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Risk factors and outcomes of fetal macrosomia in Iringa municipality hospitals: A case-control study

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Abstract
Background: Factors associated with fetal macrosomia include genetics, duration of gestation, and diabetes mellitus. This condition may lead to complications for both the mother and the neonate. Thus this study aims to determine risk factors and outcomes of fetal macrosomia in comparison to those in normal-weight neonates.
Methods: A hospital-based case-control study involving 61 cases of neonates who weighed ≥ 4000g at birth and 122 controls who were neonates delivered on term with normal weight. A questionnaire was used to collect data. Data analysis was done using SPSS version 23. Bivariate and multivariate logistic regression analyses were done to identify risk factors associated with fetal macrosomia.
Results: The incidence of macrosomia was 3.26% in the Iringa municipality. Gestation age of ≥40 weeks (AOR 3.56, 95% CI= 1.65-7.69), and weight ≥80kgs post-delivery (AOR 10.22, 95% CI=2.74-38.12) were associated with delivery of macrosomia. Women with macrosomia had higher chances of prolonged labour, 2nd-degree perineal tear, and postpartum hemorrhage while their babies had hypoglycemia (AOR=8.65, 95%CI=3.23 – 23.17) compared to controls.
Conclusions: Risk factors for fetal macrosomia included a gestation age of ≥ 40 weeks, and mother weighing ≥ 80kgs post-delivery Macrosomia is an important cause of maternal and neonatal complications.
Keywords: Fetal macrosomia, risk factors, complications, neonates

Introduction

The term macrosomia is defined as birth weight above the 90th percentile of weight for that gestation. (Choukem *et al.*, 2016) Based on the variation in cut-points, it is proposed that macrosomia can be subdivided into Class I (birthweight 4000–4499g), Class II (4500–4999g), and Class III (≥5000g). Attempts at perinatal diagnosis of macrosomia have proven difficult and are often inaccurate. (Living, 2012) Diagnosis of fetal macrosomia is made by measuring birth weight after delivery; therefore, the condition is confirmed retrospectively, after delivery of the neonate.

The prevalence of macrosomia ranges from 8 to 21 %. (Rockhill *et al.*, 2015) In the USA the incidence of macrosomia is 10%, whereas, in Nigeria, the incidence of 2.5 to 5.5% has been reported. (Adesina and Olayemi, 2003; Choukem *et al.*, 2016; Olokor *et al.*, 2015) Previous studies that were carried out in a

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tertiary hospital in Tanzania reported the prevalence of macrosomia to be 2.3 % and 3.9% respectively. (Living, 2012; Said and Manji, 2016).

Factors associated with fetal macrosomia include genetics, duration of gestation, and diabetes mellitus (and/or gestational diabetes). Genetic, racial, and ethnic factors influence birth weight and the risk of macrosomia. (Gaudet *et al.*, 2014) Genetic factors, such as parental height and weight, may play a role in determining the birth weight of the neonate. Maternal age of more than 35 years, parity of more than four, with a previous history of delivering macrosomia and having gained 13-15 kgs throughout the index pregnancy. Male neonates typically weigh more than female neonates and thus comprise a greater proportion of neonates with birth weights exceeding 4000 g at any gestational age. (Frederick *et al.*, 2008; Fuchs *et al.*, 2013; Onyiriuka, 2006; Said and Manji, 2016; Wang *et al.*, 2017).

The pathophysiology of macrosomia can be explained based on Pedersen's hypothesis of maternal hyperglycemia leading to fetal hyperinsulinemia and increased utilization of glucose. (Kc *et al.*, 2015) Hence, increased fetal adipose tissue because the glucose can cross the placenta. However, the maternal-derived or exogenously administered insulin does not cross the placenta. As a result, in the second trimester, the fetal pancreas, which is now capable of secreting insulin, starts to respond to hyperglycemia and autonomously secrete insulin regardless of glucose stimulation. (Premalatha *et al.*, 2013) This combination of hyperinsulinemia and hyperglycemia leads to an increase in the fat and protein stores of the fetus, resulting in macrosomia. (Premalatha *et al.*, 2013) Hyperglycemia in the fetus results in the stimulation of insulin, insulin-like growth factors, growth hormone, and other growth factors, which in turn, stimulate fetal growth and deposition of fat and glycogen. (Rao *et al.*, 2013).

Advanced gestational age results in macrosomia by allowing the growth process to continue in utero. Advanced maternal age contributes as well, as the basal metabolic rate and metabolic body demand decrease with the advancement of age therefore increasing the risk of macrosomia. (Frederick *et al.*, 2008; Fuchs *et al.*, 2013; Wang *et al.*, 2017).

Fetal macrosomia may cause several maternal complications such as increased risks of prolonged labor, emergency cesarean section, obstetrical trauma, traumatic deliveries and postpartum hemorrhage, and maternal death. (Vercellini *et al.*, 2015; Zamorski.MA, 2001) Uterine rupture/dehiscence is independently associated with fetal macrosomia as reported in one study. (Diaz *et al.*, 2002).

On the other hand, Fetal complications include fetal distress, and neonatal hypoglycemia, compared with those appropriate for gestation age. (Weissmann-Brenner *et al.*, 2012) Other reported fetal complications include shoulder dystocia secondary to trauma to the brachial plexus during birth, facial nerve injuries, birth asphyxia, lower Apgar score (<7 at 5 min), and fracture of the humerus or clavicle. (Nassar *et al.*, 2003; Vinturache *et al.*, 2015).

Few reports provide detailed comparable information regarding the risk factors and outcome of fetal macrosomia in Tanzania, especially in regional hospitals. Considering the paucity of studies on fetal macrosomia in the Iringa municipality, the present study was undertaken to determine risk factors and outcomes of fetal macrosomia in comparison to those in normal-weight neonates in the Iringa Municipality.

Material and methods

Study design and population

This was a hospital-based case-control study, involving neonates with birth weight equal to or more than 4000gms as cases and normal birth weight neonates as controls. The study took place at Iringa Municipality, Tanzania from September to December 2017. It was carried out in two health facilities, the Iringa Regional Referral Hospital (IRRH) and Frelimo Hospital. Administratively, Iringa Municipality

has one Division, 18 wards, 40,545 households and 192 streets. These 2 health facilities offer expert obstetrics services for Iringa's urban and suburban populations.

Inclusion and exclusion criteria

All neonates delivered at IRRH and Frelimo maternity wards in the Iringa municipality from 18th September to 27th December 2017 were eligible for the study. Cases were all neonates delivered with a birth weight of 4000g or greater and their mothers, while controls were the next two neonates of the same sex as that of cases delivered with normal birth weight and their mothers. Multiple pregnancies and preterm babies were excluded from the study.

Sample size and sampling procedure

The sample size was calculated by using the following formula.

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

Z_{β}= 0.84 for power (1-β) of study is 80%

Z_{α}=desired level of statistical significance, for 0.05 significance level= 1.96

Ratio of controls to cases =2:1. Thus controls = 61 X 2=122

Thus,

n = cases =61, controls =122 making a total sample size (N) of 183.

A consecutive sampling technique was employed in selecting cases of macrosomic neonates. Controls were selected by picking the next two neonates of similar sex as that of the macrosomic neonate with normal weight after the selected case.

Data collection

The mother and the neonate of the selected cases and controls were followed to their admission wards or observation rooms for face-to-face interviews once they were clinically stable following delivery. The purpose and procedure of the study were explained and those who gave consent and agreed to participate in the study were enrolled in the study consecutively until the sample size was achieved.

Data collection was completed using a structured questionnaire. A validated questionnaire that has been used in similar studies (Said and Manji, 2016) was adapted to suit the study. It consisted of three parts. The first part included socio-demographic characteristics of the women namely age, occupation, marital status level of education, and residency. The second part of the questionnaire comprised maternal factors such as parity, past obstetric history (history of previous macrosomic delivery, diabetes, or gestational diabetes), excessive weight gain in index pregnancy, and post-delivery weight. The last part contained questions about fetal gender as a factor. Data was supplemented with information from the antenatal card, clinical notes, partograph, and precise measures of neonatal weight and maternal height.

At recruitment, a blood sample was drawn by a nurse from neonates' heel prick for random blood sugar estimation at the second, fourth, and sixth 6 hours after delivery. The machines were checked weekly with laboratory standards and quality control samples for quality assurance. Neonates with hypoglycemia were managed based on the standard treatment guidelines of the unit.

Data analysis

The data obtained from this study were coded and analyzed using Statistical Package for Social Sciences software (SPSS) for Windows (Version 23, Armonk, New York: IBM Corp). The independent variables were defined as follows: Diabetes mellitus included those who were diagnosed with having

raised plasma glucose prior or during pregnancy, postdate gestation age above 40 weeks, previous macrosomia, weight > 80kgs after delivery, and parity.

Gestation age was estimated from the first day of the last normal menstrual period using Naegele's formula, for those not sure of their dates, extrapolations from gestation age on booking recorded in the antenatal care card (ANC) were used. The date of quickening and use of first-trimester ultrasonography was used to estimate the gestation age if it was available.

Birth asphyxia was defined as a one-minute APGAR score of <5 and a fifth-minute score of <7. Neonatal respiratory distress syndrome was diagnosed by the presence of evidence of respiratory compromise (retractions and/or nasal flaring and tachypnea) shortly after delivery and a persistent oxygen requirement for more than 24 hours. Shoulder dystocia if prolonged delivery of head with a turtling sign with the use of obstetrics manoeuvers.

Statistical analysis involves calculations of percentages, ratios, means, and confidence intervals. The Z-test, the t-test, and the Chi-square test were used in ascertaining the level of significance of differences, *p*-value < 0.05 was considered significant.

Ethical approval

The study was approved by the Institution Review Board of the Muhimbili University of Health and Allied Sciences (MUHAS) and permission to collect data was granted by the office of the District Medical Officer (DMO) of Iringa and the Medical Officer in Charge of the Hospitals. Only those participants who freely gave consent to participate were included in the study. All information was handled confidentially and access to data was only granted to the co-authors.

Results

During the data collection period, a total of 1871 deliveries were done in the study area, of which 61 (3.26%) were macrosomic neonates with birth weight ≥ 4000 grams. There were more (41, 67.2%) male than female neonates (20, 32.8%). The overall cesarean section (C/S) rate was 45.9% and C/S for the delivery of macrosomic neonates accounted for 18.5% of the total cesarean section rate.

Risk factors for fetal macrosomia

On univariate analysis, the risk factors significantly associated with fetal macrosomia were the gestational age, previous history of delivering a macrosomic child, maternal weight at delivery, mother's height, mother's age, and mother's employment status. However, upon performing an adjusted multivariate analysis, a significant association between delivering a macrosomic neonate and maternal factors like gestational age and weight at delivery was found. Women who delivered at the gestation age of ≥40 weeks were almost four times more likely to deliver macrosomic babies (AOR= 3.56, 95% CI =1.65-7.69). Women who weighed ≥80 kg at delivery had 10 times higher odds of delivering a macrosomic neonate [Table 1].

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Table 1: Bivariate and multivariate logistic regression analysis of maternal risk factors associated with the delivery of macrosomia

Risk factors associated with Fetal Macrosomia	Cases	Control	COR [95% CI]	AOR [95% CI]
Gestational age				
37-39	23	83	Ref (1)	Ref (1)
40-42	38	39	3.52 [1.85-6.69]	3.56[1.65-7.69]
Previous macrosomia				
No	47	111	Ref (1)	Ref (1)
Yes	14	11	2.73[1.18-6.35]	1.67[0.56-5.05]
Diabetes mellitus				
No	53	118	Ref (1)	Ref (1)
Pre-gestational	04	01	8.91 [0.97-81.60]	0.31[0.00-1.07]
Gestational	04	03	2.97 [0.64-13.73]	0.95[0.01-1.05]
Weight at delivery(kg)				
<80	46	117	Ref (1)	Ref (1)
≥80	15	05	7.63 [2.62-22.20]	10.2[2.74-38.12]
Height(cm)				
≤160	16	53	Ref (1)	Ref (1)
>160	45	69	2.16 [1.10-4.237]	1.05[0.48-2.28]
Age				
< 30	30	83	Ref (1)	Ref (1)
≥30	31	39	2.2 [1.18-4.23]	1.31[0.61-2.82]
Marital status				
Single	6	30	Ref (1)	Ref (1)
Married	55	92	2.99[1.17-7.64]	2.45[0.71-8.53]
Occupation				
Not employed	24	75	Ref (1)	Ref (1)
Self-employed	15	21	2.23[1.00-5.00]	1.36[0.48-3.86]
Employed	22	26	2.64[1.27-5.50]	1.26[0.38-4.16]

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Level of education				
No formal education	2	4	Ref (1)	Ref (1)
Primary	27	83	0.65[0.11-3.75]	0.37[0.05-2.73]
Secondary	28	30	1.87[0.32-11.00]	0.74[0.08-6.61]
College	4	5	1.60[0.19-13.70]	1.12[0.09-14.27]

Maternal complications and fetal macrosomia

Maternal complications that were significantly associated with delivering a macrosomic neonate included prolonged labor, 2nd degree perineal tear, and postpartum hemorrhage (PPH). The odds of prolonged labor in mothers with macrosomic children were 3 times higher than in mothers with normal birth-weight children. Mothers with macrosomic children were 9 times more likely to experience 2nd degree perineal tears compared to their counterparts, and the risk of PPH was 5-fold higher among cases [Table 2]..

Table 2: Maternal complication associated with fetal macrosomia

Maternal Complication	Cases N (%)	Control N (%)	COR [95%CI]	AOR [95%CI]
Prolonged labour				
Yes	20 (32.8)	17 (13.9)	2.33[1.04-5.25]	3.01 [1.44-6.32]
No	41 (67.2)	105 (86.1)	Ref (1)	Ref (1)
Shoulder dystocia				
Yes	03 (4.9)	01 (0.8)	1.92[0.16-22.46]	6.26 [0.64-61.48]
No	58 (95.1)	121 (99.2)	Ref (1)	Ref (1)
Perineal tear				
No	43 (70.5)	109 (89.3)	Ref (1)	Ref (1)
1st degree tear	04 (6.6)	09 (7.4)	0.51[0.04-0.52]	1.13 [0.33-3.85]
2nd degree tear	14 (22.9)	04 (3.3)	0.19[0.04-1.05]	8.87 [2.76-28.47]
Post Partum Hemorrhage				
Yes	05 (8.2)	02 (1.6)	1.60[0.25-10.09]	5.36 [1.00-28.46]
No	56 (91.8)	120 (98.4)	Ref (1)	Ref (1)

Neonate complications and fetal macrosomia

There was no significant difference in the occurrence of neonatal complications between macrosomic neonates and normal-weight neonates except for the hypoglycemic state. The macrosomic neonates were nine times more likely to suffer from hypoglycemia as compared to normal-weight neonates (COR=8.65, 95%CI=3.23 – 23.17) [Table 3].

Table 3: Immediate neonatal complication associated with fetal macrosomia

Neonatal Complication	Case N (%)	Control N (%)	COR [95%CI]
Meconium aspiration			
Yes	03 (4.9)	02 (1.7)	3.10 [0.51-19.09]
No	58 (95.1)	120 (98.3)	Ref (1)
Respiratory distress			
Yes	03 (4.9)	02 (1.7)	3.10 [0.51-19.09]
No	58 (95.1)	120 (98.3)	Ref (1)
Hypoglycemia			
Yes	19 (31.1)	06 (4.9)	8.65 [3.23-23.17]
No	41 (67.2)	112 (91.8)	Ref (1)
Low APGAR score			
Yes	03 (4.9)	02 (1.7)	3.10 [0.51-19.09]
No	58 (95.1)	120 (98.3)	Ref (1)
Stillbirth fresh			
Yes	01 (1.6)	04 (3.3)	0.49 [0.05-4.50]
No	60 (98.4)	118 (96.7)	Ref (1)

Discussion

The incidence of fetal macrosomia in the current study was less than reports from elsewhere (Fuchs *et al.*, 2013; Najafian and Cheraghi, 2012; Wang *et al.*, 2017) but higher than previous results from Tanzania. The differences in the proportions between various reports can be attributed to differences in genetics, socio-cultural and socio-economic status of the population studied. Poor socioeconomic status, and lower pre-pregnancy weight in our setting contribute to lower incidence of fetal macrosomia. (Said and Manji, 2016).

The current study depicted that gestational age of above 40 weeks and maternal weight over 80 kgs post-delivery were risk factors for fetal macrosomia in the index pregnancy. Gestational age at delivery was found to be one of the factors strongly associated with the delivery of fetal macrosomia. The current study pointed out that about two-thirds of women with a gestation age of 40 weeks and above delivered macrosomic neonates, and the odds were four-fold higher compared to those with a gestation age of less than 40 weeks. This is supported by other studies (Alberico *et al.*, 2014; Najafian and Cheraghi, 2012; Said and Manji, 2016; Toweel, 2009) which revealed similar findings, however, a study done in Cameroon did not show an association between gestation age and macrosomia. (Choukem *et al.*, 2016) This observation in the current and other parallel studies is due to continuous in-utero fetal growth in the absence of risks of intrauterine fetal growth restrictions.

Compared to the control group, the chances of delivering a macrosomic neonate were 10-fold high in women who weighed more than 80 kgs post-delivery and 16-fold high in those who were diabetics. Similar findings were noted by Said et al. (Said and Manji, 2016) Obesity and diabetes are associated with an increasing rate of macrosomia hence diet counseling and management of diabetes with insulin would lower the risk of macrosomia. (Koyanagi *et al.*, 2013).

Studies have found an association between the previous delivery of a macrosomic baby with a subsequent similar event in the index pregnancy, (Najafian and Cheraghi, 2012; Onyiriuka, 2006; Said and Manji, 2016) however, this was contrary to the findings of this study. It has been postulated that women with recurrent delivery of macrosomia have deranged glucose metabolism and thus suffer from post-gestation diabetes. An increase in circulating blood glucose levels in these mothers consequently influences the fetal epigenome, thereby influencing the expression of genes that direct the accumulation of body fat or related metabolism. (Herring and Oken, 2011).

Similar to documented complications of fetal macrosomia in the literature. (Beta *et al.*, 2019; Lao and Cheng, 2014; Vercellini *et al.*, 2015; Zamorski.MA, 2001) Prolonged labor, postpartum hemorrhage, and second-degree perineal lacerations were significant maternal complications in the macrosomia group. Prolonged labor during delivery of macrosomia was three times more than in normal-weight neonates. Similar findings were reported in a previous study from Tanzania and China. (Lao and Cheng, 2014; Said and Manji, 2016) A phenomenon of prolonged labor in macrosomia is still prevalent in poor resource areas where an intrauterine diagnosis of macrosomia and eventual assisted or operative delivery is still not common like in our setting as opposed to a study from China and Brazil. (Sá *et al.*, 2003; Wang *et al.*, 2017).

Perineal tear and postpartum hemorrhage in some occasions are an event-event consequential phenomenon, and in this study, it was found that a 2nd-degree perineal tear was 9 times more likely to occur during delivery of macrosomic infant than a non-macrosomic one. The odds of postpartum hemorrhage were 5 times more in the macrosomic group compared to the non-macrosomic group. Similar findings were reported elsewhere, (Alsammani and Ahmed, 2012; Elie, 2014) the trend of perineal tear and postpartum hemorrhage in the macrosomic group goes parallel indicating that birth trauma during delivery of macrosomia contributes to the incidence of postpartum hemorrhage. Uterine atony and perineal tear after the birth of a macrosomic neonate may explain the prevalent occurrence of postpartum hemorrhage in the macrosomic group.

Regarding neonatal complications, in the current study fetal hypoglycemia was 5 times more likely to occur in macrosomic newborns as compared to those delivered with normal birth weight. This is in agreement with studies done elsewhere. (Choukem *et al.*, 2016; Rezaiee *et al.*, 2013; Said and Manji, 2016; Wang *et al.*, 2017) This can be explained by persistent hyperinsulinemia during fetal life by pancreatic beta-cells leading to hypoglycemia.

This study has a limitation of recall bias just as in any other case-control study since most participants tend not to recall correctly their experience. We could not study the association between

pre-pregnancy body mass index and risk of macrosomia because most women did not know their weights before conceiving. Moreover, there may be some errors in ascertaining the gestation age based on the menstrual cycle pattern. Another limitation of the study is a small sample size, which was ascertained by a wide confidence interval for some factors, thus, this led to a limited statistical power to adequately account for the differences in the occurrence of complications between the two groups. However, despite these limitations, this study lays a foundation for further studies involving large samples and of multicentric nature.

Conclusion

The incidence of macrosomia in the Iringa municipality was 3.26% and it was associated with a gestation age of ≥40 weeks, and a weight ≥ 80kgs post-delivery. Delivery of macrosomia was also found to be associated with maternal complications, which included prolonged labor, second-degree perineal tear and postpartum hemorrhage. The neonatal complication was newborns hypoglycemia as the only immediate neonatal complication of macrosomia. Having discovered the risks and anticipated outcomes of macrosomia in patients, early interventions and preparedness for anticipated outcomes of macrosomia in both maternal and fetal. This can give better outcomes with timely and appropriate management of complications related to macrosomia.

Declaration of conflicting interests

The authors declare no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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