Associated outcomes to fetal macrosomia: Effect of maternal diabetes

Complications associées à la macrosomie fœtale : Effet du diabète maternel.

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RÉSUMÉ

Introduction : La macrosomie fœtale est associée à un risqué élevé de complications périnatales et maternelles.
Objectif : Déterminer les complications maternelles et périnatales associées à la macrosomie fœtale chez les mères avec ou sans diabète maternel.
Méthodes: Il s'agit d'une étude descriptive rétrospective réalisée en Tunisie. Nous avons inclus toutes les patientes ayant accouché des nouveaux nés ayant un poids de naissance supérieur ou égal à 4 kg durant toute l'année 2013. Une analyse multi-variée a été réalisée pour identifier les complications associées au diabète maternel.
Résultats : Parmi les 10186 accouchements pris en charge pendant la période de l'étude, 821 macrosomes ont été enregistrés. La prévalence de la macrosomie était de 8,1% et des nouveau-nés de poids de naissance de 4500 ou plus était de 1,06%. Le taux d'accouchement par césarienne était de 47,9%. La macrosomie était significativement plus marqué chez le sexe masculin (p <10-3). Les complications maternelles et périnatales les plus fréquentes étaient la déchirure périnéale (3,6%), l'hémorragie du post partum (0,6%), la dystocie de l'épaule (4,9%) et l'admission en unité de soins intensifs (7,6%).La proportion du diabète maternel était de 9,3%. Les complications associées au diabète maternel étaient l'accouchement par césarienne (OR=2,22), l'hémorragie du postpartum (OR=6,69) et l'admission en unité de soins intensifs (OR=4,18).
Conclusion: La macrosomie augmente le risque de morbidité périnatale et maternel en particulier en cas de diabète maternel associé.

Mots-clés
Macrosomie, diabète maternel, Complications Maternelles, Complications périnatales.

SUMMARY

Background: Fetal macrosomia is associated with an increased risk of adverse outcomes to both the mother and the infant.
Aim: To determine maternal and neonatal outcomes associated to fetal macrosomia in diabetic and non- diabetic mothers.
Methods: It is a descriptive retrospective study conducted in Tunisia. We included in this study all patients who delivered newborns having a birth weight above 4kg during 2013. Multivariate analysis was performed using binary logistic regression to identify the complications associated to macrosomic pregnancies with diabetes.
Results: Among the 10186 deliveries registered during the study period, 821 mothers gave birth to macrosomic newborns. The prevalence of macrosomia was 8.1%, and macrosomic newborns who had a birth weight of 4500 g or greater were 1.06%. Macrosomia was significantly higher in males (p <10-3). The rate of cesarean delivery was 47.9%. The most frequent adverse maternal and neonatal outcomes were perineal tears (3.6%), post-partum hemorrhage (0.6%), shoulder dystocia (4.9%) and neonatal intensive care unit admission
(7.6%).The proportion of maternal diabetes was 9.3%. Macrosomic pregnancies with diabetes appear to be significantly associated with cesarean delivery (OR=2.22), postpartum hemorrhage (OR=6.69) and neonatal intensive care unit admission (OR=4.18).
Conclusion: Macrosomia increases the risk of maternal and perinatal morbidity particularly when it was associated to maternal diabetes.

Key-words
Macrosomia, maternal diabetes, maternal outcomes, perinatal outcomes.

Fetal macrosomia which has been defined in several different ways is a term describing a newborn with an excessive birth weight (1). Macrosomia is for the majority of authors defined as a neonate with a birth weight above 4 kg regardless of gestational age or greater than 90% for gestational age after correcting for neonatal sex and ethnicity (90th percentile). In developed countries the prevalence is ranging from 5 to 20%of all births (2).

Other authors consider that macrosomia is a birth weight above 4.5 kg or a birth weight >97th centile. Depending on this definition, the prevalence of macrosomia is 1.3 - 1.5% of all births in developed countries (3).

Fetal macrosomia is associated with an increased risk of adverse outcomes to both the mother and the infant (4). The most common neonatal complications are perinatal asphyxia, death, birth injury, hypoglycemia, meconium aspiration syndrome and shoulder dystocia (4-6). Macrosomia increases the risk of caesarean section, prolonged labor, postpartum hemorrhage, infection, third- and fourth-degree perineal lacerations, and thromboembolic events among mothers of macrosome newborns (4-6).

In the literature, identified risk factors associated with increased birth weight are maternal obesity and diabetes, multiparity, advanced maternal age, ethnicity and excessive weight gain during the pregnancy (4). However, the strength of association between each of the identified risk factors and macrosomia is variable. Among these identified risk factors, maternal diabetes appears to be one of the strongest risk factors associated with macrosomia (1).

In contrast with developed countries, studies on macrosomia in developing countries such as Tunisia are scarce. Furthermore, adverse outcomes due to macrosomia can lead to additional maternal and fetal risks in a resource-limited context because of the restricted availability of obstetric emergency and other essential care (7).

In this context, we conduct this study to determine maternal and neonatal outcomes associated to fetal macrosomia in diabetic and non-diabetic mothers in the University Hospital Hedi Chaker (Sfax, Tunisia).

METHODS

This is a cross-sectional study conducted in the department of Obstetrics of the University Hospital Hedi Chaker (Sfax, Tunisia) from 1st January 2013 to 31st December 2013.The research protocol was approved by the Ethics Committee of the hospital. During the study period, 10186 deliveries were registered. The couple macrosomic newborn-mother was included in the study. Macrosomia was defined as a birth weight above 4 kg. Macrosomic newborns transferred to hospital after delivery at home or in another health facility were not included in the study.

A data collection form designed for the purposes of the present study was used to collect from the obstetrical and neonatal records the following data: maternal characteristics (age, parity, gestational term, medical history of hypertension or/and diabetes, previous history of macrosomia or/and fetal death in utero and the delivery mode), neonatal characteristics (birth weight, gender and Apgar score) and fetal and maternal outcomes. Maternal outcomes that were assessed included perineal lacerations, postpartum hemorrhage, uterine atony and uterine hypertonia. Fetal complications were perinatal mortality, respiratory distress, traumatic complications including shoulder dystocia, hypoglycemia and Neonatal Intensive Care Unit admission.

Gestational age was established by providers, and was based on the last menstrual period, ultrasound, and physical exam (6). Diabetes was defined as either pregestational or gestational diabetes of any type (6). The diagnosis of diabetes among mothers was based on the criteria for diabetes established by the American Diabetes Association (8).

Hypertension was defined as any pregestational or gestational hypertensive disorder complicating pregnancy (6), a 5-minute Apgar score below 7 was considered abnormal , perinatal mortality was calculated according to the WHO definition which is death of the child during the period between the 24th week of gestation and the end of the first week of life (including stillbirths) (9), newborns having blood glucose <40 mg per 100 ml were considered with hypoglycemia (10) and finally postpartum Hemorrhage was considered as an estimated blood loss of more than 500 ml (11).

Statistical analysis was performed using SPSS 18.0 for Windows, and Epi info 6.0.Categorical variables were described by valid percentages, and quantitative variables were described by means and standard deviation. The Chi-2 test was used to compare frequencies. Multivariate analysis was performed using binary logistic regression to identify the complications associated to macrosomic pregnancies with diabetes. A two-tailed p-value of < 0.05 was considered the threshold for statistical significance.

RESULTS

Characteristics of the population study and prevalence of macrosomia

Among 10186 deliveries registered during the study period, 821 mothers gave birth to macrosomic newborns, the prevalence of macrosomia was 8.1%.Macrosomic newborns with a birth weight above 4.5 kg represented 1.06% of all deliveries. The mean birth weight was 4225.9 g ± 226g with extremes ranging from 4000g to 5400g. Newborns with a birth weight between 4000g and 4500g represented 86.8% (n = 713) of all macrosomic newborns. Macrosomic newborns from a diabetic mother

represented 9.3%of the cases of macrosomia (n=76).
The mean age of women was 30.9 ± 5.5 years with extremes of 17 and 45 years. In 43.5% of cases, women were aged more than 30 years old. Women were married in 99.9% of cases (n = 820).Among the mothers, 72.8% (n=598) were multiparous. Pregnancies were followed by a health care provider in 99.1% of cases (n = 814), and macrosomia was suspected by ultrasound among 2.1% of them. More than half of mothers had a gestational term between 37 and 41 weeks (69.7%, n = 565), while post term pregnancy (term over 41SA) was observed among 28.7% of cases (n=233). A fundal height greater than 34cm was found among 42.6% of women (n = 344). Pregnancy-associated diseases were dominated by diabetes (9.3%, n = 76). Hypertension was found in 1.8% of cases (n=15). A history of macrosomia and an in utero fetal death were respectively noticed in 17% and 0.9% of the cases.

Maternal and neonatal adverse outcomes

In our study, cesarean delivery was performed in 53% of cases (n=435) and perineal lacerations (3.6%, n=30) were the most frequent maternal adverse outcome (Table 1).
Our results showed that macrosomia was significantly higher in males 66.3% (n = 544) (p<10-3) with a ratio between boys and girls of 1.96. Perinatal mortality rate was 0.85(6 cases of fetal death in utero and 1 case secondary to fetal distress). Among the macrosomic newborns, 1.3% (n= 11) had other traumatic complications than shoulder dystocia (Erb'splasy (4 cases), Fracture of the clavicle (2 cases), cutaneous emphysema (1 case), extensive bruising (1 case), edema of the eyelids (1 case), edema of the scalp (1 case) and paralysis of the foot (1 case) (Table1).

Table 1: Repartition of women and macrosomic newborns according to morbidity and mortality

Morbidity and mortality	Number (n)	Percentage (%) Women morbidity
Women morbidity		
Perineal lacerations	30	3.6
Postpartum hemorrhage	5	0.6
Uterine hypertonia	2	0,2
Uterine atony	2	0,2
Perinatal morbidity		
5 mn-Apgar<7	9	1,1
Neonatal respiratorydistress	25	3.1
Shoulder dystocia	40	4.9
Other traumatic complications	11	1.3
Hypoglycemia	9	1.1
Perinatalmortality	7	0.85
NICU admission	62	7.6

NCIU: Neonatal Intensive Care Unit, mn: Minutes

Associated outcomes in relation to maternal diabetes

Among the 76 diabetic women giving birth to macrosomic newborns, 64.5% (n=49) underwent a cesarean delivery. It was an elective cesarean delivery in 95.9% of cases (n=47). In only 2 patients, an emergency cesarean section was indicated during labor.
In the univariate analysis, cesarean delivery (p=0.001), postpartum hemorrhage (p=0.04) and neonatal intensive care unit (NICU) admission (p<10-3) were significantly higher among macrosomic pregnancies with diabetes (Table 2).
After binary regression, macrosomic pregnancies with diabetes appear to be significantly associated with cesarean delivery (p=0.02), postpartum hemorrhage (p=0.04) and NICU admission (p<10-3) (Table 2).

Table 2: Neonatal and maternal outcomes with and without maternal diabetes

Outcomes		Maternal diabetes n (%) Yes	No	p	ORa	95% CI	p
Cesarean delivery	**Yes**	49 (12.7)	337 (87.3)	0.001	2.22	[1.33-3.68]	0.02
	No	27 (6.2)	408 (93.8)				
Perineal lacerations	**Yes**	4 (13.3)	26 (86.7)	0.64	-	-	-
	No	72 (9.1)	719 (90.9)				
Postpartum hemorrhage	**Yes**	2 (40)	3 (60)	0.07	6.69	[1.03-3.48]	0.04
	No	74 (9.1)	742 (90.9)				
Uterine hypertonia	**Yes**	1 (50)	1 (50)	0.17	-	-	-
	No	75 (9.2)	744 (90.8)				
Uterine atony	**Yes**	0 (0)	2 (100)	0.99	-	-	-
	No	76 (9.3)	743 (90.7)				
5 mn-Apgar<7	**Yes**	1 (11.1)	8 (88.9)	0.58	-	-	-
	No	75 (9.2)	737 (90.8)				
Perinatal respiratory distress	**Yes**	2 (8)	23 (92)	0.99	-	-	-
	No	73 (9.3)	716 (90.7)				
Shoulder dystocia	**Yes**	3 (7.5)	37 (92.5)	0.91	-	-	-
	No	73 (9.3)	708 (90.7)				
Neonatal hypoglycemia	**Yes**	3 (33.3)	6 (66.7)	0.04	-	-	-
	No	72 (8.9)	733 (91.1)				
Perinatal mortality	**Yes**	76 (9.3)	738 (90.7)	0.99	-	-	-
	No	0 (0)	7 (100)				
NICU admission	**Yes**	17 (27.4)	45 (72.6)	<10-3	4.18	[2.23-7.86]	$<10^{-3}$
	No	58 (7.7)	696 (92.3)				

DISCUSSION

In our study, among the 10186 deliveries registered during the study period, 821 mothers gave birth to macrosomic newborns. The prevalence of macrosomia was 8.1%, and macrosomic newborns who had a birth weight above 4.5kg were 1.06%. Macrosomia was significantly higher in males. The rate of cesarean delivery was 47.9%. The most frequent adverse maternal and neonatal outcomes were perineal tears, shoulder dystocia and neonatal intensive care unit admission. The proportion of maternal diabetes was 9.3%. Macrosomic pregnancies with diabetes appear to be significantly associated with cesarean delivery, postpartum hemorrhage and Neonatal intensive care unit admission.

This study has limitations. First, data were collected retrospectively from a single center rather than multiple centers, therefore our sample could not be representative and results could not be generalized. In addition, the lack of the control group is another limitation and, in consequence, no comparison was performed between macrosomic and eutrophic newborns to identify the determinants and the risks of macrosomia. Despite its limitations, our study has strengths. It consists mainly of the large sample which increases the precision of our estimates and the power of the study to draw conclusions. It has also provided important Tunisian data on macrosomia.

In this study, comparison of our results with other studies should be done with caution. In fact, differences can be related to differences in methodology and/or in simple size. the prevalence of macrosomia was 8.1%. Denguezli et al (12), in their food intake survey, a cross sectional study conducted between 2002 and 2003 in Monastir, found that among the 350 surveyed pregnant women at term, 14.8% gave birth to a macrosomic infant. In a retrospective case control study conducted in 2007 in the department of Obstetrics of the Mahmoud El Matri Hospital among 209 macrosmic deliveries, El Fekih et al (13) reported a rate of macrosomia (Birth weight above 4kg) of 9.2%.

The rate of macrosomia in Tunisia is expected to increase because of the increase in risk factors for macrosomia, including obesity and diabetes (14).

The prevalence of macrosomia (birth weight above 4kg) varies between populations and ranges from 5 to 20% (2). An overall of 15 to 25% increase in the prevalence of macrosomia has been found in different populations around the world throughout the past three decades, with a few exceptions such as the United States (2, 15).

This increase may be related to higher maternal weight gain during pregnancy, increase in frequencies of maternal obesity and diabetes, and reduced smoking in pregnant women (4). Nordic countries have the highest prevalence which is around 20% (2).

In 23 developing countries in Africa, Asia and Latin America, according to a secondary data analysis with WHO's Global Survey on Maternal and Perinatal Health of 276 436 deliveries, Koyanagi et al (7) noted a large variation in the prevalence of newborns with birth weight above 4kg ranging from 0.5% in India, to 14.9% in Algeria. In our study, the prevalence of macrosomic newborns having a birth weight above 4.5 kg was 1.06%. This result was similar to that found in Turkey (16) (1.3%) and in the United States (15) (1.5-1.3%).

The mean age of women in our study was 30, 9 ± 5.5 years. Our results are consistent with several studies (1,17,18). Maternal age appears to be a non-modifiable risk factor for macrosomia (2,7). Other factors that may be considered non-modifiable include parity and fetal sex (2). The majority of women in our study (72.8%) were multiparous. These results were in concordance with those found by other studies (18). Indeed, macrosomia was significantly higher in males (66.3% versus 33.7, p <10-3) with a ratio between boys and girls of 1.96. Similarly, Akin et al (16) found a male/female sex ratio of 1.96. In the case control study of Mardani et al (19) conducted in Iran during July-September 2010 among 600 live births, the incidence of macrosomia (fetal birth weight above 4kg) in male infants is 2.33 times higher than female neonates. Various hypotheses have been proposed to explain why girls are born lighter than boys. Wilkin and Murphy (20) suggested that gender-specific genes affecting insulin sensitivity are responsible for the gender difference in birth weight. According to them, the female fetus is genetically more insulin resistant and less responsive to the trophic effects of insulin and is therefore smaller (20).

A previous macrosomic birth was found among 17% of women. In consistence with our findings, Mai et al (18) found that14.1% of women had a previous macrosomic delivery. According to The American College of Obstetricians and Gynecologist (ACOG) (21), women with a history of one macrosomic infant are at significantly increased risk of another macrosomic infant in a subsequent pregnancy.

In our study, the proportion of diabetes among women was 9.3%. In concordance with our findings, Gyurkovits et al (22) in their case control study conducted in Hungary between 2008 and 2009 among 5167 pregnant women found a proportion of 10.5% of maternal diabetes among macrosomic group. El Fekih et al (13) reported that 10.5% of the women delivering a macrosomic infant were diabetic. In the retrospective study of Alsammani et al (17) conducted in Saoudia Arabia in 2011 among 418 macrosomic newborns (birth weight above 4kg), a lower proportion of diabetes (4.4%) was found. Similarly, in the study of Mai et al (18) conducted in Algeria between 2012 and 2013, 1.8% of women giving birth to macrosomic newborns (birth weight above 4kg) were diabetic. However, Najafian et al (1), in their cohort study conducted in Iran from 2007 to 2011 among 201,102 pregnant women found that, among the macrosomic

group (birth weight above 4kg), 39.5% were diabetic. In the literature, it is well established that diabetes in pregnancy (pre-gestational as well as gestational) is associated with a significant risk of fetal macrosomia (2). Macrosomia includes several adverse outcomes for both the fetus and the mother (2). It increases the risk of maternal morbidity such as cesarean delivery, prolonged labor, postpartum hemorrhage, uterine atony and perineal tears. It is also associated with an increased perinatal mortality and morbidity including shoulder dystocia, respiratory distress and hypoglycemia (2).

In the literature, it is recognized that macrosomia generally increases the risk of cesarean delivery. In our study, 47.9% of women underwent cesarean section. This rate is similar to that reported in the studies of Alsammani et al (17) and Gyurkovits et al (22) where respectively 47.6% and 49.3% of macrosomic newborns were delivered by cesarean section. However the rate of cesarean section in our study was higher than that reported by El Fekih et al (13) in their case-control study conducted in the Mahmoud El Matri Maternity Hospital, where 24.4% of macrosomic newborns were delivered by cesarean section. This rate is also higher than the national rate of cesarean section which was 26.7% between 2008 and 2012 (23). Management of pregnancies with suspected fetal macrosomia is challenging for clinicians (21). Our high rate of cesarean section is explained by our protocol in managing cases of prior diagnosed macrosomia where elective cesarean section is proposed to prevent several of the complications associated with fetal macrosomia, particularly brachial plexus injuries and maternal perineal lacerations. Our protocol consisted in performing at 39 weeks of pregnancy a systematic elective cesarean section systematically in women with diabetes (pre-gestational and gestational diabetes) with an estimated birth weight above 4kg in cephalic presentation and above 3.8 kg in breech presentation. For non diabetic women, vaginal delivery is undertaken when birth weight is inferior to 4.25kg if the obstetric conditions were favorable. However, there are women with the indications above who underwent an emergency cesarean section because they were not followed in our university department but referred during labor from regional maternities or private clinics. Nonetheless, in our study, because of the retrospective character of data collection, we could not give the evidence specifying the contribution of the large fetus in the choice of the cesarean delivery.

According to the recommendations of the ACOG, prophylactic cesarean delivery may be considered for suspected fetal macrosomia with estimated fetal weight above 5 kg in pregnant women without diabetes and above 4.5kg in pregnant women with diabetes (21,24). Other studies initiated a quality improvement tool to reduce primary caesarean section rates (25).

In our study, maternal complications have included perineal lacerations (3.6%), postpartum hemorrhage (0.6%) and uterine atony (0.6%).The low rates of postpartum hemorrhage and uterine atony can be explained by the high rate of cesarean section. In the literature, proportions of maternal complications were approximately similar to those found in our study. Thus, Alsammani et al (17) reported that respectively 1.7% and 1.2% of the macrosomic deliveries were complicated by perineal tears and postpartum hemorrhage. Najafian et al (1) noted in their study, that vaginal lacerations and uterine atony have been complicated respectively in 4.9% and 11% of deliveries of macrosomic newborns. The risk of perineal tears (grade III) increased 3 to 6 times when birth weight exceeds 4500g in comparison of a birth weight below 4500g. This risk is highest if shoulder dystocia occurs and/or operative vaginal delivery is performed (2).

In our study, perinatal adverse outcomes were shoulder dystocia (4.9%), NICU admission (7.6%), hypoglycemia (1.1%), respiratory distress (3.1%), low 5min-apgar (1.1%) and perinatal mortality (0.85%). Shoulder dystocia was found in respectively 9.6% and 11% of macrosomic infants in the studies of Alsammani et al (17) and Najafian et al (1). Gyurkovits et al (22) reported that the prevalence of hypoglycemia, respiratory distress, NICU admission and a 5-min apgar< 7 were respectively 6.1%, 5.1%, 5.1% and 0.9%.

In our study, comparing the maternal and perinatal outcomes in relation with macrosomia with and without maternal diabetes, macrosomic pregnancies with diabetes appear to be significantly associated with cesarean delivery, postpartum hemorrhage and NICU admission.

In a similar comparison, Gyurkovits et al (22) found that neonates of diabetic mothers had significantly higher incidence of hypoglycemia, hyperbilirubinemia and cardiomyopathy.

Esakoff et al (5) in their retrospective cohort conducted in USA (California, San Francisco) between 1982 and 2006 comparing adverse perinatal outcomes in macrosomic infants (birth weight above 4 kg) in women with and without gestational diabetes, found that the risk of hypoglycemia, shoulder dystocia, respiratory distress syndrome and brachial plexus injury were higher among neonates of diabetic mothers. When both macrosomia (birthweight above 4kg) and gestational diabetes are present, the effect estimates of these outcomes appear to be more than additive. Shoulder dystocia and Erb's palsy carry the greatest risk increase compared with the other outcomes. Authors suggested that the greatest risk increase compared with the other outcomes could be due not only to the increased birth weight but also its anthropometric distribution (5).

The association of maternal diabetes and macrosomia lead to an increase in the abdominal transverse diameter / biparietal diameter ratio and in consequence an increase

in the risk of shoulder dystocia and the brachial plexus injury. However, in our study, shoulder dystocia as well as the brachial plexus injury were not found to be more associated to fetal macrosomia and maternal diabetes. This could be explained by our protocol consisting in performing an elective cesarean when macrosomia is associated with maternal diabetes. In addition, this group (maternal diabetes associated to macrosomia) represents only 9.3% of our macrosomic sample. A study with a larger sample may have found this risk.

In addition to its short term adverse outcomes, macrosomia is associated with long term risks that seem to include diabetes, overweight, metabolic syndrome, asthma, persistent plexus injuries and cancer (2), but these complications were not evaluated in our study.

Regarding its well established associated maternal and neonatal complications, macrosomia should deserve a continual attention.

Despite the paucity of studies focusing on the effect of intervention before and/or during pregnancy on the risk of macrosomia, preventive measures should primarily be implemented before pregnancy and should include appropriate education of mothers about nutrition and physical activity in order to reduce the prevalence of overweight (2).

In addition, good blood glucose control both before and during pregnancy helps to prevent macrosomia and other complications such as maternal and neonatal trauma during birth, induction of labor and/or cesarean section, neonatal hypoglycemia and perinatal death in women with pre-existing or gestational diabetes.

Further prospective and multicenter researches are required to determine the factors involved in the occurrence of macrosomia and its short and long term risks.

Conflicts of interest

Authors declare no conflicts of interest.

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