Impact of maternal and antenatal factors on small-for-gestational-age outcome among infants in Anuradhapura district, Sri Lanka: A retrospective case-control study.

Master thesis, Programme in Medicine 2017, University of Gothenburg

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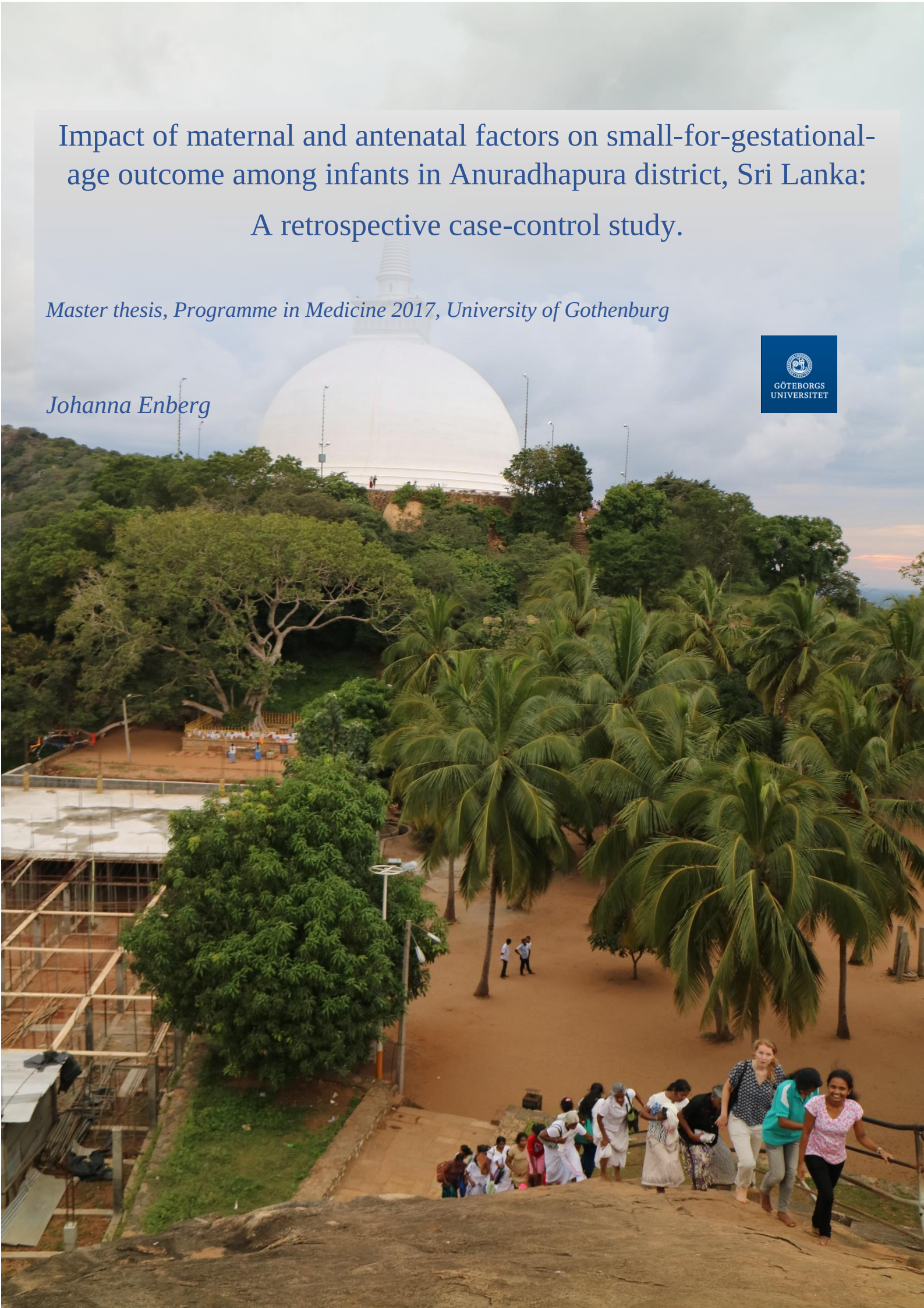

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Abstract

Background: Intrauterine growth restriction (IUGR) is a common diagnosis in obstetrics and carries an increased risk of neonatal morbidity and mortality, especially in developing countries. Because valid assessment of IUGR often is unavailable in low-resource settings, small-for-gestational-age (SGA) has been used as a proxy for IUGR. Several risk factors for SGA/IUGR outcome are recognized. However, the important risk factors in a specific area depend on the prevalence and pathology within the population of interest.

Aims: Primary aim was to identify risk factors for SGA infants in Anuradhapura district, Sri Lanka. Secondary aim was to investigate if these infants have an increased risk of neonatal adverse outcomes and whether SGA outcome is related to a specific mode of delivery.

Methods: The present study was a retrospective case-control study carried out in two demographically different areas in Anuradhapura district. SGA infants were identified by a population-based "weight-for-gestational-age" chart. The study sample was matched with two controls (2 n=272) for each case (n=136). Maternal, antenatal and postnatal information were collected from pregnancy records during the data collection period and later analysed.

Results: Logistic regression analysis identified four significant factors; maternal pre-pregnancy weight <50 kg (OR 2.18), BMI <18.5 (OR 2.24) respectively ≥ 25 (OR 1.95), maternal height ≤150 cm (OR 1.98) and previous low birth weight (LBW) child (OR 3.87).

Conclusion: The significant maternal factors observed in this study may be a result of physiological or/and pathological influences and depending on which, modifiable or not. Further studies regarding this matter and studies including socioeconomic confounders are needed to determine the underlying cause of SGA infants in Anuradhapura district.

Key words: *Risk factors, small for gestational age, intrauterine growth restriction, case-control study, Sri Lanka.*

Abbreviations

AGA	appropriate for gestational age
CS	caesarean section
EDD	expected date of delivery
GNI	gross national income
IUGR	intrauterine growth restriction
LBW	low birth weight
LGA	large for gestational age
LMP	last menstrual period
MOH	medical officer of health
NCP	northern central province
PHM	public health midwife
POA	period of amenorrhea
SFH	symphysis-fundal height
SGA	small for gestational age
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

Definitions

Anaemia in pregnancy - The World Health Organization (WHO) presents a haemoglobin (Hb) cut-off level of 11 g/dl (110g/L) or less in pregnant women. In this study, anaemia in first and second trimester is taken in consideration. Primary cause of anaemia during third trimester is plasma volume expansion and lacks the same clinical significance.

Gestational hypertension - Blood pressure > 140/90 mm Hg after 20 weeks of pregnancy in a previously normotensive woman. Two measurements at separate occasions are required.

Pre-eclampsia – A pregnancy induced high blood pressure > 140/90 mm Hg after 20 gestational weeks, together with proteinuria ≥ 0.3 g protein/day or a urine dipstick test of ≥ 2 + (1).

Small for gestational age (SGA) – Foetal weight below the 10^{th} percentile.

Intrauterine growth restriction (IUGR) – Atypical reduced growth of the foetus indicating underlying pathological process.

Large for gestational age (LGA) – Foetal weight above the 90^{th} percentile.

Low Birth Weight (LBW) – A birth weight less than 2,500 grams.

Premature birth – Birth before gestational week 37 + 0.

Symphysis-fundal height measurement – A method used to screen for intrauterine growth restriction. The distance from the lowest part (pubic symphysis) to the highest part (fundus) of the uterus is measured (2).

Neonatal mortality – Death during the first 28 days of life.

Stillbirth - Delivery of a baby at or after 28 weeks of gestation without any signs of life. This definition is recommended by WHO for international comparison.

Introduction

General introduction

Low birth weight (LBW) is defined by WHO as "weight at birth of less than 2,500 grams (5.5 pounds)" (3 , p. 1). This group contributes with 60 - 70 per cent of all neonatal deaths globally. Overall, it is estimated that of all births worldwide 15.5 per cent are LBW and this represents over 20 million births a year (3). More than 95 per cent of these babies are born in low-and middle-income countries (4). Despite the high percentage of LBW, reliable data in this field is limited in less developed countries. In Sri Lanka, as a low-middle-income country, the LBW birth rate was 16.7 per cent in 2013 (5). According to the hospital statistics, out of 11,560 live births, 1966 births (17%) were classified as LBW in the year 2011 in Anuradhapura district (6). Any population with a LBW incidence above seven per cent is at risk of having a high perinatal mortality, which could be counteracted by analysing the roots of the LBW problem (7).

LBW is a complex syndrome and can be divided into two main components; preterm birth and small-for-gestational-age (SGA) (4). The latter sometimes due to intrauterine growth restriction (IUGR). IUGR is a clinical term and usually approximated by the statistical term SGA which is defined as birth weight below the tenth percentile, or two standard deviations from the mean, at a particular gestational week (8).

Prematurity and SGA have different causes and risks of mortality, morbidity, impaired growth and non-communicable diseases later in life (9). Numerous studies have focused on risk factors of LBW/prematurity and not the subgroup SGA. In most low-and middle-income countries, SGA contributes to the larger portion of LBW babies (10). The lack of division of the concept LBW may be a reason of incorrect focus in terms of interventions aimed to reduce country-/region-specific risk factors. Thus, to identify the specific risk factors for SGA is of great importance, especially in low-and middle-income countries where the burden of SGA generally is higher than that of prematurity (11).

Birth weight related to gestational age has long been recognized to be one of the most powerful predictors of perinatal outcome (12). It is important to use the appropriate "weight-for-gestational-age" chart to calculate the correct prevalence of SGA. The use of inappropriate charts may lead to misdiagnosis and misjudgement of risk factor and thereby potential unnecessary interventions. At the time of writing, Sri Lanka has not developed a national population-based birth weight reference chart of their own. There have been attempts, but the charts created are limited and not completed to be used at a national level. However, the prevalence of SGA in Colombo district has been calculated to 19 per cent by using one of these pilot study charts (7). Gianpaolo Maso et al. compared European and Bangladeshi growth charts on a Sri Lankan population and the prevalence of SGA differed between charts by 39 per cent (13). This study demonstrates the huge margin of error using an unfitting chart. Despite the difficulty finding the accurate chart, Shanumugaraja Y et al. performed a prospective study to validate the foetal/birthweight reference derived from WHO data and showed that WHO's global reference chart adapted to Sri Lankan population centiles can be efficiently used (14).

The small baby

There are three main reasons for a small foetus. Firstly, an important and often forgotten cause of a SGA foetus is incorrect calculation of gestational age, hence, these foetuses are not truly SGA. Important sources of error are maternal recall bias of last menstrual period (LMP), absence of ultrasound accessibility and availability, and usage of inappropriate weight-for-gestational -age curves. Despite the lack of official data on this matter, incorrect estimation of age ought to be more widespread in countries with limited resources.

The two remaining reasons for SGA are heredity and IUGR, which act differently on foetal growth. Foetal growth, the increase in weight and size with increasing gestational age, is

primarily dependent on the genetic growth potential, the supply of nutrients and oxygen and on various growth factors.

Symmetrical or asymmetrical babies

Infants with a birth weight below the tenth percentile are a heterogenous group and their long-term prognosis vary in a wide range, from severe growth restriction to normal growth and development (7). The SGA baby can either be symmetrically or asymmetrically small, and the two types cause diverse severity in outcome. A foetus affected by growth inhibition in an early stage of the pregnancy becomes symmetrically small. The growth of vital organs, such as the brain, is reduced in the same way as other organs and the risk of mental retardation is consequently more impending (15). This type of growth restriction can devolve upon early intrauterine infections, substance abuse or chromosomal aberration. Another reason to small, proportionate babies are genetic influence of the parents, but these are accordingly not growth restricted (7).

The other category of IUGR babies is the ones whose weight is abnormally low in relation to their length, termed asymmetrical growth restriction. These babies usually have normal length and head circumference for full-term infants. This category represents the largest proportion in parts of the world with high prevalence of maternal malnutrition. Asymmetrical restriction is also encountered in multiple pregnancies, pre-eclampsia and other clinical conditions featuring an inadequate placental function. Historically, the prognosis has been considered better for the asymmetrical than for the symmetrical IUGR babies. However, these findings have more recently been challenged and studies have shown evidence of morbidity despite brain sparing in asymmetrical IUGR foetuses (16).

Etiology of IUGR

The most crucial purpose to find SGA infants is intrauterine growth restriction. According to Deepak Sharma et al., IUGR is defined as “the rate of fetal growth that is below normal in light

of the growth potential of a specific infant as per the race and gender of the fetus" (17, p. 1). IUGR is a clinical definition and applies to infants with features of malnutrition and in-utero growth retardation, irrespective of their birth weight percentile. The condition refers to a state when the predetermined genetic potential is not reached because of some pathologic insult (18). This insult can be categorized as placental, maternal, foetal or genetic, and are in some cases multifactorial.

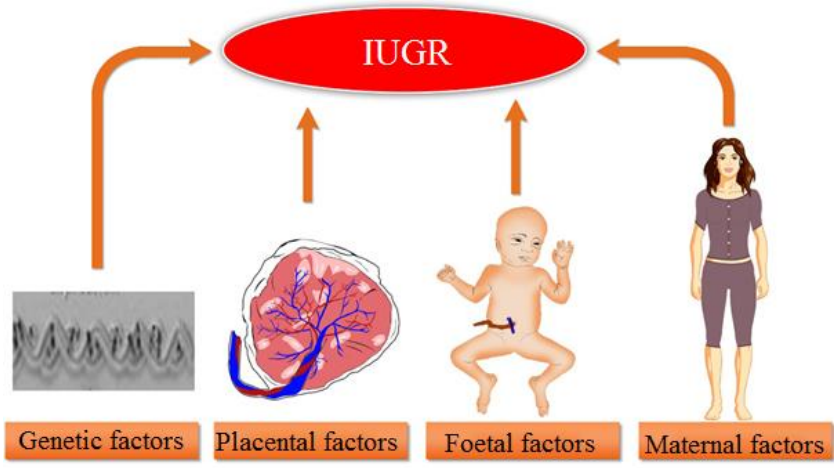

Figure 1. Main groups of risk factors of IUGR. Image used with permission from copyright owner Dr Deepak Sharma MD (Paedia), DNB Neonatology, NIMS Medical Collage, Jaipur.

The most common insult in high-income countries is placental insufficiency, where the transport of nutrients and oxygen to the foetus decreases (19). The changes in placental function can be primary, without identified pathology, or conditional influence of intercurrent maternal diseases or pregnancy complications. Sometimes infarcts, haemorrhage and even abruption are seen in the placenta explaining an inferior function, but more often no explanation can be found. If this process is very severe the result can be a stillbirth (17). Individual-level maternal risk factors continue to play a significant role in explaining LBW and IUGR outcomes. The nutritional state of the mother before and during pregnancy is a key factor and maternal malnutrition is the major cause of IUGR in low- and middle-income countries (20). Iron deficiency anaemia during pregnancy has in some studies been presented to correlate to IUGR

(21). Other identified risk factors are maternal diseases, for instance diabetes and chronic hypertension, and pregnancy complications such as gestational hypertension and pre-eclampsia (19, 22). Among the foetal causes to IUGR you find the intrauterine infections rubella, toxoplasmosis, cytomegalovirus infections, malaria and syphilis. These can cause permanent growth inhibition (15). Moreover, structural abnormalities of organ systems may be linked to IUGR (23). The genetic aberrations chromosomal trisomy 13, 18, 21 and different rare genetic syndromes are only responsible for IUGR in few cases (17).

Table 1. List of important risk factors established to cause IUGR. Adapted from Bryan and Hindmarsh (24) and Karel Marsal et al (23).

Maternal social conditions	***Abnormalities of the placenta***
Malnutrition	Reduced blood flow
Low pregnancy BMI	Reduced area for exchange
Low maternal weight gain	Partial abruption
Delivery at age <16 or >35 y	Hematomas
Low socioeconomic status	Infarcts
Drug use: smoking, alcohol, illicit drugs	***Foetal problems***
Medical complications	Multiple births
Pre-eclampsia	Malformation
Chronic hypertension	Chromosomal abnormalities
Gestational hypertension	Inborn errors of metabolism
Antepartum haemorrhage	Intrauterine infections
Severe chronic disease	***Environmental problems***
Severe chronic infections	High altitude
Systemic lupus erythematosus	Toxic substances
Antiphospholipid syndrome	
Anaemia	
Malignancy	
Abnormalities of the uterus	

Most IUGR infants are born with a birth weight below the lower normal range, and accordingly become SGA infants. Nevertheless, among children born with a normal birth weight, appropriate for gestational age (AGA), some are growth restricted because of pathological insults which prevent them from reaching their genetically programmed weight. This group of

AGA infants is hard to identify during pregnancy but even though growth restriction can influence the foetus negatively, relatively few babies fall into this group and the clinical relevance therefore becomes negligible. It is important to remember that not all SGA are pathologically small. However, since IUGR is a critical pregnancy complication, the diagnosis of SGA should be investigated and confirmed in order to detect threatening foetal hypoxia and prevent intrauterine death, which is the worst possible outcome for a growth stunted foetus (23).

Epidemiology

The incidence of IUGR is appraised to be six times higher in low- and middle-income countries when compared to high-income countries, although it is difficult to approximate the exact number. In figure 2 the estimated national prevalence of SGA is visualised (11). A majority of SGA/IUGR infants are found in Asia, which accounts for approximately 75 per cent of all affected infants. This is followed by the African and Latin American continents. In the Asian continent, the highest incidences of IUGR are seen in decreasing order in the following countries: Bangladesh, India, Pakistan, Sri Lanka, Cambodia, Vietnam and the Philippines, Indonesia and Malaysia, Thailand, and the People's Republic of China (17).

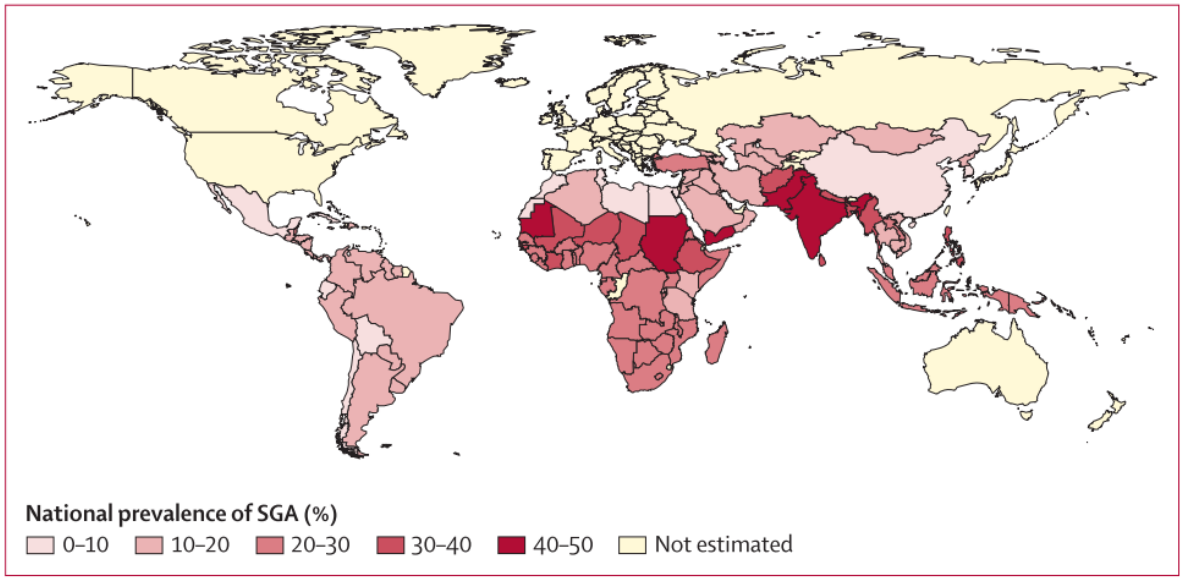

Figure 2. Estimated national prevalence of SGA births in low-income and middle-income countries in 2010. Figure published in The Lancet, the world's leading medical journal of global health (11).

Diagnosis and treatment

IUGR is not generally associated with any clinical signs during pregnancy and therefore it is essential to actively search for foetuses that deviate from the normal growth curve. Theoretically, aberration in intrauterine growth could be discovered during pregnancy through ultrasound and Doppler screening. With this equipment SGA foetus with IUGR can be detected by biometric measurements, where abnormal umbilical artery blood flow is one of the findings (19). The golden standard for screening and diagnosis of IUGR in high-resource settings is thus foetal ultrasonography. Repeated ultrasound is also used for surveillance of SGA foetuses. Unfortunately, frequent ultrasound examination is inappropriate and practically impossible in a country with limited resources (9). Nevertheless, SGA is a commonly accepted proxy measure of IUGR and health care workers should search for features indicating risk for SGA infants. One established way to do this is to measure the symphysis-fundus height (SFH). One abnormal SFH-measure value has a low predictive value, but due to the method's simplicity and low cost measuring can be repeated. By serial measurements, 55-60 per cent of SGA foetus can be recognized (23). However, there are studies showing that SFH-determination only detects a small fraction of all SGA infants in low-risk population (25).

Another way to identify pregnant women with risk of growth restricted foetuses is to pay attention to risk factors. It can be anamnestic information, predisposing diseases or complications during current pregnancy (23). Lindquist and Molin manifested in a large retrospective single-centre trial that SGA detected during pregnancy have significant better outcome and prognosis than the ones first diagnosed after the delivery (26).

Currently there is no specific treatment for IUGR. The initial management comprises elimination of recognized sources of impaired growth and encouragement of a healthy intrauterine environment. Measures such as improved nutrition, smoking cessation and control of maternal illnesses are important. When present, treatment of infection diseases is mandatory.

For the time being, the primary intervention consists of establishing structured antenatal surveillance programs. It is of immense importance to deliver the child before severe hypoxia has been established in order to prevent permanent brain damage or stillbirth (27).

Short- and long-term consequences

The problems of being small at birth was already described in 1988 by Arja Tenovuo et al. It starts at first breath with hypoxemia, hypoglycaemia, polycythaemia and difficulties maintaining normal body temperature. These are only some of the obstacles SGA babies have to face to a higher extent compared to babies with normal birth weight (28). Some studies describe more adverse outcomes of small infants born with a gestational weight below the 5th and 3rd percentile (29). The most severe outcome is nevertheless a stillbirth. A systematic review and meta-analysis describes that the risk factors placental abruption and SGA have the greatest population-attributable risk of stillbirth (23% respectively 15%) (30).

Lately more research has focused on long-term consequences of being small at birth. Follow-up studies on growth restricted infants state that SGA children remain small for their age into school age. Stunting during this period is related to poor outcomes in health, cognitive development, and educational and economic attainment later in life (31). These individuals have somewhat lower IQ, neurological abnormalities and changes in cardiovascular function compared to controls born AGA (23). When it comes to cardiovascular diseases, people born SGA have an increased incidence of metabolic syndrome, coronary artery disease and stroke as adults (32). The increased morbidity of adulthood creates severe and unnecessary suffering, especially at an individual level, but likewise puts strain on the resources of the society.

Global health goals

Low birth weight has been established as an important public health indicator. Globally, LBW is a good summary measure of a complex public health problem including long-term maternal

malnutrition, bad health, hard work and poor pregnancy health care (3). Even though LBW is ordinarily used as an indicator of child health, LBW-index has its limitations due to discounting gestational age. This makes the index a heterogenous entity that includes both infants who are SGA and those who are preterm (19). Assessing gestational age cannot be overemphasized as it helps to anticipate complications the neonate might have to face. Differentiation of infants born SGA respectively preterm, rather than with merely low birth weight, may guide prevention and management strategies to speed progress towards the goal to reduce global child mortality (9).

WHO's global targets for 2025

Member states of WHO endorsed in 2012 six global targets to improve the nutrition in mothers, children and infants by the year 2025. One of the targets was a 30 per cent reduction in LBW rate. This would in numbers correspond to a reduction from approximately 20 million to 14 million infants born with a birth weight below 2,500 grams. A number of actions have been listed to prevent LBW: peri-conceptional daily folic acid supplementation, foetal growth monitoring and neonatal size evaluation at all levels of care, decrease in non-medically indicated caesarean deliveries and antenatal balanced protein–energy supplementation to selected women. In context to these actions, WHO declares that the goal will not be achieved if not pregnancy care is combined with appropriate neonatal medical and nutritional care for preterm respectively SGA (33).

Sri Lanka

The national situation

Sri Lanka is an island state in South Asia, situated south-east of India, with a population of 20.77 million people (2015). According to The Wold Bank Group, Sri Lanka is rated as a low-middle-income country and the gross national income (GNI) is 3.8 USD per capita (2015). Poverty is major problem, but despite this people live longer than in many other countries with

similar GNI. The life expectancy at birth is one of the highest in South Asia and was 74.8 years in 2014 (34). Sri Lanka, as a low-middle-income country, has done huge progress when it comes to public health actions. Development can be observed in terms of health indicators such as rise in average life expectancy and lower child mortality. At present, 99 per cent of all childbirths take place in medical institutions and almost 99 per cent of all deliveries receives trained assistance (35). Despite the large investments within the health sector, the nutritional status of children has not significantly improved over the years. Child undernourishment is especially pronounced among the population in the northern and eastern parts and UNICEF declares Anuradhapura as one of the districts with the highest prevalence (36). Christian et al. provides strong evidence of a positive association between malnutrition and SGA in an extensive meta-analysis of 19 longitudinal birth cohorts (37). Furthermore, the local researcher Dr Ruwan Pathirana state that the stagnation of LBW rates in Sri Lanka is explained by an increase rate of SGA babies while the rate of premature babies has decreased over the last decade (38).

Maternal and child health care system

Health units of Sri Lanka have a defined geographical area. The units correspond to the administrative divisions of the country and each area is managed by a Medical Officer of Health (MOH). This person is supported by a team of different public health personnel. One personnel category is the Public Health Midwives (PHM) and one MOH is supported by 20-25 PHMs.

The smallest working unit in the government health system is the Public Health Midwife area (PHM area), which comprise several villages consisting 2,000-4,000 people. The PHM provides domiciliary maternal and child health care service and is in this way the “front line” health worker. The work is accomplished by systematic home visits during antepartum and postpartum. To routine and plan the daily visits the PHM use a system of record keeping. The pregnancy record is one of these records and it contains vital information about the health state

of the mother during antepartum, information about the intrapartum period as well as postpartum period. Medical officers have the possibility to document in the pregnancy record during mother's hospital visits (35).

Medical relevance

The morbidity and mortality of SGA infants can be reduced if maternal risk factors are detected in an early stage and managed by simple methods. Thus, it is necessary to identify current risk factors responsible for SGA in a specific area as IUGR depends on the prevalence of risk factors and pathology within the population. The risk factor profile among women in Anuradhapura district has not been previously investigated. The findings of this study could contribute to understanding and help to distinguish were to direct interventions of maternal care before and during pregnancy. Results could be useful to set up a more individual care plan for the mother regarding to her risk profile. The study can also contribute to current knowledge about low birth weight, and more specific, small for gestational age.

Aim

The primary aim of this study was to identify significant maternal and antenatal factors that correlate with birth of SGA infants in Anuradhapura district, Sri Lanka. The second aim was to investigate whether SGA outcome correlate with increased risk of adverse outcomes, such as birth or postpartum complications and neonatal deaths, but also to investigate if SGA is associated to a specific mode of delivery.

Material and methods

Settings and study population

A retrospective case-control comparative study was achieved and the data collection was done during a six-week period in Sri Lanka. Data were taken from pregnancy records from the years 2014-2017 in 13 PHM areas. The records were stored in PHM offices, which happened to be either a clinic or more often the PHMs home. Data was collected from two demographically different MOH areas; the more rural Mihintale area and the urban area Nuwaragam Palatha.

Cases were identified as infants with a birth weight below the tenth percentile. All SGA children with mothers resident in the two MOH areas during time of birth were eligible for inclusion. Controls had a birth weight between the 10^{th} and 90^{th} percentile and thereby AGA. Thus, infants born large for gestational age (LGA) were excluded in this study. Exclusion of multiple pregnancies was also done as the risk of low birth weight are impending. Births after 43 weeks of gestation were excluded. Because of no registrations of birth weight of stillborn babies, these could not be included in the study.

The final sample size was calculated to *n*=136 cases and 2 *n*= 272 controls. Two controls were matched for each case, assembled as a set. Four groups were used for matching; extremely preterm (< 30+0 weeks), preterm (≥ 30- 36+6), term (≥ 37- 41+6) and postterm (≥42+0 weeks). To optimize the matching, same gestational week of birth of case and controls was preferable

chosen if possible. All matched sets except three came from the same PHM area and the remaining three were from the same MOH area.

As a first step, all records from a PHM office were screened for SGA by examination of the birth weight. Possible case-subjects were identified as infants with a birth weight lesser than 2938 grams. This specific weight equals the heaviest infant born SGA in week 43. To decide if an infant was SGA or not, the second step was to assess the gestational age. Below is an explanation how this assessment was carried out.

Study instruments needed to determine category of infant

*Gestational age at birth***.** At the first antenatal visit, assessment of gestational age was performed by calculating the number of completed weeks since the first day of the mothers LMP. Determination of gestational age from an early ultrasonic measurement (<20 weeks) is the golden standard and was used if registered. To calculate the gestational week of birth, the expected date of delivery (EDD) was used. The due date is considered 280 days after the start of LMP, known as Naegele's rule. The number of days between the EDD and the actual date of birth was reckoned. The gestational age at birth was registered in whole weeks. If the age was calculated to 38+3 it meant that 38 weeks of gestation had been fulfilled.

Birth weight. The weight-chart reference extended from gestational week 24-41. To avoid exclusion of infants born week 42 and 43, an extrapolation was made in collaboration with Dr Håkan Lilja, Sahlgrenska University.

Weight-for-gestational-age chart. The population-based weight chart used in this study is based on a computer program. This program is created on foetal weight equation proposed by Hadlock et al. (39) and further technical details is described in the journal article of Mikolajczk et al. (40). The mean birth weight (SD) at 40 weeks of gestation was determined to 3140 grams (432g), in accordance to a previous study carried out on a Sri Lanka population (14).

Table 2. WHO's global reference birth weight-chart based on Sri Lankan mean birth weight (SD) at 40 weeks of gestation; 3140 grams (432g), used to find cases and controls.

Weight percentiles for the local population											
Gestational age	Percentile										
	99th	97th	95th	90th	75th	mean	25th	10th	5th	3rd	1st
24	782	750	733	707	663	615	567	523	497	480	448
25	913	876	856	825	775	718	662	611	580	561	523
26	1058	1015	992	957	898	833	767	708	673	650	607
27	1219	1169	1142	1102	1034	959	883	815	775	748	699
28	1393	1336	1306	1259	1182	1096	1010	932	886	855	799
29	1581	1516	1482	1430	1342	1244	1146	1058	1005	971	906
30	1782	1709	1671	1611	1512	1402	1291	1192	1133	1094	1022
31	1994	1913	1869	1803	1692	1569	1445	1334	1268	1225	1143
32	2216	2125	2077	2004	1880	1743	1606	1483	1409	1361	1270
33	2445	2345	2292	2211	2074	1923	1772	1636	1554	1502	1402
34	2679	2569	2511	2422	2273	2107	1941	1792	1703	1645	1536
35	2914	2795	2732	2635	2472	2292	2112	1950	1853	1790	1671
36	3147	3019	2951	2846	2671	2476	2281	2106	2001	1933	1804
37	3376	3238	3165	3052	2864	2656	2447	2259	2146	2073	1935
38	3595	3448	3370	3251	3051	2828	2606	2406	2286	2208	2061
39	3802	3646	3564	3438	3226	2991	2756	2544	2417	2335	2180
40	3992	3829	3742	3609	3387	3140	2893	2671	2538	2452	2289
41	4162	3992	3902	3763	3531	3274	3017	2785	2646	2556	2386

The third step, when possessing the infant's gestational age and birth weight, was to apply WHO's birth weight chart to identify a possible case. A weight below the tenth percentile for the specific gestational week was defined as SGA. The same three-steps procedure was done to recognize controls. The selected controls were the two matched, AGA babies born closest before respectively after the case-subject within maximum one year. A one-year span limit was selected with the intention of diminishing social and environmental changes within the PHM area.

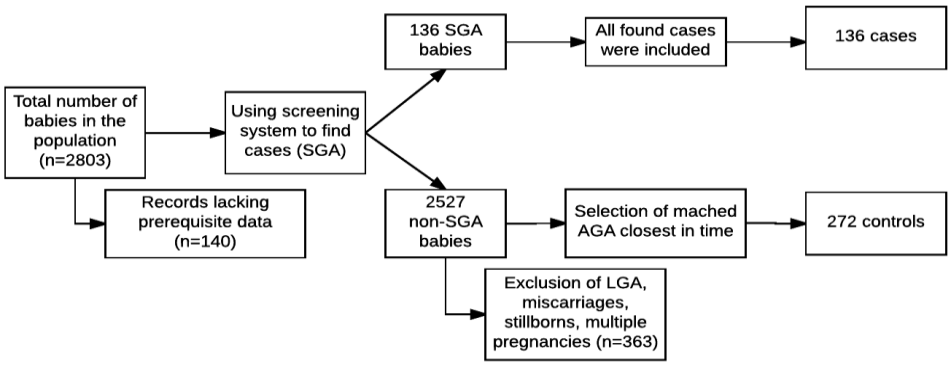

Figure 3. Flow chart of the selection of the sample.

Data collection

When finding a case and associated controls, a premade datasheet of all parameters of interest was used to gather the data. To save time, photo copies were taken to be able to fulfil the collection later out of PHM office. Variables required translation, as well as hardly readable notes and other question marks, were filled in out in field. If anything had to be clarified later on, there were always possibilities to get hold of the PHM afterward.

Local assistance

The pregnancy records were written by hand in Sinhalese by the PHM. Translation from the local language to English was carried out voluntarily by 20 students from the Health Promotion Study Programme at Rajarata University, Mihintale. All students were doing their third and last year of study and some basic medical knowledge is included in their programme. Before the sampling, they were informed about the study during a two hour long gathering, reviewing the study design, objectives, methods, data variables and important aspects of data collection at the PHM office. They also had a lecture about how to calculate gestational age in order to reduce the time with the PHM.

Exposure variables

All variables were taken from the pregnancy record and comprised previously known risk factors as well as less studied ones. The major part of variable selection was done a head of departure in consultation with the Swedish supervisor. In attempt to capture the overall perspective, not only medical but social risk factors such as education, occupation and marital status were also considered. Unfortunately, because of discrepancy in received information the influence of several interesting variables such as smoking, substance abuse and chronic hypertension turned out to be impossible to investigate. Furthermore, the

evaluative measure "Apgar score", considered to be a proxy measure to report morbidity at birth, was lost.

Table 3. Variables sampled from pregnancy records; described and categorized in collaboration with Dr Håkan Lilja, Sahlgrenska University.

Variable	**How data was logged***
Maternal risk factors	
Age of mother	<18 **18-34** ≥ 35
Level of education	Grad 1-9 **Higher education**
Occupation	**Unemployed/housewife** White collar Blue collar
Parity	Primiparous **Multiparous**
Obstetric history: - Previous LBW (<2500g) - Previous miscarriage - Previous CS (caesarian section)	Yes/**no**
Family history of: - Diabetes mellitus - Hypertension - Hemorrhagic disease	Yes/**no**
Marital status	Unmarried **Married**
Consanguinity	Yes/**no**
History of subfertility	Yes/**no**
Antepartum haemorrhage (in current pregnancy)	Yes/**no**
Present diseases: - Diabetes mellitus - Malaria - Cardiac disease - Renal disease - Asthma	Yes/**no**
Pre-pregnancy weight (kg) (before 12 weeks of POA)	<50 **>50**
Maternal height (cm)	≤ 150 **151–160** >160
Weight gain during pregnancy	Below **Within** Above
Pre-pregnancy BMI[a] (before 12 weeks of POA)	<18.5 **18.5-24.9** ≥ 25
Gestational hypertension	Yes/**no**
Pre-eclampsia	Yes/**no**
Syphilis	Yes/**no**
HIV	Yes/**no**
Anaemia in pregnancy (<11 g/dl, <110 mg/ml)	Yes/**no**

Antenatal and delivery factors	
Folic acid supplementation in early pregnancy (before POA 12 weeks)	**Yes**/no
SFH-chart data	**Normal** Pathologic
Mode of delivery	**Vaginal delivery** Caesarean section
New-born	
Prematurity (<37 weeks)	Yes/**no**
Sex	**Male** Female
Birth complications	Yes/**no**
Postpartum complications	**No** Infections Abnormalities
Neonatal death	**No** < 8 days 8-28 days

*Bold subgroup of each specific variable indicates references group in the statistical analysis. [a]Body mass index.

Clarifications of primary aim variables

Consanguinity. In this study consanguinity is defined as a marriage between two individuals who are related as second cousins or closer.

Weight gain during pregnancy. A pregnant woman was at the first antenatal visit (≤ 12 weeks) addressed to a specific BMI-group (A-D) based on her height and weight. The total pregnancy weight gain was estimated by subtracting the pre-pregnancy weight from the last measured weight before delivery, which always was registered in third trimester. With this information, it was possible to determine if the woman had gained the adequate number of kilograms regarding to her BMI-group. The total weight gain could be below, within or above her expected weight gain range.

Table 4. Normal weight gain during pregnancy in relation to BMI-group. Guidelines issued by the Institute of Medicine (IOM).

Group	BMI (kg/m^2)	Expected weight gain (kg)
A- Undernutrition	<18.5	12.5-18
B- Normal	18.5 – 24.9	11.5-16
C- Over weight	25 – 29.9	7.0-11.5
D- Obese	≥ 30	≤ 6.8

SFH-chart data. The chart used was based on a Western population, which meant that the birth weight means drawn as two parallel lines in the chart was not equivalent to the mean in our study population. The chart was designed to detect growth abnormalities with a series of measurements and abnormal growth would be caught by the shape of the curve rather than from a single plotted value (41). Consequently, if only one measurement was registered it was handled as missing data.

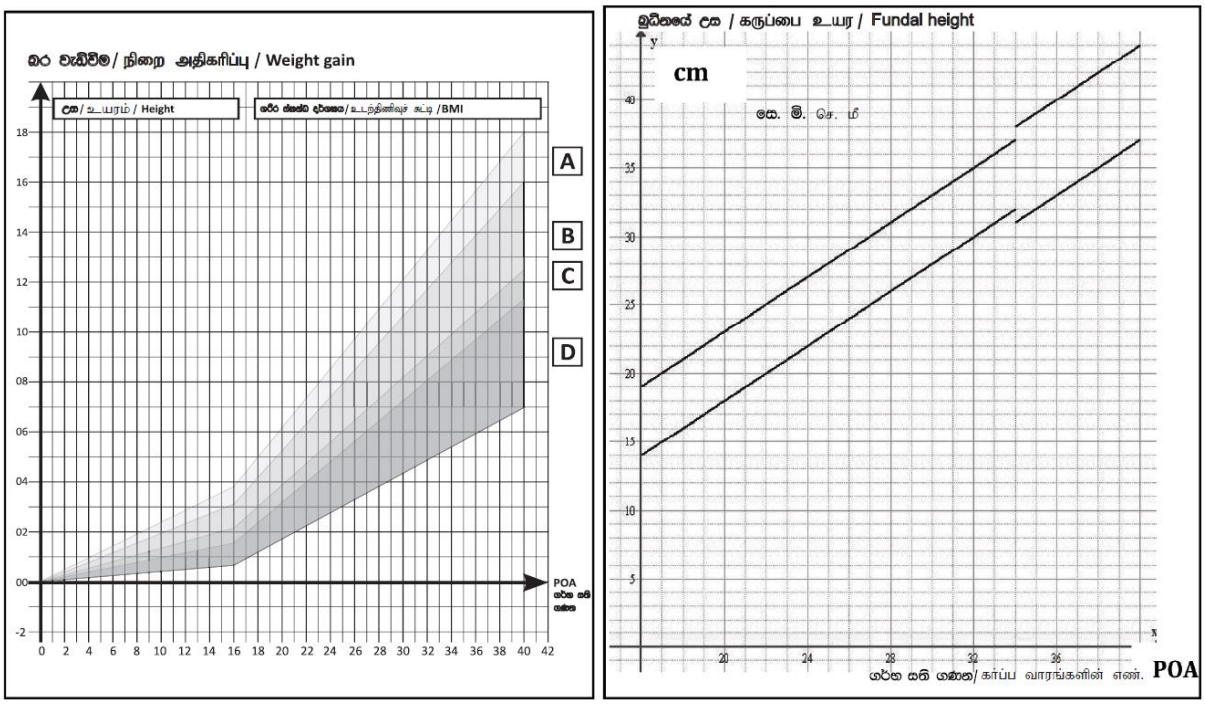

Figure 4. On the left hand, the weight gain chart and on the right the SFH-chart, both extracted from the A card of the pregnancy record. In the weight chart, the mothers weight gain during pregnancy was plotted and the areas A-D represent her initial BMI-group. In the SFH-chart, fundal height was plotted in relation to gestational age.

Level of education. In Sri Lanka, schooling is compulsory for children aged 5 to 14 years old, corresponding to grade 1-9. Mothers who had continued higher studies, and eventually completed university entrance exam and later a degree, were in this study referred to as "higher education".

Occupation. It was possible to distinguish two types of occupations; blue- and white-collar job. The blue-collar worker was a mother who had a physically demanding job and typically worked under adverse and strenuous conditions (for example monotonous work, lifting and carrying

heavy loads, poor posture). In contrast, the white-collar worker had a more mentally and emotionally demanding job, which meant a greater psychological stress. The distinction between white-and blue-collar job was performed by the author.

Secondary aim outcomes

Birth complications. Complications during labour; acute asphyxia, prolonged and obstructive labour, meconium aspiration and abnormal heart rate pattern.

Postpartum complications. Divided into two types of observations; infections and abnormalities. "Infections" included respiratory infections, infection in the umbilicus and neonatal sepsis. The term "abnormalities" included any congenital abnormality.

Mode of delivery. Vaginal delivery included assisted delivery with forceps and ventouse.

Assumptions

The variable "hypertension in pregnancy" was noted as present or not in the pregnancy record. Confirmed by the PHM, this hypertension related to the current pregnancy and were documented by the medical doctor at the clinic. In some of the records there was a diagnosis of hypertension in pregnancy, but no registrations of high blood pressure were documented. We assume that the medical doctor has completed unregistered measurements and is acquainted with the definition of gestational hypertension. Furthermore, another assumption was that the pre-pregnancy weight was similar to the mother's weight at the first antenatal visit ($\leq$ 12 weeks).

Statistical analysis

The data were stored and coded in Excel and analysed using IBM SPSS statistic version 24. In the description of demographic and clinical variables, continuous data was presented as means and standard deviations, whereas discrete (nominal and ordinal) data as numbers and percentages. Logistic regression assumes linearity of independent variables. Whilst it does not need the dependent and independent variables to be connected linearly, the independent variables must be linearly connected to the log odds. Otherwise the test underestimates the strength of the relationship and a potential correlation is rejected too easily. In order to circumvent this problem, interval variables were categorized and made nominal before analysis.

To test the probably of independence, Pearson's chi square test was used and Fischer´s exact test when appropriate due to small cell size (less than five observations in one cell). From the unadjusted tests, the variables which presented p-values <0.1 where further analysed in the multivariable adjusted analysis. To not lose potential confounders in the logistic regression, a change of alpha level from <0.05 to <0.1 was made. Spearman's rank correlation test was performed to examine the degree of correlation between variables intended to be included in the multivariable analysis. All variables of interest with a p-value below 0.1 in the unadjusted tests presented a correlation coefficient <0.2, indicating independence of each other.

To measure the obtained associations, adjusted odds ratio and confidence intervals were calculated with binary logistic regression. Hosmer and Lemeshow test were used as goodness of fit statistics. To investigate maternal pre-pregnancy BMI, weight and height independently, two separate models were created. Since the number of cases was relatively small, two models with fewer independent variables in each model would also strengthen the results of the analysis. Statistical significant p-value was considered when $p < 0.05$. Infant sex was entered as a predictor for SGA and added to both regression models. Even though maternal age, level

of education or parity showed no correlations to the studied outcome in the unadjusted tests, they were considered potential confounders and therefore included in the models.

Ethical considerations

Ethical approval for data collection was received from the Ethics Review Committee, Faculty of Applied Sciences of Rajarata University of Sri Lanka (see Appendix, Annex 1). All pregnancy records were formerly given identity number and there by impossible to connect to the individual. The obtained data was subsequently treated anonymously. The study obeys the human rights and the Declaration of Helsinki ethical principles for medical research.

Results

Study population

Data were collected from 408 pregnancy records of women in Anuradhapura district including maternal and pregnancy characteristics, antenatal care, labour characteristics, neonatal complications and death. 136 cases respectively 272 controls were included in the study, where 51.7 per cent (n=215) were males and 46.4 per cent (n=193) were females. 53.7 per cent (n=219) of the population came from Mihintale MOH area and 46.3 per cent (n=189) from Nuwaragam Palatha MOH area. All mothers to cases and controls included were married. The SGA prevalence among new-borns in these two areas were 5.4 per cent in this study. To access the severity of SGA, calculation of the 5^{th} and 3^{rd} percentile was performed. Out of the total number of SGA (n=136), 57.4 per cent (n=78) was below the 10^{th} centile, 14.7 per cent (n=20) below the 5^{th}, and 27.9 per cent (n=38) below the 3^{rd} percentile. 15 of 136 (11%) SGA infants were preterm and the residue were born term SGA. No extremely preterm or postterm infants were found during screening. Additional clinical characteristics of the study population are presented in table 5.

Table 5. Maternal and new-born clinical characteristics of the study population; in total and comparison between the case and control group.

	Controls. AGA infants			***Case. SGA infants***			***Total study population.***		
	Mean (SD)	***Min.***	***Max.***	***Mean (SD)***	***Min.***	***Max.***	***Mean (SD)***	***Min.***	***Max.***
Birth weight (g)	2806 (319)	1446	3600	2257 (329)	700	2760	2623 (413)	700	3600
Gestational age (wk)	38 (2)	31	41	39 (2)	30	41	38 (2)	30	41
Maternal age (y)	28 (6)	16	41	27 (5)	17	44	28 (6)	44	16
Pre-pregnancy weight (kg) (missing =48)	52.7 (10.5)	34.0	85.0	49.1 (11.5)	30.5	83.6	51.6 (10.9)	30.5	85.0
Height (cm) (missing =12)	155 (6)	142	172	152 (6)	139	180	154 (6)	139	180
Initial BMI (kg/m^2)	21.9 (4.2)	13.6	37.3	21.1 (4.8)	12.7	37.2	21.7 (4.4)	12.7	37.3
Weight gain (kg)	9.7 (4.1)	1.0	23.6	9.5 (4.5)	1.7	22.0	9.7 (4.2)	1.0	23.6

Abbreviations: SD; standard deviation. Min.; minimum. Max.; maximum.

Unadjusted univariate analysis

As seen in table 6, Pearson's Chi-square test presented a significant connection for the maternal anthropometric factors pre-pregnancy weight, height and pre-pregnancy BMI, indicating an association between both maternal weight respectively height and having a small infant for gestational age. Previous LBW child and mode of delivery also showed significant association to outcome of interest. Because of limited observations in some of the subgroups, analysis of marital status, present malaria, infections (HIV/syphilis), pre-eclampsia and SFH-chart data could not be completed with valid results. Consequently, these specific variables could not be tested for predictors of having a SGA infant. Analysis of family history of haemorrhagic diseases, present diabetes, heart- and renal diseases as well as gestational hypertension yielded no association to SGA (p-value 1).

Table 6. Description and unadjusted univariate analysis of demographic, clinical, antenatal and postnatal factors. Number of cases, controls and valid percentage. Missing subjects in numbers.

	No. (%)			
Maternal factors	***Total study population (n=408)***	***Case, SGA (n= 136)***	***Control, AGA (n=272)***	***P-value***
Maternal age (y)				0.509
<18	10 (2.4)	5 (3.7)	5 (1.8)	
18-34	350 (84.1)	116 (85.3)	234 (86.0)	
≥35	48 (11.5)	15 (11.0)	33 (12.1)	
Marital status				NA
Unmarried	0	0	0	
Married	408 (100)	272 (100)	136 (100)	

Consanguinity	24 (5.8)	12 (8.8)	12 (4.4)	0.074
Level of education				0.459[a]
Grad 1-9	176 (42.3)	55 (40.4)	121 (44.5)	
Higher education	232 (55.8)	81 (59.6)	151 (55.5)	
Occupation				0.912
Unemployed/housewife	301 (74.1)	102 (75.0)	199 (73.7)	
White-collar	91 (22.4)	30 (22.1)	61 (22.6)	
Blue-collar	14 (3.5)	4 (2.9)	10 (3.7)	
Missing	2	0	2	
Family history of				
Diabetes mellitus	55 (13.2)	17 (12.5)	38 (14.0)	0.682
Hypertension	52 (12.5)	15 (11.0)	37 (13.6)	0.462
Hemorrhagic disease	2 (0.5)	1 (0.7)	1 (0.4)	1.0[a]
Present diseases				
Diabetes mellitus	5 (1.2)	2 (1.5)	3 (1.1)	1.0[a]
Malaria	1 (0.2)	0 (0)	1 (0.4)	NA
Cardiac disease	2 (0.5)	1 (0.7)	1 (0.4)	1.0[a]
Renal disease	2 (0.5)	1 (0.7)	1 (0.4)	1.0[a]
Asthma	13 (3.1)	5 (3.7)	8 (2.9)	0.767[a]
Infections (Syphilis/HIV)	0/0 (0)	0/0 (0)	0/0 (0)	NA
Pre-pregnancy weight (kg)				<0.001*
<50	165 (45.8)	68 (59.1)	97 (39.6)	
>50	195 (54.2)	47 (40.9)	148 (60.4)	
Height (cm)				0.007*
≤ 150	118 (29.2)	52 (38.8)	66 (24.4)	
151-160	229 (56.7)	69 (51.5)	160 (59.3)	
>160	57 (14.1)	13 (9.7)	44 (16.3)	
Missing	4	2	2	
Pre-pregnancy BMI (kg/m^2)				0.003*
<18.5	93 (26.0)	41 (36.0)	52 (21.3)	
18.5-24.9	185 (51.7)	45 (39.5)	140 (57.4)	
≥25	80 (22.3)	28 (24.6)	52 (21.3)	
Missing	50	22	28	
Obstetric history				
Parity				0.177
Primiparous	170 (40.9)	63 (46.3)	107 (39.3)	
Multiparous	238 (57.2)	73 (53.7)	165 (60.7)	
History of subfertility	13 (3.1)	7 (5.1)	6 (2.2)	0.136
Previous LBW	74 (17.8)	40 (29.4)	34 (12.5)	<0.001*
Previous miscarriage	64 (15.4)	21 (15.4)	43 (15.8)	0.923
Previous CS	52 (12.5)	14 (10.3)	38 (14.0)	0.294
Antenatal and delivery factors				
Weight gain during pregnancy				0.471
Below	170 (47.8)	58 (51.3)	112 (46.1)	
Within	133 (37.4)	37 (32.7)	96 (39.5)	
Above	53 (14.9)	18 (15.9)	35 (14.4)	
Missing	52	23	29	
Antepartum haemorrhage	9 (2.2)	4 (2.9)	5 (1.8)	0.489[a]
Gestational hypertension	11 (2.6)	4 (3.0)	7 (2.6)	1.0[a]
Pre-eclampsia	1 (0.2)	1 (0.7)	0	NA
Anaemia in pregnancy	111 (26.7)	45 (33.8)	66 (25.1)	0.067
Folic acid				0.062
No	134 (32.2)	53 (39.0)	81 (29.8)	
Yes	274 (65.9)	83 (61.0)	191 (70.2)	
SFH-chart data				NA
Normal	281 (100)	88 (64.7)	193 (71.0)	
Pathologic	0	0	0	
Missing	127	48	79	
Mode of delivery				0.012*
Vaginal delivery	271 (66.4)	79 (58.1)	192 (70.6)	
CS	137 (33.6)	57 (41.9)	80 (29.4)	
New-born				
Sex				0.161
Female	193 (46.4)	71 (52.2)	122 (44.9)	

Male	215 (51.7)	65 (47.8)	150 (55.1)	
Birth complications	0	0	0	NA
Missing	5	2	3	
Postnatal complications				NA
No	369 (88.7)	124 (99.2)	245 (99.6)	
Abnormalities	1 (0.2)	1 (0.8)	0 (0)	
Infections	1 (0.2)	0 (0)	1 (0.4)	
Missing	37	26	11	
Neonatal death	0	0	0	NA

Abbreviations: NA, non-analytical. Analysis of some variables could not be done since the number of observations was too few to get results of enough reliability. These affected variables were; marital status, present infectious diseases, pre-eclampsia, SFH-data, birth complications, postnatal complications and death. [a] Fisher's exact test. *p-value <0.05

A total of 127 (31.1%) pregnancy records were missing complete SFH-chart data and could not be analysed. Out of the remaining 281 (68.9%) records, all presented a normal plotting of measurements in the chart. No abnormalities such as stagnating or declining curves were found indicating possible pathologic growth restriction.

Logistic Regression Analysis

Multivariable logistic regression analysis was performed to assess to what extent factors obtained from the univariable analysis were affecting SGA births. In the adjusted analysis, clinical variables low maternal pre-pregnancy weight (<50 kg), low maternal stature (≤ 150 cm), pre-pregnancy BMI <18.5 and ≥ 25 were significantly higher in the SGA group (table 7). The odds ratio was more than 1 for all statistical significant variables in the analysis, expressing more extreme values of these variables, the greater is the odds to have a SGA infant. Shown in both regression models, mothers with previous LBW child (< 2500g) were approximately four times (OR 3.8) at higher risk for having a SGA infant as compared to mothers with no history of LBW birth (p <0.001). A tendency to significant increased risk of SGA was seen in the univariable test for the variables consanguinity, lack of folic acid supplementation in early pregnancy and anaemia in pregnancy. However, these borderline associations were gone in the multivariable analysis.

Table 7. Result of binary logistic regression analysis. Odds ratio for the dependent variable (SGA outcome) with 95% confidence interval and significance, is shown for maternal and antenatal factors. Model 1 and 2 were mutually adjusted for maternal age, level of education, parity and infant sex.

	Independent variable	***OR***	***Lower (CI 95%)***	***Upper (CI 95%)***	***Sig.***
Model 1	Consanguinity	1.95	0.69	5.58	0.210
	Folic acid	1.44	0.84	2.49	0.186
	Anaemia in pregnancy	1.37	0.77	2.41	0.285
	Pre-pregnancy weight (kg)				
	<50	2.18	1.28	3.69	0.004*
	>50 (reference)	1			
	Height (cm)				0.028*
	≤ 150	1.98	1.14	3.45	0.015*
	>160	0.82	0.37	1.82	0.615
	151–160 (reference)	1			
	Previous LBW	3.87	1.98	7.57	<0.001*
Model 2	Consanguinity	1.61	0.59	4.44	0.354
	Folic acid	1.33	0.78	2.28	0.295
	Anaemia in pregnancy	1.32	0.76	2.32	0.325
	Pre-pregnancy BMI (kg/m^2)				0.010*
	<18.5	2.24	1.27	3.94	0.005*
	≥ 25	1.95	1.04	3.64	0.036*
	18.5-24.9 (reference)	1			
	Previous LBW	3.87	2.01	7.47	<0.001*

Abbreviations: Odds ratio (OR), confidence interval (CI), significance (Sig.). *P-value <0.05.

Mode of delivery and neonatal outcome

In the SGA-group, 41.9 per cent (n=57) were delivered by caesarean section (CS) compared to 29.4 per cent (n=80) in the AGA-group, representing a significant difference between the groups (p-value 0.012). Regarding the second aim of the study, which was to investigate the link between SGA infant and adverse neonatal outcomes such as birth and postpartum complications, too few observations made it impossible to analyse the data statistically. Only two postnatal complications were documented in total; upper respiratory tract infection requiring neonatal intensive care and retentio testis. No birth complications were documented and there were no neonatal deaths.

Discussion

The present study shows that maternal body size is associated with a higher risk of having an infant too small for gestational age in the investigated MOH areas. More exactly short stature (≤ 150), low pre-pregnancy weight (<50 kg) and BMI (<18.5 and ≥25). An increased risk of SGA among mothers with a previous history of LBW birth was also found.

The result regarding short stature is in line with several prior studies where the study outcome has been both SGA respectively IUGR (42-44). Likewise, many researchers have demonstrated that mothers of SGA infants by population centiles have lower initial weight than those of AGA infants (44-46). In the light of these findings, it is not remarkable that low BMI (<18.5) is associated with a more than twofold increased risk of SGA. In Vietnam, Ota et al. showed an increased risk of SGA among women with BMI <18.5 (47). However, more outstanding is the significant relation between high pre-pregnancy BMI (≥ 25) and the likelihood of having a small infant. Other researchers have earlier presented no or a reverse association, reporting BMI ≥ 25 as a protective factor (43, 48). A likely explanation to the association between overweight and SGA could be that there is no direct effect of BMI ≥ 25, what we see is rather an indirect effect mediated by hypertension and diabetes with vascular disease (49). The disparity in result could also be explained by the failure of taking important social confounders into consideration.

It is seen in previous studies that LBW tend to repeat in families (50). However, most of these studies have not considered LBW as a composition of prematurity and SGA. It is well-recognized that one of the main risk factors for premature delivery is previous premature delivery. Bakewell at al. investigated LBW repetition and demonstrated an increased risk for LBW with previous LBW divided into three groups; preterm non-SGA (OR 7.9), preterm SGA (OR 10.0) and term SGA (OR 6.3) (51). Despite the division into groups, it is still difficult to make a completely fair comparison as all included infants in the study had a birth weight <2500

grams. Hinkle et al. found that women whose first pregnancy was complicated by a SGA birth had more than a four-fold increased risk for another SGA infant. An additional finding in the study of Hinkle et al. was that maternal short stature and pre-pregnancy underweight were significantly associated with a greater risk of both incident and recurrent SGA (52). These two studies present a similar conclusion; it is possible that the same factors responsible for LBW/SGA births in previous pregnancy may be operative in the current one. These factors may or may not be modifiable, indicating a need for a better understanding of the underlying pathophysiology of LBW/SGA delivery.

To summarise, in our study maternal anthropometric factors and previous LBW child were the only variables significantly associated to SGA. This result is probably due to the etiology of SGA in the investigated areas and could be interpreted in mainly two ways, both which will be discussed further.

The physiological explanation of SGA

One possible theory to SGA outcome in this study population could be attributed to small but healthy parents, thus due to parental genetics and not IUGR. It is essential to keep in mind that the rate of IUGR is neither static or general but depends on the prevalence of risk factors and pathology within the population of interest. According to Deepak Sharma et al. 50-70 per cent of all SGA infants are constitutional small with foetal growth appropriate for maternal size and ethnicity (17). In a conversation with Dr Harindra Ranaweera, consultant obstetrician and gynaecologist at Thambuttegama Base hospital in Anuradhapura district, even a more extreme picture is emphasised. Based on his own clinical experience, he approximates more than 75 per cent of all SGA new-borns in the district to be small because of genetic predisposition. This statement is in accordance with the significant and high correlation of maternal weight, height and low BMI in this study. Moreover, factors responsible for LBW/SGA births in a previous pregnancy may operate during subsequent pregnancies as described earlier. By this means, it is

not odd that petite healthy mothers continue to give birth to small healthy children, which clarifies the almost four-fold increased risk of having a SGA infant with previous LBW birth. The absences of pathologic SFH-charts and clinical significant birth or postnatal complications in the study group also support the hypothesis that infants are constitutionally small rather than IUGR.

The pathological explanation of SGA

Despite the above-mentioned theory of constitutionally small babies, it is necessary to consider IUGR as a possible underlying driving force of SGA in the study group. Furthermore, several aspects tend to point in the direction of IUGR. First of all, the reliability of SFH measurements has been an issue of great debate since many studies have verified high false-negative rates for SGA (53). For example, the clinical condition polyhydramnios (high amount of amniotic fluid) can conceal a growth inhibition. It is also important to recall that the chart used in this study was based on a Western population and that the design made it unsatisfactory to interpret single measurements. In addition, many of the pregnancy records had no documented measurements at all. Missing SFH-data is a problem that has previously been noted. A nationwide evaluation carried out on the proper use of SFH-charts during antenatal follow-up in Sri Lanka have confirmed that the use of the charts is improper (54).

Second, the significant association of maternal anthropometric factors and SGA seen in this study could be interpreted as operating through underlying factors correlated with maternal body size and thus be a function of confounding. Although available confounders were controlled for in the analysis, the found associations still may be partly driven by absent external factors. For instance, short stature may be correlated with malnutrition and low socioeconomic status, both highly associated with infant growth.

Third, evaluation of gestational hypertension and pre-eclampsia was performed by the author of this rapport. Data was taken from registered measurements of blood pressure and urine

protein and interpreted according to the definitions. The definition of both variables requires two separate measurements of blood pressure >140/90. In some of the pregnancy records, one single measurement >140/90 was documented, however follow-up measurements were missing. In one of the records a single value of 140/90 was documented together with three plus on the dipstick right before delivery, and accordingly it looks like this delivery may have been a result of upcoming pre-eclampsia. Due to lack of further information in these regards, an underestimation of the incidence of gestational hypertension and pre-eclampsia may have occurred. In addition, handwritten information in the margins of the pregnancy records was common. These marks could be everything from important medical events to meaningless notes. Although the students had basic medical knowledge, in the end it is hard to appraise the validity of the information. Furthermore, inadequate documentation practice by the PHMs and medical officers is a presumable reason for low rate of neonatal complications documented in the pregnancy records. Given all previous aspects, presence of growth restricted infants in the investigated population must be considered. It seems that a combination of parental genetics and IUGR is the most likely source to SGA outcome in Anuradhapura district and that limitations of the study made it problematic to fully capture the whole picture.

Borderline associations

Consanguinity (p=0.074), anaemia in pregnancy (p=0.067) and absence of folic acid supplement in early pregnancy (p=0.062) gave borderline associations in the Chi square test, whereas in the multivariable analysis, none of these variables turned out to be significant. Previous research regarding these variables have reported contradictory results and they probably vary because of slightly dissimilar definitions, but also because of different reference populations for SGA.

Marriage between relatives, consanguinity, has been associated with adverse child health outcomes since it increases homozygosity of recessive alleles. In some previous studies, the

outcome analysed has simply been LBW and they have demonstrated significant increased risk of LBW in consanguineous parents (55, 56). Out of the reviewed literature for this report, no study presenting a relation between consanguinity and SGA has been found. Nevertheless, a study from another developing country reported a significant decrease in birth weight for gestational age and no significant difference was observed between the first-and second-cousin marriages (57).

As far as anaemia in pregnancy is concerned, prior studies have provided inconclusive evidences and it may be due to incomparable cut-off levels and analysis methods. This thesis showed no increased risk of SGA outcome in the final analysis. In a prospective study from another part of Sri Lanka, also conducted within two MOH areas, a similar result was publicized. In that study, no significant association between anaemia at first visit and delivery of a SGA baby was seen (58).

Neither there was a beneficial effect of folic acid supplement in early pregnancy on decreasing the risk of SGA in the study group. A large prospective cohort study of 3647 women who were followed from the first trimester of pregnancy reported corresponding result (59).

Although the three variables showed borderline associations, odds ratio and upper confidence intervals in the regression analysis were above one (>1), indicating that there could be a difference though it is not significant in this study. However, the variables may be clinical relevant and further investigations regarding these variables, preferably in a lager study group including socioeconomic and nutritional confounders, should be considered.

Secondary aim findings

Unfortunately, the question regarding weather SGA increases the risk of neonatal adverse outcomes could not be answered. A larger sample size would be necessary to be able to draw more reliable conclusions. However, caesarean section was more common among SGA infants than AGA infants. The indications of the CS were not recorded in the pregnancy records which

makes it difficult to clarify the underlying reason of the association. A possible explanation to the increased CS rate in the group of SGA could be intrauterine asphyxia, a condition which often demands a CS. WHO has set up a goal for 2025 to decrease non-medically indicated caesarean deliveries. This goal implies the need of further research in order to address the high rates of CS among SGA infants in Anuradhapura district.

Study strength and weaknesses

This is the first study to report risk factors for SGA infants in Anuradhapura district, Sri Lanka. The retrospective study design is a strength of this study as it gave opportunity to screen and sample a large amount of data from the pregnancy records. With interviews or surveys, socioeconomic factors would be easier to explore, but the required sample size is unreachable for a student thesis. Moreover, clinical factors would be lost. Including subjects from two demographically diverse MOH areas made the study sample more representative of the entire district. Another strength is that the studied population was matched for gestational age.

Nevertheless, there are several possibly important limitations of this study. Firstly, the aim was originally to investigate an extensive range of potential risk factors. Due to discrepancy in received information, data about chronic hypertension and socioeconomic factors could not be studied as planned. This is believed to be the main weakness of the study. Chronic hypertension is considered one of the most common medical conditions in pregnancy and a review article performed by McCowan et al. demonstrates that studies from several countries have shown association with SGA (22). Consequently, it is essential to be aware of that these lost factors may be key determinants of SGA in Anuradhapura district, or confounders essential for accurate analysis. Secondly, all available records could not be screened as planned because of practical circumstances. For example, all PHMs battled the stress of heavy workload and to keep up they had to visit numerous mothers per day out in the field. Thus, all PHMs offices could not be visited and this diminished accordingly the study sample. Furthermore, in contrast

to some prior studies, young maternal age and antepartum haemorrhage presented no connection to the examined outcome. An explanation to this contradictory result could be low statistical power, which made it impossible to detect significant differences. A lager sample size may have allowed more conclusive results, as multivariable regression analysis in a larger population can reveal or reject correlations in a more confident manner. In addition, a fairly large part of the data was missing because of poor pregnancy record documentation by the PHMs and medical officers. As a consequence of a limited study sample and missing data, the results must be interpreted with caution.

A third limitation relates to the studied outcome. Different study outcomes limit and make comparisons between studies more complex. In Sri Lanka, economic and medical resources are still relatively limited and to examine IUGR rather than SGA would be more problematic. The general difficulty of exploring IUGR is illustrated in the literature by the fact that studies on risk factors for LBW respectively SGA are more common than those for IUGR. By studying SGA instead of IUGR, the risk of healthy foetuses becoming subjects to extra monitoring and other types of interventions increases, which may waste resources in an already resource-poor country. However, this must be put in perspective to the profit of reducing neonatal morbidity and mortality.

Implications

This was a small case-control study with residual confounding and the results should therefore be viewed primary as hypothesis-generating. The findings of this study suggest further examination whether women in Anuradhapura district are small because of physiologic or pathologic effects. This distinction is essential since pathologic maternal growth restriction and malnutrition can be improved. Maternal stature is a composite indicator representing parental genetics and environmental effects on the growing period of childhood. Researcher Karri Silventoinen states that unlike modern Western societies, in poorer settings a larger percentage

of variation in height within the population is attributable to the environment over genetics (60). According to data from UNICEF, Sri Lanka has been struggling with child undernutrition and stunting for many years now, and it is still a problem. Girls that are born LBW/SGA grow into women of short stature, who themselves are more likely to have LBW/SGA children. Unless the cycle is broken at some point, this situation will continue over generations resulting in an intergenerational cycle of undernutrition (61). To decrease future SGA infants in Anuradhapura district, a possible intervention might be improvement of the nutritional status of children and adolescents. UNICEF also present data of pre-pregnancy undernutrition in Sri Lanka. WHO´s global nutrition targets for 2025 recommend balanced protein–energy supplementation to selected women to reduce SGA and this could be a solution to the postulated issue of pre-pregnancy undernutrition. Although poor dietary intake and poor availability of nutrients already are established as direct causes of undernutrition in women in South-Asia, underlying social determinants have in the last decade been emphasised to be important aspects when it comes to maternal nutrition and pre-pregnancy weight (62). This signifies that the combination of nutrition specific interventions and interventions to assess and tackle wider social determinants could be valuable. Focus on empowerment of women and reduction of gender and income inequity may be an effective method to eventually lessen SGA outcome in Anuradhapura district. Nevertheless, regardless of the discussion above no causal relationship of undernutrition and SGA has been confirmed by this study. For the time being, prevention programs to provide special attention to mothers with previous history of LBW child are suggested.

Customized versus population-based birth weight-for-gestational-age chart

Gardosi et al. state that population-based weigh-for-gestational-age charts do not fully capture the burden of growth restriction and they promote customized charts, adjusted for pre-pregnancy weight, height, infant sex, parity and ethnic origin (63). This research group state

that customized charts would improve the distinction between physiological and pathological variation in foetal size and provide a better estimate of infants with high morbidity and mortality (64). There are studies pointing at SGA infants by customized centiles are more likely to have abnormal umbilical artery doppler velocimetry findings, to be stillborn, to have low Apgar scores and to die in the neonatal period (65). Application of a customized chart might be successful in a high-income country, but it can be more difficult in a population with poorer living conditions, where small mothers not only are a result of physiological effects. It is important to emphasize the need of a systematic investigation of the reason of small women in Anuradhapura district before customized charts becomes praxis, this as a normalization of pathologically small women may have profound consequences.

Conclusions

SGA infants in Anuradhapura district have a significant relation to the maternal factors low pre-pregnancy weight and BMI, short stature and previous LBW births. Based on the result from this study, it is not possible to conclude if these observed risk factors depend on parental genetics or environmental factors, and hence are modifiable or not. Further studies investigating whether mothers in the district are small because of physiological or pathological effects would be an important next step. In the meantime, special attention directed towards mothers with previous LBW child is suggested. In future research, the result and methodological considerations from this study could be used to improve study design and methods. Taken together, the need of studies with larger sample size and inclusion of nutritional and socioeconomic confounders should be highlighted in order to come closer the truth regarding risk factors of SGA in Anuradhapura district.

Populärvetenskaplig sammanfattning

Riskfaktorer för tillväxthämmade barn i distriktet Anuradhapura, Sri Lanka.

Låg födelsevikt är ett stort globalt hälsoproblem som bidrar till en majoritet av alla dödsfall under nyföddhetsperioden. Att ett barn har låg vikt vid födseln beror i huvudsak på två saker; en för tidig födsel eller att barnet fötts för litet för tiden (för små för sin födelsevecka), där den sistnämnda ibland beror på ogynnsam tillväxthämning inne i livmodern. Denna grupp utgör även majoriteten av de barn som föds med för låg vikt i låg- och medelinkomstländer.

I denna fall-kontroll studie, genomförd i distriktet Anuradhapura i centrala Sri Lanka, undersöktes 36 olika faktorer samlade från graviditetsjournaler från åren 2014–2017 och deras koppling till att föda ett för litet barn. Totalt samlades 136 fall och 272 kontroller in. Man fann att en initial vikt hos mamman <50 kg, Body Mass Index (BMI) <18.5 respektive ≥ 25 och längd ≤150 cm ökade risken för ett för litet barn. Dessutom nära fyrfaldigades risken om mamman tidigare fött ett barn med låg födelsevikt. Att övervikt visade sig innebära en riskökning tros beror på en indirekt effekt medierad av andra faktorer som inte gavs möjlighet att studera.

Det är dock inte uppenbart att utifrån den här studien säga om resultatet beror på fysiologiska eller sjukliga mekanismer. En tänkbar förklaring till för små barn är kortväxta men friska mödrar. Denna orsak ger således inte ökad risk för barnet att drabbas av sjukdom eller död, utan grundar sig i normal ärftlighet och dessa mammor kommer även i fortsättningen att föda barn med låg födelsevikt. Emellertid finns det en risk att resultatet istället beror på att mammorna under sin egen barndom varit utsatta för undernäring och därmed inte kunnat växa sig så långa som deras gener avsett. Dessutom kan mammans låga vikt före graviditet bero på långvarig undernäring. Om denna förklaring till små barn stämmer finns det möjlighet till åtgärder som skulle kunna minska andelen framtida födslar av för små barn i distriktet Anuradhapura.

Den andra fråga man ställde i studien var om barn för små för sin födelsevecka hade en ökad risk för ogynnsamma utfall i form av komplikationer eller död, men även om det fanns en association till en särskild förlossningsmetod. Gällande frågan om ökad risk för ogynnsamma utfall gick materialet tyvärr inte att analysera statistiskt på grund av för få observationer. Däremot visade det sig att hela 41,9 procent av de för små barnen förlöstes med kejsarsnitt jämfört med endast 29,4 procent av de normalviktiga barnen.

Slutsatsen man kan dra är att i distriktet Anuradhapura har en kort mamma med låg vikt före sin graviditet en förhöjd risk att föda ett för litet barn. Det är dock svårt att utifrån denna studie säga något om orsaken till att mammans kroppskonstitution påverkar utfallet – kan det vara ärftlighet eller kanske undernäring? Det behövs följaktligen vidare studier för att kunna dra säkrare slutsatser. Fram till dess föreslås att mammor som tidigare fött barn med låg födelsevikt riktas särskild uppmärksamhet i preventionsprogram.

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Appendix

Annex 1

Ethics Review Committee
Faculty of Applied Sciences
Rajarata University of Sri Lanka

Contact:

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30th January 2017

Dear Mr. Duminda Guruge

Ethical Clearance for the research "The effect of maternal and environmental factors on intrauterine growth and neonatal outcome among infants in Anuradhapura District, Sri Lanka"

The Ethical Review Committee (ERC), Faculty of Applied Science of Rajarata University of Sri Lanka has reviewed and discussed the protocol of research study with the above title submitted by Mr.Duminda Guruge on 03.01.2017. In the committee meeting held on the 27th Junuary 2017, the committee has decided to approve the referenced protocol subject to the following conditions:-

- The ERC understood that the study is being conducted as a student research project by Ms. Johana Enberg during her internship program in the Health Promotion Division of the Faculty of Applied Sciences of Rajarata University of Sri Lanka. Hence, any future presentations and publications result from this research should be submitted to the ERC of the Faculty of Applied Sciences of Rajarata University of Sri Lanka.

- Any amendment or deviation to this study protocol should not be implemented until it is reviewed and approved by the ERC of the Faculty of Applied Sciences of Rajarata University of Sri Lanka.

- This certificate is valid until 30.01.2018, when an extension is required; a properly filled Protocol Extension Submission Form should be submitted to the ERC, Faculty of Applied Science of Rajarata University of Sri Lanka, one month before the termination date.

- Upon completion of the research, a final report should be submitted to the ERC of the Faculty of Applied Sciences of Rajarata University of Sri Lanka.

- The study to be conducted in compliance with the approved protocol; failing to oblige may terminate approval.

.....
Dr. Lalith Senarathna
Secretary ERC

.....
Dr. C Bamunuarachchige
Charperson

.....
Dr. B A Karunarathne
Dean
Faculty of Applied Sciences

Dr. B.A. Karunaratne
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