project (8).

In Visits, 2,075 cases of pregnant women who had BMI less than 18.5 kg/m^2,12,410 cases with BMI 35 kg/m^2 or greater and 30,666 records with no information on BMI were excluded. BMI was computed from the given weight and height of a pregnant women before week 12. In addition, one record of severe preeclampsia was excluded from the Visits.

Likewise, from Pregnancies, three records of premature birth with major congenital malformation, 346 records for smoking during pregnancy, 182 records for use of psychotropic drug during pregnancy and 16 records of pregnant women who consumed more than two units of alcohol per week were excluded. Information on predictor and outcome variables were missing for most of the births that occurred between January 1st 2016 and May 1st 2016. Hence,16,132 births that occurred before May 2nd, 2016 were removed from the Pregnancies.1,891 pregnant women were excluded because information about their pregnancy outcome was not registered. Similarly, 761 records having maternal age younger than 18 and 3,924 records having maternal age older than 35 years were also excluded from Pregnancies. Maternal age was calculated from given mother's date of birth and date of delivery.

From Newborns, all singleton births with a complete gestational week ranging from 23 to 44 weeks were included in the study. 553 records of stillbirths, 211 records with missing field for sex, 16,668 births before May 2nd , 2016 were excluded. Likewise, 703 twins and 17 triplets births, 160 babies with birth defect genetic abnormalities and 1,608 births with no information on birth defect were excluded. Similarly, using the WHO guideline for lower and upper limit of birth weight for analysis, birth weight less than 500 g and more than 6000 g were excluded. In addition, 1,213 births with missing gestational age were removed from the Newborns.

Step 3: Merging of data

After removing the records from the three data file as per the exclusion criteria, there were 39,352 records from Visits, 66,296 from Pregnancies and 36,889 records from Newborns. All three datasets were then merged by a common variable, Pregnancy ID number. After merging, there were 14,290 records of newborns for analysis.

Step 4: Removal of Outliers

To identify and exclude erroneous data arising from recording errors, scatter plots of birthweight for each gestational age and sex were generated for preliminary analysis .Outliers were identified by initial visual inspection and applying Tukey's modified methodology (50). In this method, first the 25th percentiles (p25) and 75th percentiles (p75) were computed for each gestational age and sex. Then, for each sex and gestational age combination, outliers were identified as birthweights below the first quartile minus twice the interquartile range (IQR), or above the third quartile plus twice the interquartile range. Sixty records were excluded using Tukey's methodology.

John Tukey’s method of leveraging the IQR is applicable to most ranges for identification and removal of outliers. This method is not dependent on distributional assumptions and the quartiles are more robust to skewed or heavy-tailed distributions. It ignores the mean and standard deviation, making it resistant to being influenced by the extreme values in the range (51).

2.6 Study population.

The study population included infants born from May 2nd, 2016 to February 8th, 2017. Altogether, 14,230 newborns were included after exclusion and removing the implausible values for birth weight.

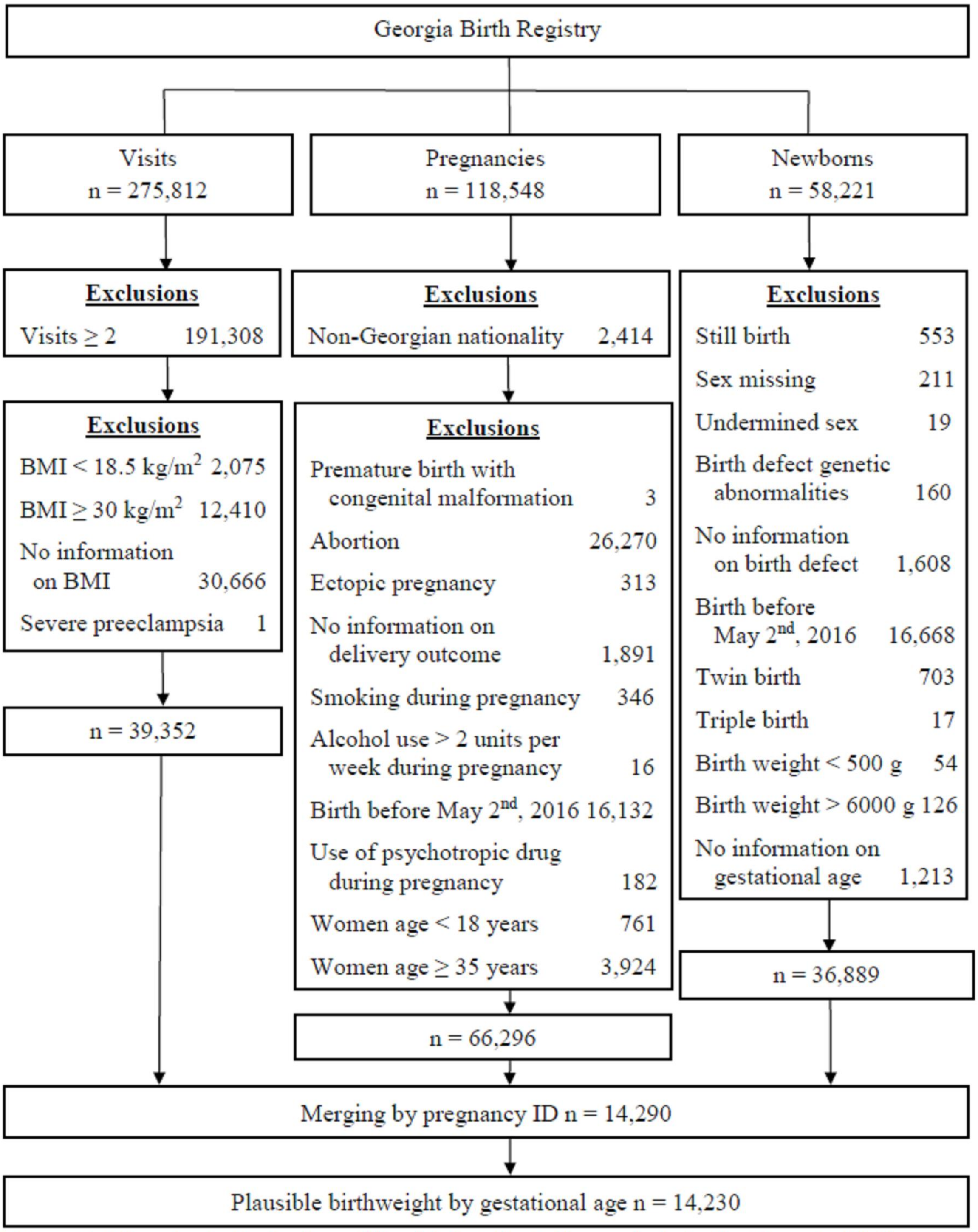

Figure 2: Flowchart of selection of live birth infants for analysis in the Georgia Birth Registry

In the above flow chart, the total number of exclusions does not add up to the difference between numbers before and after exclusions as some individuals were excluded for more than a single reason.

2.7 Statistical methods

The data from GBR were analysed using R 3.2.5 statistical software. Descriptive statistics were used to display the birthweight distributions, and compute mean, SD and percentiles (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th and 99th) for each completed gestational age and sex.

As the distribution of birthweight at gestational ages was not normal and the general pattern of relationship between birth weight and gestational age was not linear, the generalized additive model for location scale and shape (GAMLSS) approach from R was used for developing smoothed curves (52). This approach is highly flexible as it relaxes the traditional distributional assumptions about normality to include even skewed and kurtotic distributions. It extends not only to model mean but all other parameters (SD, skewness and kurtosis) of the distribution as linear, nonlinear or smoothing functions of explanatory variables (gestational age) (26, 36, 52, 53). For analyses, Box-Cox t (BCT) distribution was used for modelling birthweight as non-parametric cubic spline functions of gestational age. All models were fitted separately for male and female. At least, 50 observation were required for constructing the standard (8), so for the male the birthweight percentile curve was created for 34 to 41 weeks of gestational age. However, for female 35 weeks was the lower limit and 41 weeks was the higher limit.

2.8 Ethical considerations

The GBR is an official national registry in Georgia and UiT has no responsibilities concerning data storage. The NCDC in Tbilisi has approved transfer and use of data by UiT. All data used in this thesis were anonymized. This includes removal of any personal data that may be used to identify individuals or vulnerable groups of people. All the women and children in the GBR have been assigned a random number and there is no possibility to link information to the original data files. The database used for the research is confidential and the researcher cannot get personal information from the study materials.

On the part of UiT, this study was a part of the master thesis and as no primary data was collected, Regional Ethics Committee (REK) approval was not needed.

CHAPTER 3: RESULTS

Table 2: Maternal and infant characteristics of all live singleton births, The Georgia Birth Registry

Characteristics	Number (%)	Mean
Total	14,230	
Sex of infant		
Male	7265 (51%)	
Female	6965 (49%)	
Birthweight(g)		3276
<1500	71 (0.4%)	
1500-2499	582 (4%)	
2500-4499	13,487 (95%)	
≥4500	90 (0.6%)	
Gestational age(weeks)		38.76
20-31	90 (0.6%)	
32-36	628 (4.4%)	
37-41	13,457 (94.6%)	
42-44	55 (0.4%)	
Maternal age(years)		25.79
<20	1127 (8%)	
20-24	4808 (33.7%)	
25-29	5007 (35.2%)	
30-35	3285 (23%)	
Not stated	3 (0.02%)	
Birth order		
1st births	3049 (21.4%)	
2nd or greater	5016 (35.3%)	
Not stated	6165 (43.3%)	

The frequency and percentage of maternal and infant characteristics for 14,230 live births are presented in Table 2. Among the total newborn, 51% were male. The mean birthweight was 3276 g and the mean gestational age at birth was 38.76 week. Among the total newborn, 95% of the babies had a birthweight between 2500 g and 4499 g and most of the babies (94.6%) were born during the gestational age 37- 41 week.

Table 3: Observed birthweight statistics for male infants, The Georgia Birth Registry

Gestational age (weeks)	Number of births	Mean (s) birthweight(g)	Birthweight percentile(g)										
			1st	3rd	5th	10th	25th	50th	75th	90th	95th	97th	99th
23	1	800(NA)	800	800	800	800	800	800	800	800	800	800	800
24	1	500(NA)	500	500	500	500	500	500	500	500	500	500	500
25	4	800(91)	701	704	707	715	737	800	862	885	829	895	898
26	2	1025(35)	1000	1001	1002	1005	1012	1025	1037	1045	1047	1048	1049
27	9	968(156)	708	724	740	780	900	980	1100	1120	1160	1176	1192
28	5	1094(250)	823	830	836	852	900	1100	1200	1350	1400	1420	1440
29	13	1261(186)	1006	1018	1030	1060	1150	1200	1350	1490	1560	1596	1632
30	10	1523(135)	1400	1400	1400	1400	1412	1500	1560	1710	1755	1773	1791
31	11	1916(218)	1484	1532	1580	1700	1840	1940	2000	2200	2225	2235	2245
32	30	1795(370)	1058	1174	1222	1376	1525	1775	2022	2260	2350	2382	2527
33	27	2144(248)	1713	1739	1765	1860	2030	2120	2225	2340	2435	2571	2857
34	60	2329(288)	1688	1788	1800	2000	2175	2350	2500	2700	2800	2823	2941
35	75	2529(299)	1824	2022	2100	2200	2350	2500	2700	2900	3015	3089	3189
36	164	2702(418)	1782	2000	2013	2165	2442	2700	2962	3136	3485	3611	3818
37	570	3058(384)	2200	2400	2500	2599	2800	3050	3300	3573	3700	3800	4000
38	1626	3273(382)	2350	2582	2664	2800	3000	3300	3500	3785	3907	4000	4200
39	2439	3431(400)	2538	2700	2800	2900	3150	3425	3700	3900	4100	4200	4481
40	1762	3529(407)	2600	2778	2900	3000	3260	3500	3800	4000	4200	4300	4569
41	427	3602(412)	2700	2900	2963	3050	3350	3600	3872	4166	4300	4400	4600
42	27	3539(451)	2552	2797	2906	3028	3300	3600	3850	4040	4170	4266	4422
43	1	4220(NA)	4220	4220	4220	4220	4220	4220	4220	4220	4220	4220	4200
44	1	2900(NA)	2900	2900	2900	2900	2900	2900	2900	2900	2900	2900	2900

Table 4: Observed birthweight statistics for female infants, The Georgia Birth Registry

Gestational age (weeks)	Number of births	Mean (s) birthweight(g)	Birthweight percentile(g) 1st	3rd	5th	10th	25th	50th	75th	90th	95th	97th	99th
23	2	775(177)	652	657	662	675	712	775	837	875	887	892	897
24	1	800(NA)	800	800	800	800	800	800	800	800	800	800	800
25	1	500(NA)	500	500	500	500	500	500	500	500	500	500	500
26	2	875(177)	752	757	762	775	812	875	937	975	987	992	997
27	3	940(227)	687	702	716	752	860	1040	1070	1088	1094	1096	1099
28	5	960(143)	756	768	780	810	900	970	1080	1092	1096	1098	1099
29	6	1380(114)	1300	1300	1300	1300	1307	1340	1387	1500	1550	1570	1590
30	6	1238(150)	1007	1022	1037	1075	1162	1265	1345	1375	1387	1392	1397
31	8	1784(332)	1360	1381	1402	1455	1575	1785	1900	2065	2257	2334	2411
32	22	1784(222)	1263	1389	1503	1562	1600	1845	1942	2000	2047	2087	2129
33	19	2013(393)	1254	1362	1470	1660	1775	1900	2250	2500	2525	2515	2750
34	47	2236(333)	1673	1700	1700	1746	2000	2250	2430	2640	2800	2843	2935
35	63	2415(371)	1500	1758	1805	1900	2200	2400	2700	2900	2939	3014	3100
36	121	2599(409)	1660	2000	2050	2200	2350	2500	2900	3100	3220	3420	3850
37	529	2928(371)	2106	2300	2356	2500	2700	2900	3200	3400	3600	3652	3800
38	1504	3153(379)	2301	2461	2500	2700	2900	3116	3400	3650	3800	3900	4019
39	2352	3265(377)	2400	2600	2700	2800	3000	3240	3500	3754	3900	4000	4200
40	1792	3373(373)	2500	2700	2800	2900	3100	3400	3600	3879	4000	4063	4282
41	456	3453(390)	2577	2800	2850	3000	3200	3445	3700	4000	4100	4200	4500
42	26	3392(268)	2900	2900	2957	3165	3255	3345	3500	3800	3930	3955	3985

Tables 3 and 4 present the plausible values for all gestational age with number of observation, mean, SD and the percentiles. Generally, males were heavier than females at all gestational ages except at 24 and 29 week. For both sexes, it was found that the maximum number of births occurred at the gestational age 39.

The 10th and 90th percentile values of birthweight were higher for males in most of the gestational age except for few weeks. For gestational ages, 24, 29, 32, 36 and 42, the 10th percentile values were higher for females. Similarly, for gestational ages 23, 24, 29 and 33, the 90th percentiles values were higher for females.

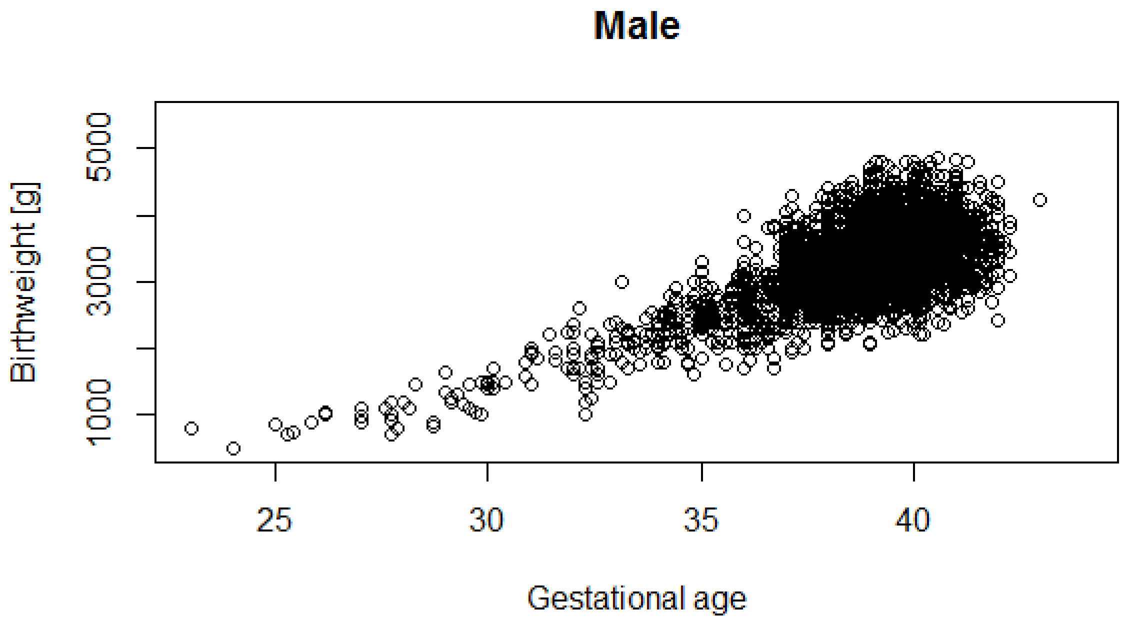

Figure 2: Plot 1A for Birthweight versus Gestational age with days for males (plausible values)

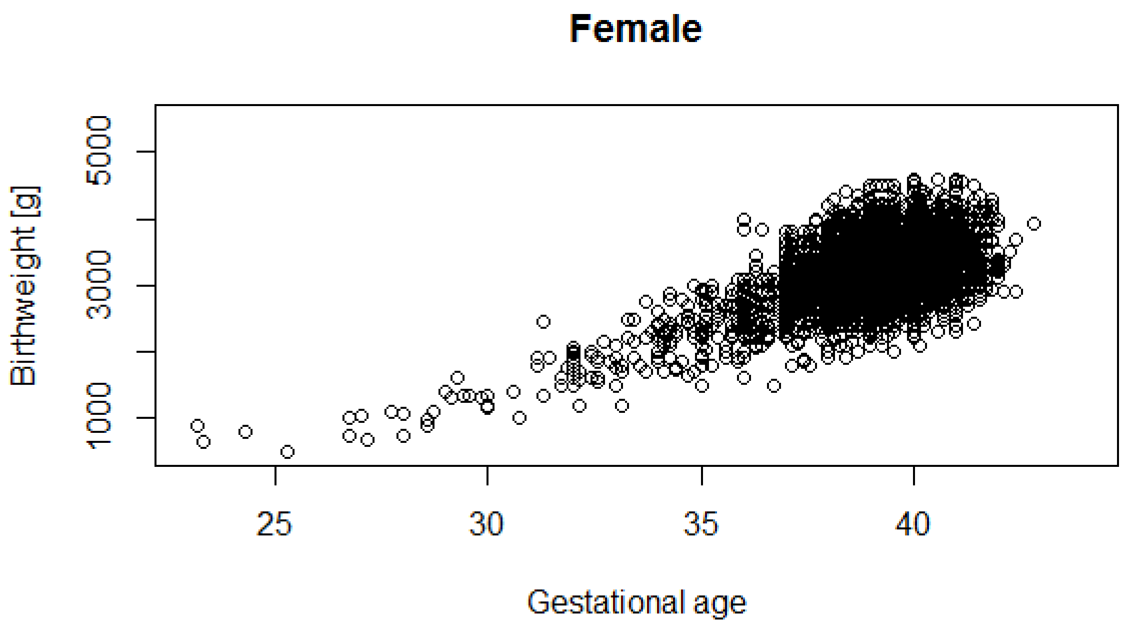

Figure 3: Plot 1B for Birthweight versus Gestational age with days for females (plausible values)

The above plots shows the plausible values for birthweight by gestational age including the days for males and females separately.

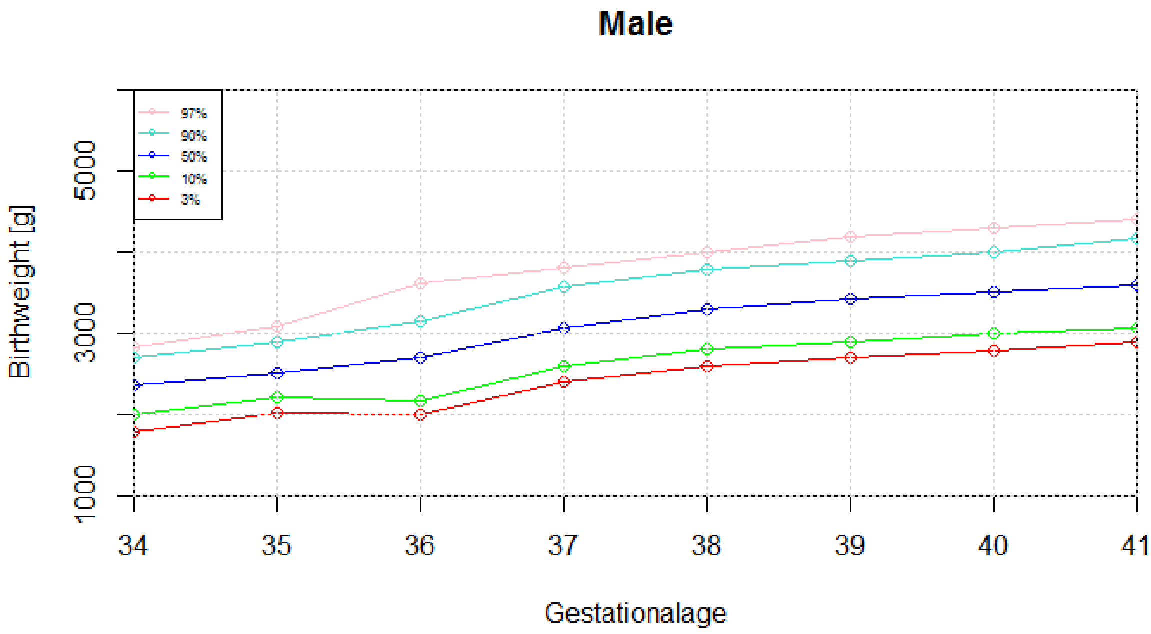

Figure 4: Plot 2 A for Observed percentiles (plausible values) for Gestational age with at least 50 observation for males.

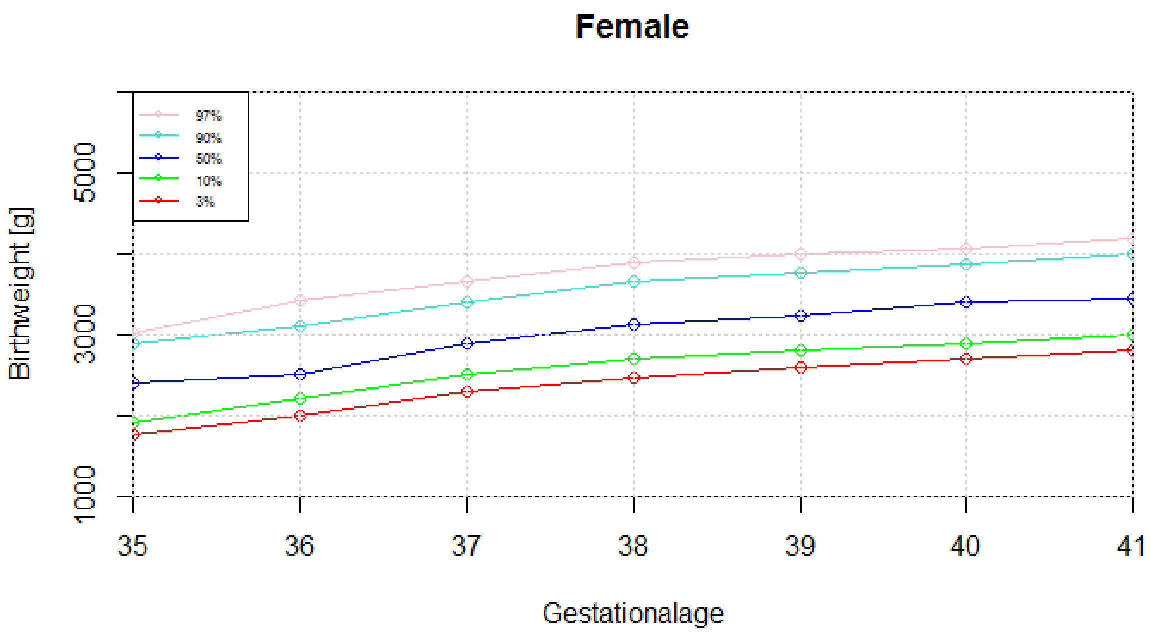

Figure 5: Plot 2 B for Observed percentiles (plausible values) for Gestational age with at least 50 observation for females.

The above plots shows the observed birthweight percentiles (plausible values) for gestational age with at least 50 observations for males and females separately.

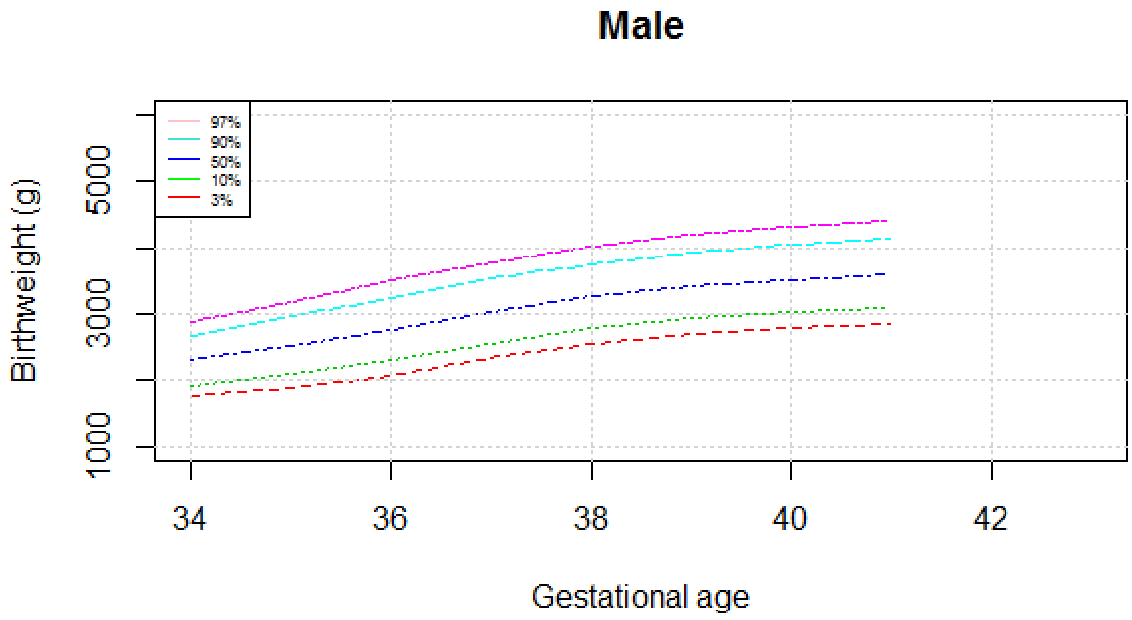

Figure 6: Plot 3 A for smoothed percentiles GAMLSS (plausible values) for males

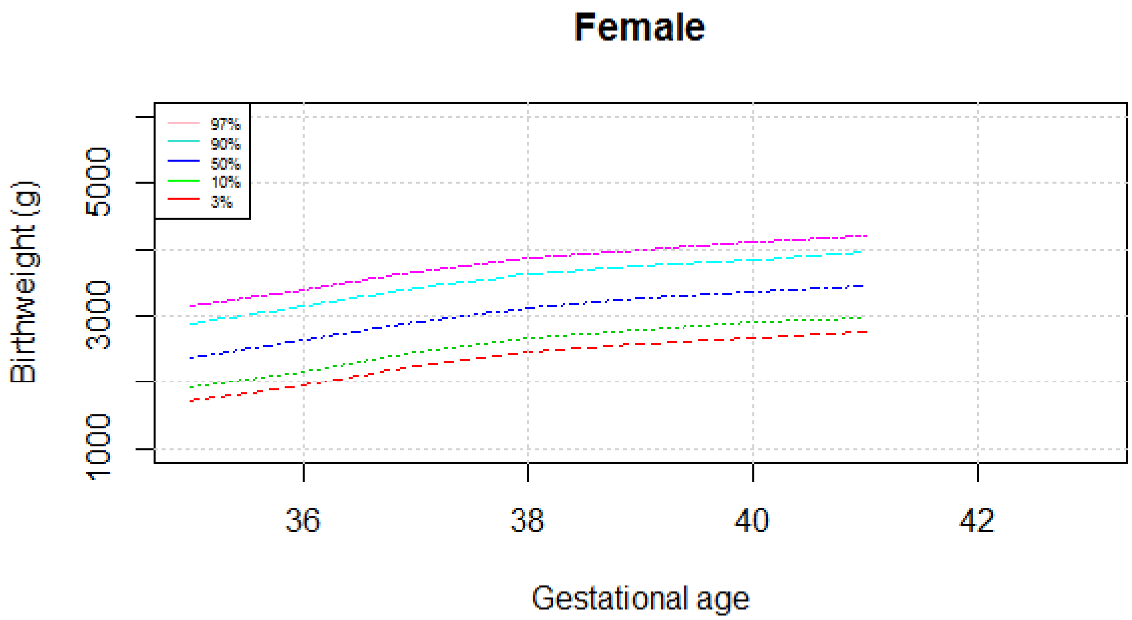

Figure 7: Plot 3 B for smoothed percentiles GAMLSS (plausible values) for females

The above plots shows the smoothed birthweight percentiles (plausible values) for gestational age with at least 50 observations for male and female using GAMLSS model separately. The lower limit for male was 34 while for female it was 35. However, the upper limit for both sex was 41.

CHAPTER 4: DISCUSSION

In this study, sex-specific birthweight percentiles chart and curves by gestational age were created for the first time using the GBR. Percentile charts included 1st, 3rd, 5th, 10th, 25th, 50th (median), 75th, 90th, 95th, 97th and 99th percentiles and mean and SD for male and female newborns at each completed gestational age after removing implausible values. Similarly, the curves included 3rd, 10th, 50th, 90th and 97th percentile for both sex. The percentile chart and curve provides the cut-off values for classifying babies as SGA, AGA or LGA.

4.1 Comparison of main findings with other studies

The sex-specific birthweight percentiles by gestational age, mean and SD of this study was compared with the WHO international standard for newborn weight and also with different published studies of other countries.

The mean birthweight for newborn based on the WHO international standard (INTERGROWTH-21st Project) (8) was 3300 g while for Georgia it was 3276 g. Some variations in the values for 10th and 90th percentiles were observed between WHO data and this data. For instance, for males at gestational age 36, the 10th and 90th percentiles values were higher for WHO by 15 g and 114 g, respectively compared to that of Georgia. However, at 39th week of gestation, the 10th and 90th percentiles values were higher for Georgia by 150 g and 110 g respectively.

The 10th percentile value for females for WHO was higher only at gestational age 35 while for other gestational ages, the values were higher for Georgia. The value for 90th percentile for female at 34th week of gestation was the same for both WHO and Georgia (2640 g). The

90th percentiles values for WHO were higher compared to Georgia only at gestational ages 36 and 42 while for all other gestational ages, the values were lower than that of Georgia.

Similarly, comparison with Australian birthweight chart (13) showed variations in terms of mean, SD and 10th and 90th percentiles. It was found that the mean birthweight, SD, and 10th and 90th percentiles were higher for Australia in all term (37-41) weeks and post-term (more than 41) weeks. For few preterm (less than 37) weeks, the values were higher for Georgia. However, it was noteworthy to find that the 10th percentile value of male at 38 week of gestational age was same for both countries i.e. 2800 g.

Comparing the data of this study with Norwegian birthweight percentile chart (35), the mean, SD, 10th and 90th percentiles of birthweight for both sex were higher in Norway compared to Georgia for term and post-term weeks. However, at preterm weeks, the values were higher for Georgia.

Similarly, comparing the mean birthweight of this study with the study from Finland (54) showed that for all term weeks the mean birthweight for Finland was higher in both male and female at all gestational age except for few early preterm.

Compared with the chart developed for Brazil (55), it was observed that between 34 to 41 weeks of gestational ages, the 10th percentiles values of males were higher for Brazil only at week 36. However, for females, from 36 to 41 weeks of gestational ages, the values were higher for Georgia. The 90th percentiles values for males were higher for Brazil compared to Georgia from 34 to 38 gestational ages. However, at 39th week of gestation the value was same i.e., 3900 g for both countries. For females, the values for 90th percentiles were higher for Brazil from 35 to 38 weeks of gestational ages. However, from 39 to 41 weeks of gestational ages, the 90th percentiles were higher for Georgia.

Comparing the percentile chart of this study with the percentile chart of Ukraine (56) also showed variations in estimates of 10th and 90th percentiles. For males, the 10th percentiles of birthweight for Ukraine were high only at gestational ages 36 and 41. For other gestational ages, the values were higher for Georgia. For females, the 10th percentiles were higher for Ukraine at gestational ages 35 and 36. From week 37 to 41, the percentiles estimates were higher for Georgia.

The 90th percentile value for male was found to be equal for both countries at 39 week of gestation i.e., 3900 g. However, at most of the gestational ages, the estimates were higher for Ukraine compared to Georgia. For females, the values for 90th percentiles were also higher for Ukraine at gestational ages 36 and 41.

Comparing the data with Turkey (14) showed that for both male and female, at most of the term weeks of gestation, the 10th percentiles values were higher for Georgia. Similarly, the 90th percentiles estimates were higher for Georgia at all term weeks of gestation except at 37 week. However for females, the estimates for Turkey were higher for all weeks of gestation from 35 to 41 weeks compared to Georgia.

4.1.1 Summary of main findings

The birthweight percentile charts of this study showed that at term weeks with increase in gestational age, birthweight also increases for both males and females. However, at post -term week it decreases. For both sex, maximum number of births occurred at 39 week of gestation.

This study also showed that, for all term (37-41) weeks of gestation, the cut-off values for both SGA and LGA were higher in males. However, there were variations in the 10th and 90th percentiles across preterm (less than 37) weeks and post- term (more than 41) weeks values for detecting SGA and LGA in both sex.

4.1.2 Summary of comparison of main findings with other studies

The variations in the 10th and 90th percentiles values among males and females across preterm week in this study were consistent with the findings of the Turkey study (14) where the 10th and 90th percentiles of females were found to be higher than for males. However, for Australia, Norway, Brazil, and Ukraine the mean birthweight, the 10th and 90th percentiles values were higher for males at all gestational ages. In all of the above compared studies, maximum number of births occurred at 40 week of gestational age, which contradicts with this study finding where maximum number of births occurred at 39 week of gestational age.

Comparing the cut-off values of this study with other study revealed that for all term and post term weeks of gestation, the 10th and 90th percentiles , mean and SD were higher for Norway, Australia and Finland compared to Georgia. The percentile values for Georgia was found to be higher than these countries only at preterm weeks.

On the contrary, for both sex, the 10th and 90th percentiles values of Georgia were higher at term and post-term weeks compared to WHO, and Brazil. These studies values were higher at preterm weeks compared to Georgia. Comparing the cut-off values with Ukraine showed that for both sex the 10th percentile values were higher for Ukraine at preterm weeks. However, on post-term weeks the 90th percentile values were higher for Ukraine compared to Georgia. Similarly, the 10th and 90th percentiles value of Georgia for both males and females were higher at most of the term and post-term weeks compared to Turkey.

It was also noteworthy to found that at the 39 week of gestation, the 90th percentile value of male was similar for Ukraine, Brazil and Georgia.

4.1.3 Methodological and other variations across studies

The variations in the 10th and 90th percentiles for detecting SGA and LGA among countries may be explained in part by differences in the methodological discrepancies, socioeconomic diversities, environmental and genetic factors as outlined in other studies. (27, 55, 57).

It should be noticed that the variation among these studies may be attributed to the methodological differences across studies. The Georgian charts differ from the other charts in that they are based on data recorded from different sources and had a larger sample size or was conducted on regional basis (13, 14, 35, 55, 56). This study was based on birth registry data but had a smaller sample size. Similarly, the differences in the measurement of predictor and outcome variables were observed across the studies. In Australia, the birthweight was recorded in nearest 5 g while in this study there was no uniformity in recoding the birthweight. It was found that the birthweight were either recorded in nearest 10 g or in many cases in nearest 100 g. For other studies the procedure for recording of birthweight was not described. Similarly, the assessment of gestational age was not uniformly based on ultrasound scan for this study and also for Brazil and Turkey. The study from Norway excluded the casearean section deliveries (35) while these deliveries were included in this study.

The variation in percentile values may be also explained by multiple factors that influence birthweight, such as smoking, low weight gain during pregnancy, low pre-pregnancy BMI or demographic changes by increasing numbers of multicultural families. Most of these factors were excluded in this study and also in WHO and Ukraine to construct standard chart, but in other studies these factors were not excluded as they had developed a reference chart.

The differences observed with other charts are partly due to methodological discrepancies, but a role of differences among populations, such as diet, environment, genetic and prevalence of risk factors, cannot be excluded.

4.2 GBR data quality

As this study represents the first analysis of the GBR data, one objective of this study was to perform quality control on the variables used. Over the past years, the number of birth registries have increased sharply and are being considered as an important source that provides many opportunities for meaningful analysis regarding maternal and perinatal health. To be useful, data in a registry must be of good quality. In practice, however, there are inherent challenges to obtain valid inferences from the data. In many registries, a high rate of missing data or inaccurately recording of the variables has often primarily lead to data quality problem (58-60) .

Missing data can be a challenge for any registry-based analysis by reducing the information yield of the study and in many cases, by introducing bias (60). One such challenge was found in this data as well.

In Visits, information about pregnant women were established before 12 weeks of gestational age when women in Georgia need to have registered in order to receive the allowance given by the government. Since, most women came for antenatal checkups more than once, there were 275,812 records in the file. After limiting the records to only one visit, there were 84,504 records remaining. In this case, if a pregnant woman had an abortion or ectopic pregnancy for the first pregnancy but again become pregnant and if her visit was recorded other than first visit for a new pregnancy then such women were also excluded. Also, after excluding for BMI (< 18.5 kg/m^2 or ≥ 30 kg/m^2) and for missing BMI, the number of records in the Visits was reduced to 39,352. This is because, more than 30% (30,666) records from the Visits had missing information about BMI. One reason why BMI is missing in most of the pregnant women is due to the time lag. There is on average close to 26 weeks between the first visit and the birth. When GBR started to register information in January 2016, BMI could not have been possibly registered for those who gave birth before June or July that year. Since, BMI should be reported at first visit and those women who were in their second or third trimester of pregnancy when GBR started, recording of their BMI was not possible This resulted in a lot of BMI missing. Also, many pregnant women lacked values on body height, weight or both at their first visit.

Many authors who have used birth registry data have mentioned the problem of missing BMI. In a country where the birth registry database has been established for many years and its quality control is considered, less than 20% of missing values for BMI was found. However, for other countries more than 30% of missing values for BMI was found to be recorded (59, 61).

Similarly, over or underestimation of both height and weight might have resulted in large number of women falling under excluding criteria for BMI (< 18.5 kg/m^2 or ≥ 30 kg/m^2) (62, 63).

Although GBR was established on January 1st, 2016, it was only made mandatory to register information about pregnancy and newborn from May 1st, 2016. During the preliminary analysis, it was found that most of the records until May 1st, 2016 had missing records on important variables such as birth weight, gestational age and sex. Similarly, some of the variables in the Pregnancies during that period were inaccurately recorded or not recorded.

Because of these reasons, all birth records before May 2nd, 2016 were excluded from the Newborns and Pregnancies.

Similarly, Pregnancies initially had 118,548 records and after exclusion, it was reduced to 66,296 records. It was assumed that Pregnancies contain information about the women outcome of pregnancy i.e delivery, abortion or ectopic pregnancy. However, after excluding for abortion and ectopic pregnancy, also the number did not match in these two data file. This might be either because Pregnancies also had information about those pregnant women who had been registered but the outcome had not yet occurred (delivery, abortion or ectopic pregnancy). Another reason could be that the information about the newborn from remaining pregnant women had not been registered in the newborn data file.

Likewise, a difference in number of births before May 2nd, 2016 among Newborns (n=16,668) and Pregnancies (n=16,132) was observed. This was because in Pregnancies the births before May 2nd, 2016 were excluded only after excluding the records for non-Georgian nationality, premature birth with congenital malformation, smoking during pregnancy, smoking and alcohol use. So, it can be speculated that the less number of births before May 2nd, 2016 in Pregnancies was because it got excluded while excluding for the above mentioned cases.

Similarly, in Newborns, there were 58,221 records of newborns. However, the records reduced to 36,889. Apart from the obvious reason, that the number reduced because of being under the exclusion criteria, was the exclusion of 16,668 births before May 2nd 2016.

Likewise, when these three data files were merged, only 14,230 records of newborn were left for final analysis. One of the reason for this reduction was that when the Newborns were merged with Pregnancies file by Pregnancy ID number, the record of newborns whose mother were smoking during pregnancy, consuming alcohol or having psychotropic drugs eventually got excluded as those mothers were excluded from the Pregnancies. Similarly, the newborn born from mother less than 18 years or more than 35 years of age were also excluded. Likewise, merging with Visits also reduced the number as most of the mothers were excluded because of missing BMI, or BMI (< 18.5 kg/m^2 or ≥ 30 kg/m^2). In addition, another reason was the information about the mothers of most of the newborns were missing on both Pregnancies and Visits.

The problem of missing data is inevitable in any registry-based database. As the challenge of missing data prevail in database which had been established for several years (58) so it is natural to have the similar problem in the new GBR as well and even at a larger scale.

Similarly, it was found that there was variation in the recording of the outcome variable (birthweight). Although, it was considered that the birthweight was recorded to the nearest 10 g but it was found that the birthweight were either recorded to nearest 10 g or in many cases to the nearest 100 g.

Hence, in this study, missing data and inappropriate entry of data was found to be a major problem in the GBR.

4.3 Strength and weakness of the study

This study has both strengths and weaknesses regarding the methodological aspect that was developed, and applied for constructing birthweight percentile chart and this should be considered while interpreting the result of this study. The strengths and weaknesses of the study are described in accordance to the validity of the study.

4.3.1 Validity of the study

Validity tell us in what extent we measure the phenomenon we basically want to measure. Validity is divided in internal validity, which is related to the fact that we actually measure what we want to measure and external validity, which refers to the generalization from the study population into other population. High reproducibility is a prerequisite for high validity (64).

4.3.1.1 Internal validity

Choosing an appropriate sample representative of the source population is important for the internal validity. Since the study population was retrieved from the GBR which include information about the mother and infant from the entire Georgia, so the sample from this study can be considered as a reference population.

Obtaining accurate assessment of the primary outcome (birthweight) by standardisation of equipment and measurement method is important in this kind of study. However, one of the major weakness of this study is the unreliability in the measurement of both predictor and outcome variable. In this study, it was found that the birthweight was recorded either to nearest 10 g or in many cases, it was recorded to nearest 100 g. This result in non uniformity in the recording of birthweight and introduce bias in the estimate of birthweight.

Similarly, another important concern is the mechanism by which accurate gestational age is assessed. The accurate determination of the gestational age in such studies is an open challenge for all charts and the practical adequacy of different measures is a stirring investigation problem. In GBR, the weeks of gestation was assessed according to the LMP or ultrasound estimate. Estimation of gestational age from LMP may lead to error as it can be confounded by bleeding in early pregnancy or pregnant women might not exactly mention the same date of last menstrual period, introducing recall bias to those dates. Also, it can be influenced by the irregularity of the menses, individual variation of the cycle length, and oral contraceptive use. In such cases, there might have been dissonance between birth weight in given gestational ages.

Selection bias, information bias, and confounding are other factors that can threaten internal validity. An important issue in constructing standard birthweight percentile charts is which cases to include in the analysis and which to exclude. In order to avoid the methodological constraints of clinical use of a percentile chart, different literature have argued that a set up exclusion criteria can be defined, concerning mothers. Highly restrictive criteria aiming to exclude all neonates who are exposed to any known risk factor primarily define the characteristics of infants who fully expressed their growth potential. Such characteristics establish a model to which a neonate should conform, and a basis for a prescriptive standard or norm that indicates how growth should be (3, 8, 65).

The advantage of a standard chart is that they are prescriptive i.e, they describe optimum size in newborn infants without any congenital abnormalities whereas reference chart describe only newborn infant size at a given place and time. The standard are universal and does not depend on time. It is not intended to be representative of a given population or a region at a given time, as opposed to that of reference. Moreover, they can be used to assess the size of the newborn infants, regardless of ethnicity, area, socio-economic status or health care provision. Different studies have also highlighted the advantage of use of standard charts for estimating birthweight percentile (3, 8, 65). Keeping this in consideration, in this study, a low-risk population was selected based on WHO standard criteria. This reduced the chance of selection bias and confounding in this study and is also one of the major strength of this study.

In addition, to reduce any inadvertent errors in the data set, outliers at each gestational age were removed using the Tukey's modified method (66). Although, in Tukey's exploratory analysis, the IQR is multiplied by 1.5 before subtracting it with 1st quartile or adding with lower 3rd quartile (50). There is no any statistically driven reason for this. So, it has been argued that one can use either 2 x IQR or even 3 x IQR to identify the extreme outliers .Hence, in this method 2 x IQR was used as outlined in other studies that developed birthweight percentile chart which is another strength of this study (13, 66-68).

On the other hand, the information about smoking, alcohol consumption are more subjected to underreporting leading to information bias. In addition, the problem of missing data in GBR is also one of the weakness of this study.

4.3.1.2 External validity

The variation observed across percentile estimate for diagnosis of SGA and LGA among different countries that was found while comparing the findings of this study with other countries showed that the findings of this study could not be generalized to other countries. It has often been argued that because of the observed differences in charts, each country should have its specific birthweight chart and caution should be used against the extension of any national chart to other countries (3, 27). Hence, the birth weight percentile chart developed from this study does not seem to be applicable to other countries.

4.4 Limitations of the study

The relatively low number of births at early gestational age may make the percentile estimates for these infants less accurate. Similarly, inability to develop birthweight curve by gestational age for gestational age less than 34 for males and less than 35 for females and more than 41 for both is another limitation of this study. From the available literature, it is known that a large number of mothers had to be enrolled to enable such assessment (3, 8, 68). Although, initially we had large numbers of newborn, but due to missing data problem the number was much reduced. However, since the vast majority of births occur between 37 and 41 weeks, the chart that has been developed would still be useful as an indicator for these babies (14).

Likewise, in this study the cases for caesarean mode of delivery was not excluded. Georgia has 41% cesarean sections and most of them are planned cesarean section. It was found that that most of the babies were delivered before 40 week of gestation, often in 38 week. This planned cesarean section deliver in Georgia can therefore introduces a bias in this study. Similarly, no separate charts for neonates from primiparous and multiparous mothers was constructed. It is well known that birth weights of infants of multiparous mothers are heavier than those of primiparous mothers by 20-50 g (14).

However, it should be considered that the exclusion criteria and the methods used for this study was solely based upon the WHO study where no separate analysis was done according to birth order or the caesarean delivery were excluded. In addition, the birth weight by gestational age chart developed in this study is the first standard chart for Georgia and the methodological aspect used in this study can be used to construct the standard birthweight percentile chart with larger number of observation.

4.5 Implications of the study

Birthweight percentile for gestational age charts of Georgia may be used as a reference tool for providing relevant information to clinicians regarding which neonates may be at higher risk of neonatal morbidity and subsequent mortality or developmental delay.

Similarly, the data quality problem found in the variables can be used as a reference for conducting data quality assessment of GBR.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

Sex specific standard birth weight percentile chart and curve has been presented in this study as the first analysis from the newly established GBR database. While interpreting the result of this study it should be considered that statistics based cut-off points were used to define small or large for gestational age babies. The 10th and 90th percentiles for males were mostly higher at all weeks except for few preterm weeks. Similarly, comparing the 10th and 90th percentiles of this study with other studies showed variation. The 10th and 90th percentiles of Georgia were found to be higher at preterm weeks compared to that of Australia and Norway. However, the 10th and 90th percentiles of Georgia were found to be higher at post-tem weeks compared to WHO, Brazil, Ukraine and Turkey.

5.2 Recommendations

The recommendations that can be drawn from the findings of this study are presented below:

5.2.1 GBR data quality

Considerable shortcomings regarding the registration of data have been revealed in this study leading to many necessary improvements in future registration.

5.2.2 Future studies

i. It is recommended to construct the standard birthweight percentile chart and curve using the large number of newborn after improving the GBR data quality.

ii. Similarly, the future studies on the prevalence of SGA and LGA babies needs to be conducted based on the standard birthweight percentile chart.

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