A cross-sectional study of non-diabetic macrosomic infants

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Objective: To determine risk factors and short term outcomes in infants with fetal macrosomia independent of gestational diabetes.

Method: Patient records of babies born in Bolu Izzet Baysal Obstetrics-Gynaecology and Paediatrics Hospital between 1st January 2007 and 31st December 2010 with weights of 4000g or more were assessed retrospectively. Data were analysed using SPSS version 17.0. Babies born outside hospital and infants of diabetic mothers were excluded. Control group comprised 500 healthy infants weighing 2500-3999g, born during the same period. Chi-square test, student-t test, Mann-Whitney test and multiple regression analysis were the statistical tests used.

Results: Of 10,898 babies delivered in our hospital during the 4 year study period, 509 (4.7%) weighed 4000g or more. Significantly more non-diabetic macrosomic babies were male compared to controls ($p<0.001$). Significantly more non-diabetic pregnant women older than 35 years delivered macrosomic infants compared to non-diabetic pregnant women 35 years or less ($p<0.001$). Significantly more non-diabetic pregnant women who delivered macrosomic infants were multipara compared to controls ($p<0.001$). No significant statistical differences were detected in mode of delivery between cases and controls ($p>0.05$). The 5th minute Apgar scores in the non-diabetic macrosomic group was significantly lower than in controls ($p<0.001$). Non-diabetic macrosomic babies had significantly more birth injuries than controls ($p=0.009$). Risk of developing hypoglycaemia and hypocalcaemia were significantly higher in non-diabetic macrosomic babies compared to controls ($p<0.05$).

Conclusion: In our study the risk factors for non-diabetic fetal macrosomia were advanced age pregnancy, multiparity and male sex.

(Keywords: Fetal macrosomia; perinatal mortality; risk factors; morbidity; birth trauma; outcomes)

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Introduction

Macrosomia is generally defined as birth weight of 4000g or greater[1]. A multifactorial interference comprising genetic factors, fetal nutrition and environmental factors is considered to regulate fetal development. During fetal development there are two mechanisms, hormone-dependent and non-hormone-dependent. In hormone-dependent development the most important factor is insulin[2]. In non-hormone-dependent mechanism the structure of the placenta, the blood flow to the placenta and the substrates like oxygen, glucose, amino acid provided with this flow play an important role[2]. In studies on macrosomic infants of non-diabetic mothers, a significant relationship was found between birth weight and cord leptin and insulin-like growth factor-1 levels but no relationship with cord insulin levels[3].

The frequency of macrosomia has increased in the last 50 years, the changing nutritional habit increasing maternal obesity and resulting in an increase in fetal macrosomia[2,4]. A high maternal body mass index (BMI >29) may be a risk factor for macrosomia by itself[5]. Other risk factors for fetal macrosomia are: maternal diabetes, maternal impaired glucose, prolonged gestation, maternal obesity and male sex[6]. If one of these risk factors exists the possibility of macrosomia is determined to be 38%; if two or more risk factors exist then the possibility of macrosomia is determined to be 32%[6]. Macrosomia, in addition to the perinatal problems, is associated with long term health problems. An increased risk of obesity and diabetes are found in adolescent and in advanced age groups, and it is reported that some childhood cancers are also detected[7]. The complications in infants of diabetic mothers are well known. However, nondiabetic macrosomic children are barely mentioned in the literature. We analyzed the non-diabetic pregnant women and their macrosomic infants.

Objective

To determine risk factors and short term outcomes in infants with fetal macrosomia independent of gestational diabetes

Method

Patient records between 1st January 2007 and 31st December 2010 in Bolu Izzet Baysal Obstetrics-

Gynaecology and Paediatrics Hospital were assessed retrospectively after receiving approval from the Local Ethical Committee. Our hospital in the west side of Turkey is the location where 80% of the births in the region take place. The prenatal records corresponding to the pregnant women and the files corresponding to babies born within 38-42 gestational weeks were studied. The collected data were loaded into SPSS version 17.0 programme. Among the medical records the pregnant women without gestational diabetes and who delivered macrosomic infants and their macrosomic infants were included in the study.

Macrosomia was defined as birth weight of 4000g and above[8]. Babies born outside the hospital and infants of diabetic mothers were excluded from the study. Five hundred healthy infants weighing 2500-3999g, born during the same period were chosen to constitute the control group. The mothers' ages, pregnancy numbers, gestational ages, modes of delivery, birth weights, 1st and 5th minute Apgar scores and caesarean section indications were assessed. The gestational weeks of the cases were determined according to the ultrasound examination and to the last menstrual period. Fetal (intrauterine) death and neonatal death (between 0 – 28 days postnatal) were recorded. 5th minute Apgar ≤7 was accepted as asphyctic birth[9]. Newborns with clinical problems were monitored in the neonatal intensive care unit (NICU) until they were clinically stable. For babies without any clinical problems, the records of monitoring in the hospital for postnatal 48-72 hours were considered.

All infants were routinely evaluated for hypoglycaemia at the first and fourth hour. Hypoglycaemia was defined as blood glucose <40 mg/dL. These infants were also evaluated for polycythaemia at the fourth hour of life. Polycythaemia was defined by a haematocrit value greater than or equal to 65%. Macrosomic babies were compared to the control group during the study. Chi-square test, student-t test, Mann-Whitney test and multiple regression analysis were used to determine statistical significance.

Results

During the 4 year study period there were 10,898 babies of whom 10,861 babies were born in the hospital (alive/dead) and 37 babies were born alive outside the hospital. The birth weights of 509 (4.7%) of these babies were 4000g or more. Birth weights of 21 macrosomic babies born to gestational diabetic mothers and one macrosomic baby born outside the hospital were excluded from the study. Birth weights of the 487 macrosomic babies included in the study ranged from 4000g to 5770g with a mean of 4245±212g. Of the 487 macrosomic infants, 428 (88%) were between 4000-4499g, 53 (11%) between 4500-4999g and 6 (1%) were 5000g and above. Of the babies included in the study, 336 (69%) were male with a male/female ratio of 2.2. In the control group of 500 babies, 235 (47%) were male with a male/female ratio of 0.9. Significantly more macrosomic infants were male compared to controls (p<0.001).

Among the 10,898 pregnant women, 4.1% of 9913 pregnant women aged 35 years or less and 7.3% of 985 pregnant women older than 35 years delivered non-diabetic macrosomic infants. This was significant (p<0.001). Ages of pregnant women delivering non-diabetic macrosomic infants ranged from 15 to 46 years with a mean age of 29.1±5.2 years. Mean age of the controls was 27.7±5.0 years. This was significant (p=0.018). Four percent pregnant women who delivered non-diabetic macrosomic infants were under 20 years of age, 81% between 21-35 years and 15% over 35 years. The number of non-diabetic pregnant women over 40 years was 3%. In 18 of the 19 non-diabetic pregnancies under 20 years of age, in 350 of the 396 non-diabetic pregnancies between 21-35 years of age and in 60 of the 72 non-diabetic pregnancies over 35 years of age, the birth weights of the infants were below 4500g. In 46 (9.4%) non-diabetic pregnancies infants were born with weights above 4500g. Of the 487 non-diabetic pregnant women delivering macrosomic infants 62% were multipara and 38% were nullipara with a mean parity of 2±1. In the control group the mean parity was 1.6±0.7. The parity of non-diabetic pregnant women delivering macrosomic infants was significantly high (p<0.001). Forty seven percent of the macrosomic babies were delivered vaginally and 53% pregnant women underwent caesarean section. In the control group, 52% babies were delivered vaginally and 48% pregnant women underwent caesarean section. No significant statistical differences were detected in mode of delivery between the 2 groups (p>0.05).

In 4 (0.8%) non-diabetic macrosomic babies, birth asphyxia was detected. No statistically significant differences were determined between mode of delivery and birth asphyxia (p>0,05). In the non-diabetic macrosomic babies the mean 1st minute Apgar score was 8.9±0.8 whilst in the controls it was 8.9±0.6. This was not statistically significant (p>0.05). In the macrosomic babies the mean 5th minute Apgar score was 9.7±0.8 compared to 9.9±0.5 in the controls. This was statistically significant (p<0.001). Birth trauma occurred in 20 (4.1%) non-diabetic macrosomic babies compared to 7 (1.4%) control babies. This was statistically significant (p=0.009). The type of birth trauma in the study group is shown in table 1.

Table 1: ***Type of birth trauma***

Birth trauma	Number
Intracranial hemorrhage	01
Brachial plexus paralysis	07
Cephalhaematoma	12
Total	20

During monitoring, 62 (12.7%) non-diabetic macrosomic newborns were hospitalized. Their hospitalization diagnoses are given in Table 2.

Table 2: ***Hospitalization diagnosis of the 62 cases***

Hospitalization diagnosis	Number
Cleft-oral palate	01
Acute renal impairment	01
Neonatal transient tachypnea	02
Respiratory distress syndrome	02
Meconium aspiration	03
Sepsis	09
Neonatal jaundice	44
Total	62

The laboratory findings of the 62 hospitalized non-diabetic macrosomic babies are shown in table 3.

Table 3: ***Laboratory findings in the 62 cases***

Laboratory finding	Number
Polycythaemia	05
Hypocalcaemia	08
Hypoglycaemia	19
Total	32

The mean hospitalization period of the infants was 3.7±2.1 days (range 1-10 days).

Fetal death occurred in 2 (0.4%) non-diabetic macrosomic babies compared to 1 (0.2%) control baby. This was not statistically significant ($p>0.05$). In our study no neonatal deaths occurred.

A multiple regression analysis of risk factors associated with the mode of delivery was carried out. This is shown in table 4.

Table 4: ***Multiple regression analysis of risk factors associated with mode of delivery***

Specification	Caesarean	Vaginal	Odds ratio	%95 CI	p value
Age of pregnant women (years)	28.6 ±5.1	28.5±5.1			0.6
Advanced age pregnancies (n)	38	34	1	0.7-2.9	0.3
No. of pregnancy (n)	1.7±0.8	2.2±1.2			<0.001*
Perinatal mortality (n)	1	1	1.1	0.07-18.2	0.9
Birth weight (g)	4262±218	4216±203			0.058
Apgar 1st score	8.9±0.6	8.9± 0.8			0.4
Apgar 5th score	9.7± (0.7)	9.7± 0.8			0.8
Sex (Male/Female) (n)	182/77	154/74			0.5
Babies weighing over 4500 g (n)	39	20	0.5	0.3-0.9	0.034*
Birth trauma (n)	12	8	0.7	0.3-1.8	0.5
Hypoglycemia (n)	15	4	0.2	0.09-0.8	0.022*
Hypocalcemia (n)	4	4	1.1	0.2-4.6	0.8
Polycythemia (n)	5	0	0.5	0.4-0.5	0.035*
Additional diagnosis (n)	39	19	0.5	0.2-0.9	0.022*
Demand for taking antibiotic (n)	11	6	0.6	0.2-1.6	0.3
Demand for hospitalisation (n)	23	20	1	0.6-1.6	0.9

**Statistically significant*

The number of pregnancies were significantly more in non-diabetic macrosomic babies born vaginally compared to those born by caesarean section ($p<0.001$). Significantly more non-diabetic macrosomic babies weighing over 4500g were delivered by caesarean section ($p=0.034$). The risks of developing hypoglycaemia ($p=0.022$), polycythaemia ($p=0.035$), and additional diagnoses such as respiratory distress syndrome and transient tachypnoea of the newborn ($p=0.022$) were higher in babies born by caesarean section compared to those born vaginally. (Table 4)

Discussion

The frequency of fetal macrosomia varies between 3.4% and 28%[10]. Oral et al. determined the frequency in Turkey to be 6%[11]. The frequency of births over 4500g varies between 0.5% and 6%[10]. In our study, fetal macrosomia was found in 4.7% and infants above 4500g constituted 0.5% of our cases. In our study 88% of the macrosomic infants had birth weights between 4000-4499g, 11% between 4500-4999g and 1% 5000g and above. In the study of Demirören et al., these rates were 68%, 24% and 8% respectively, and in the study of Akin et al., 80%, 17% and 3% respectively[12,13]. Increase

in parity is an important risk factor for fetal macrosomia. Civak, in his study, reported that 58% of the mothers delivering macrosomic infants were multiparous, while Berard et al., found that 78% such mothers were multiparous[14,15]. In our study 62% of the mothers delivering macrosomic infants were multiparous. The parity rate in our study group was significantly high when compared to the control group (p<0.001). The fetal death rate in macrosomic infants is between 0.3% to 0.7%[13,14]. In our study fetal death occurred in 0.4% of the cases. When the macrosomic infants in our study group were compared with the control group, there was no significant difference in fetal death rates (p>0.05). No neonatal deaths were found in our study group. Perinatal mortality in macrosomic infants ranges between 0.8% and 2.6%[14]. The perinatal mortality in our study group was 0.4%.

Majority of macrosomic infants are male[7]. In our study, 69% were male. When macrosomic infants in our study were compared to the control group significant male dominance was noted (p<0.001). The caesarean delivery rate in macrosomic infants varies between 37% and 54%[13]. In our study 53% of macrosomic infants were delivered by caesarean section. In macrosomic fetuses low 1st and 5th minute Apgar scores are reported[16]. In our study group no statistically significant difference was detected in terms of 1st minute Apgar score compared to the control group (p>0.05); however, the 5th minute Apgar score in the macrosomic group was deemed to be significantly low (p<0.001). Perinatal asphyxia in macrosomic infants varies between 0.9% and 4.6%[13]. In our study perinatal asphyxia was found in 0.8% of the cases.

In the study of Essel et al. pregnant women under 20 years constituted 5.7% of the entire series, and pregnant women over 40 years constituted 4.9% of the series[17]. In our study, 3.9% of the pregnant women were under 20 years and 3% were over 40 years. Gestational age over 35 year is an important risk factor for macrosomic infant deliveries[11,13]. The macrosomic infant delivery rate in pregnant women at 35 years and above is determined to be 10.1%[14]. In our study, 4.1% of pregnant women under 35 years and 7.3% of pregnant women over 35 years delivered macrosomic infants. This was statistically significant (p<0.001). Thus, pregnancy after the age of 35 years is an important risk factor for delivering macrosomic infants.

Of the live born macrosomic infants 9.1% were hospitalized[13]. In our study 12.7% were hospitalized. Of the macrosomic infants 2% were detected to have oral-cleft palate, 4% neonatal transient tachypnea, 4% meconium aspiration and 38% neonatal jaundice[12]. In our study 0.2% had acute renal impairment, 0.2% oral-cleft palate, 0.4% respiratory distress syndrome, 0.4% neonatal transient tachypnea, 0.6% meconium aspiration syndrome, 1.8% sepsis and 8.8% neonatal jaundice. When compared to controls, in our study 4.1% of the cases had birth injuries (p=0.009). As the risk of birth trauma in macrosomic infants is high, they should be closely monitored. Birth trauma occurred in 6.4% in the study of Akin et al.[13].

In the study of Schaefer-Graf et al. hypoglycaemia rate in the non-diabetic group was 15%[18]. In our study hypoglycaemia was found in 3.8% cases. In the study of Civak metabolic complications were found in 14.5% cases[14]. With one study reporting that C-peptide level is high in the cord blood of the infants with non-diabetic mothers, it is necessary to measure blood glucose regularly like in the infants with diabetic mothers[19]. In the study of Demirören et al. in 2% of the cases hypocalcaemia and in 4% polycythaemia was detected[12]. In our study in 1.6% of the cases hypocalcaemia and in 1% of the cases polycythaemia were detected. Nassar et al. identified that hypoglycaemia is observed more among macrosomic babies born through caesarean section[20]. The same result was found in our study as well (p=0.022). This result has been related to the fact that mothers do not breast feed their babies for some time until they become conscious and the effects of the anaesthesia during cesarean section has waned.

Polycythaemia is an expected finding in babies born to diabetic mothers[21] and all macrosomic infants have increased red blood cell volume[22]. The risk of developing polycythaemia is significantly more in babies born through caesarean section compared to babies born through vaginal birth (p=0.035). Nassar et al. identified that respiratory morbidity is observed more among macrosomic babies born through caesarean section[20]. In our study morbidity was found to be significantly higher in babies born through caesarean section compared to babies born through vaginal birth (p=0.022).

Conclusion

Advanced age pregnancy, multiparity and male sex were the main risk factors for non-diabetic fetal macrosomia in our study.

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