

THE ROLE OF UMBILICAL CORD THICKNESS AND GLYCATED HEMOGLOBIN (HBA1C) LEVELS FOR PREDICTION OF FETAL MACROSOMIA IN PATIENTS WITH GESTATIONAL DIABETES MELLITUS

By

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ABSTRACT

Background: Diabetes with pregnancy is a known clinical risk factor associated with fetal macrosomia. The rationale for performing an elective cesarean section includes a potential reduction in perinatal complications, especially those related to macrosomia.

Objective: This study aimed to assess the accuracy of Glycated hemoglobin (HbA1c) and umbilical cord thickness in prediction of fetal macrosomia in diabetic pregnant women.

Patients and methods: The study included 100 diabetic pregnant, 27 - 28 weeks gestation, gathered from Inpatients and Obstetric Outpatient Clinic of Bab Alshariya University Hospital during the period between November 2018 and August 2019, attending for routine antenatal care.

Results: At a criterion of > 211 mm², the umbilical cord area measured at 27 – 28 weeks of gestation was able to predict high birth weight (macrosomia), with a sensitivity of 90.5% and a specificity of 91.7%. The area under the curve for the receiver operating characteristic (ROC) was 0.9294, with a 95% confidence interval of 0.8608 to 0.9702, which was found to be statistically significant. When compared the ROC curves of both the umbilical cord area and the glycated hemoglobin, it was found that umbilical cord area was more reliable in predicting fetal macrosomia at the right criterion, the difference between the predictive efficiency for both parameters was found to be statistically significant.

Conclusion: Macrosomia is a cause of the worst of obstetric emergencies such as shoulder dystocia, birth asphyxia and postpartum haemorrhage. Shoulder dystocia cannot always be predicted accurately. However, predicting macrosomia can help to identify the population at risk of such complications.

Keywords: Umbilical cord thickness, Glycated hemoglobin (HbA1c), Macrosomia, Gestational diabetes mellitus.

INTRODUCTION

The umbilical cord is responsible for maternal-fetal blood flow. Normally, it is composed of two arteries permeated with venous blood and a vein that transports arterial blood, cushioned by a special type of mucous connective tissue known as

Wharton's jelly (WJ) and by remnants of the allantoides (*Marino et al., 2019*).

Reported risk factors of macrosomia are body mass index (BMI) before pregnancy, gestational weight gain, gestational diabetes mellitus (GDM), mother's age and gender (*He et al., 2015*).

GDM is associated with many adverse pregnancy outcomes such as macrosomia and CS delivery (*Barakat et al., 2010*). At the same time macrosomia is a well-known indicator of maternal diabetes in fetus which is strongly associated with prematurity, respiratory distress syndrome, birth trauma, fetal death and adverse maternal outcome (*Yessoufou and Moutairou., 2011*). Obesity in pregnancy is also recognized as a risk factor for many maternal and neonatal adverse outcomes including macrosomia, increased rate of cesarean section (CS), preeclampsia and gestational diabetes (GDM) (*Athukorala et al., 2010*). In addition, the placenta, as the interface between mother and fetus, is central to prenatal growth control. The fetus is dependent upon the placenta for its supply of nutrients and oxygen from the mother. Previous research found that the placental weights in the macrosomic fetuses were significantly higher than those with normal weight and placental weight was positively correlated with birth weight (*Zhang et al., 2015*). Fetal macrosomia is associated with a higher frequency of operative deliveries, post-partum hemorrhages, birth injury during vaginal delivery and neonatal hypoglycemia. Known maternal risk factors are only identified in 40% of women who deliver macrosomic babies (*Auger et al., 2013*). Macrosomia has been suggested as one of the possible risk factors for obesity in many studies (*Mandal et al., 2011*).

Diabetes represents a major public health concern and efforts to control hyperglycemia are an important element of the management of patients with type 2 diabetes. Hyperglycaemia is measured using hemoglobin A1c (HbA1c) test,

which assesses the average level of blood glucose in the preceding 60-120 days. For diabetic patients an HbA1c target of 6.5% (48 mmol/mol) is recommended (*International Diabetes Federation, 2013*).

Gestational diabetes mellitus (GDM) affects 2-6% of pregnant women and is associated with increased risk of important adverse perinatal outcomes, including macrosomia and birth injury (*Beta et al., 2019*). Therefore, for the prevention of traumatic birth and adverse outcomes, many studies have been performed for predicting birth weight accurately. Through the accurate prediction of macrosomic fetuses that have risk of traumatic birth, the route of delivery may be changed. Ultrasound-based birth weight prediction is still insufficient. Investigators have attempted to improve ultrasound-based prediction of fetal macrosomia by various methods, such as the assessment of fat deposition at different locations. None of these methods have gained wide popularity because of the inability to accurately estimate fetal weight against conventional biometric formulas (*Elessawy et al., 2017*).

Studies that have assessed umbilical cord components to predict fetal weight have shown that there is a correlation between umbilical cord diameter, area and fetal biometric parameters (*Cordero et al., 2015*). In addition, some observers have suggested that combination of these two methods should give more reliable results for estimating macrosomic fetuses (*Birol et al., 2012*).

PATIENTS AND METHODS

Setting: Bab Alshariya Hospital, Al-Azhar University.

Duration: during the period between November 2018 to August 2019.

Design: Prospective - observational study to assess the accuracy.

Population: The study included 100 diabetic pregnant, 27 - 28 weeks gestation, gathered from Obstetric Inpatients and Outpatient Clinic of Bab Alshariya University Hospital attending for routine antenatal care. The required sample size has been calculated using IBM® Sample Power® version 3 (IBM® Corp., Armonk, NY).

Diagnostic criteria of gestational diabetes mellitus:

1. Fasting plasma glucose level 126 mg/dl (7.0 mmol/l).
2. Random plasma glucose level 200 mg/dl (11.0 mmol/l).
3. HbA1C 6.5%.

All included women after informed consent was subjected to:

- a. Full history taking including personal, menstrual and past history.
- b. Calculation of gestational age was based on the date of their last reliable menstrual period according to Naegele's rule and confirmed by ultrasound examination within the first trimester.
- c. Abdominal examination to assess the fundal height and estimated fetal weight.
- d. Ultrasound examinations were performed with a Medison RS 3.7-mHz

Convex transabdominal probe to measure umbilical cord thickness at 27-28 weeks gestation and repeated at 36-37 weeks gestation.

- e. Ultrasonographic examination included fetal anthropometric parameters, biparietal diameter (BPD), femur length (FL) and estimated fetal weight (EFW), which were calculated automatically according to Hadlock's formula.
- f. HbA1c levels were measured at 27 - 28 weeks and at full term. Measuring HbA1c can reveal as to how high the blood glucose has been on an average, over the past 8-12 weeks.

A normal non-diabetic HbA1c value is 3.5-5.5%. In diabetics, range of 6.5% to 7% is good. In individuals with poorly controlled diabetes, the quantity of this Glycated Hb is much higher than in healthy people (*Kuenen et al., 2011*).

- g. Macrosomia was considered when estimated fetal weight is over 4,000 gm.
- h. Follow up of the patients at birth included mode of delivery, birth weight and fetal sex.
- i. Population variability included age, BMI, parity, mode of delivery, estimated birth weight by ultrasound, birth weight, HbA1c and umbilical cord thickness.

Inclusion criteria:

Pregnant women with:

1. 27 - 28 weeks gestation
2. Diabetes mellitus
3. Singleton gestation

4. Normal umbilical morphology (two arteries and one vein).

Exclusion criteria:

1. The presence of fetal congenital anomalies
2. Multifetal pregnancy
3. Pregestational diabetes mellitus
4. Maternal chronic diseases (hypertension, renal disease, cardiac and pulmonary disease, etc.).
5. Patients with a diagnosis such as placenta previa, oligohydraminous, preeclampsia and intrauterine growth restriction.
6. Smoking or alcohol consumption during pregnancy.
7. Preterm delivery

The hospital Ethics Committee approved the study: The population sample under study was instructed about research protocol and signed informed consents were taken from each woman before inclusion in the study.

Statistical methods

Data were collected, tabulated, then analyzed using IBM© SPSS© Statistics version 22 (IBM c Corp., Armonk, NY). Normally distributed numerical data was

presented as mean and SD and skewed data as median and interquartile range. Qualitative data was presented as number and percentage. Comparison of normally distributed numerical data was done using the unpaired student t-test. Skewed data was compared using Mann-Whitney U test. Categorical data were compared using Chi-squared test, or Fisher's exact test when appropriate. Receiver-operating characteristic (ROC) curve analysis was used to examine the value of the umbilical cord thickness or HbA1c level for prediction of fetal macrosomia. A two-sided p-value less than 0.05 were considered statistically significant. This sample size had a power of 91% (type II error, 0.09) to detect statistical significance for a difference of 0.25 between a null area under the ROC curve (AUROC) of 0.5 and an alternative AUROC of 0.75 associated with the umbilical cord thickness or HbA1c level. An AUROC of 0.75 has been chosen as it is considered to be the least AUROC for a diagnostic/predictive test to be clinical relevance.

This calculation used a two-sided z test with a confidence level of 99% (type I error, 0.01).

RESULTS

The primary outcome was the feasibility of prediction of fetal macrosomia using umbilical cord area (thickness) and the Glycated hemoglobin (HbA1c) level.

The maternal age did not differ significantly between both groups, most of them were between 20 and 30 years of age

(36%, 39%, respectively), However, almost one-third of group (2) women were above 30 years of age (31 – 35 years; 25%, respectively), however, still no significant difference was noted when compared the proportions in the two groups. Group (1) had a mean maternal age of 26.6 ± 4.4 years, group (2) had a

mean maternal age of 27.1 ± 3.8 years and the total sample had a mean maternal age of 27.2 ± 4.1 years old. As regards the gravidity, both groups differed significantly where group (1) subjects/women had a mean of 3.6 ± 1.3 against 2.5 ± 1.2 for group (2) subjects/women, however, both group did not differ in parity. Macrosomic group had a higher proportion of female sex fetuses (60%) against 40% male fetuses and non-macrosomic group showed 44% males and 56% females. however, when compared males and females proportion against each group did not differ significantly. Among the 15 patients who delivered macrosomic fetus, 5 women (33%) were obese, 8 (54%) were

overweight and 2 (13%) were normal. As regards the gestational age at delivery, the total sample had a mean gestational age 37.1 ± 1.2 weeks. In comparing both groups regarding the number of deliveries at full term and post-term, no statistically significant difference was found. However, both groups differed in the birth weight of the delivered fetuses, group 1 had a mean birth weight of 3924.9 ± 418.3 gm (for 15 fetuses) versus 3332.3 ± 296.1 gm (for 85 fetuses), which was highly significant ($p < 0.0001$). Moreover, due to large baby size, both subgroups differed significantly as regards the mode of delivery, where 74% of group (1) women delivered by cesarean section against 42% of group (2) women (Table 1).

Table (1): Comparison between both groups as regards the baseline parameters/ characteristics

Parameters		Group 1: Macrosomic fetuses (n= 15) Mean \pm SD	Group 2: Non- Macrosomic fetuses (n= 85)	P-value	Total sample (n=100)	
Maternal age (years)		26.6 ± 4.4	27.1 ± 3.8	.65	27.2 ± 4.1	
	20 – 25	5 (33%)	29 (34 %)		0.85	36 (36 %)
	26 – 30	7 (47 %)	34 (40 %)			39 (39 %)
	31 – 35	3 (20%)	22 (26 %)			25 (25 %)
Gravidity		3.6 ± 1.3	2.5 ± 1.2	0.01	3.0 ± 1.1	
Parity		3.0 ± 1.4	2.7 ± 1.2	0.2	2.3 ± 1.2	
Fetal sex	Male	6 (40%)	38 (45%)	0.7	44 (44%)	
	Female	9 (60%)	47 (55%)		0.62	56 (56%)
Body mass index (BMI)	19- 24.9	2 (13%)	45 (53 %)	<0.002	47 (47 %)	
	25-29.9	8 (54%)	34 (40 %)		42 (42 %)	
	≥ 30	5 (33%)	6 (7 %)		11 (11 %)	
GA at delivery (Weeks)		36.1 ± 2.2	36.9 ± 1.7	0.52	37.1 ± 1.2	
	34 - 40	13 (95%)	78 (92%)		91 (91 %)	
	> 40	2(5%)	7 (8%)		9 (9 %)	
Birth weight (gm)		3924.9 ± 418.3	3332.3 ± 296.1	<0.001	3418.3 ± 378.2	
Mode of delivery	Cesarean Section	11 (74%)	36 (42 %)	< 0.03	47 (47 %)	
	Vaginal Delivery	4 (26%)	49 (58 %)		53 (53 %)	

As regards the glyated hemoglobin, both groups did not differ significantly when compared at 27 – 28 weeks of gestation, where subgroup 1 had a mean HbA1c of $6.1 \pm 0.2\%$ vs $6.3 \pm 0.3\%$ for subgroup 2, while the total sample had a mean of $6.2 \pm 0.4\%$. At 36 – 37 weeks of gestation, we found that group 1 had a higher HbA1c levels than group 2 ($6.4 \pm 0.3\%$ vs $5.8 \pm 0.4\%$, respectively), which was statistically significant ($p < 0.0001$), while the total sample had a mean of $6.1 \pm 0.3\%$.

Both subgroups differed significantly as regards the umbilical cord area, group 1 had a mean UCA of $213.1 \pm 2.8 \text{ mm}^2$ at 27 – 28 weeks of gestation against $204.2 \pm 2.1 \text{ mm}^2$ for group 2. While the total sample had a mean UCA of $209.1 \pm 3.2 \text{ mm}^2$. At 36 – 37 weeks of gestation, the total sample had a mean UCA of $219.1 \pm 6.8 \text{ mm}^2$. Group (1) had a mean of $232.1 \pm 3.1 \text{ mm}^2$ against $215.4 \pm 4.3 \text{ mm}^2$ for group (2) (**Table 2**).

Table (2): Comparison between both groups as regards the glyated hemoglobin levels (HbA1c %), and the umbilical cord area (UCA mm²), measured at 27 – 28 weeks and 36 – 37 weeks of gestation

Parameters		Group 1 Macrosomic fetuses (n= 15)	Group 2 Non- macrosomic fetuses (n= 85)	P-value	Total sample (n= 100)
HbA1c (%)	27- 28 Weeks of Gestation	6.1 ± 0.2	6.3 ± 0.3	0.02	$6.2 \pm .4$
	36- 37 Weeks of Gestation	6.4 ± 0.3	5.8 ± 0.4	<0.0001	6.1 ± 0.3
UCA (mm ²)	27- 28 Weeks of Gestation	213.1 ± 2.8	204.2 ± 2.1	<0.0001	209.1 ± 3.2
	36- 37 Weeks of Gestation	232.1 ± 3.1	215.4 ± 4.3	<0.0001	219.1 ± 6.8

When correlated the birth weight to the umbilical cord area in group 1 (Macrosomic fetuses), it was found that there was a strong, dependent and positive (direct) correlation between both parameters, either measurement at 27 – 28 weeks or measurement at 36 – 37 weeks of gestation ($r = 0.7340$ & 0.7483 , respectively). Moreover, these correlations

were found to be statistically highly significant ($p = 0.0002$ & 0.0001 , respectively). The glyated hemoglobin neither had a strong nor significant correlation with the birth weight, neither measurement at 27– 28 weeks nor measurement at 36– 37 weeks of gestation (**Table 3**).

Table (3): Relationship between birth weight (gm), the umbilical cord area (UCA mm²), and the glycated hemoglobin (HbA1c %) measured at 27 – 28 weeks and 36 – 37 weeks of gestation in group 1 (Macrosomic fetuses; n= 15)

Parameters \ Relationship		Correlation Coefficient value (r)	95% CI for r	P-value
HbA1c %	27 - 28 Weeks of Gestation	-0.06735	-0.4912 to 0.3844	0.7
	36 - 37 Weeks of Gestation	0.3886	-0.06157 to 0.7102	0.08
UCA (mm ²)	27 - 28 Weeks of Gestation	0.7340	0.4452 to 0.8903	0.0002
	36 - 37 Weeks of Gestation	0.7483	0.4611 to 0.8934	0.0001
CI: Confidence Interval,				

DISCUSSION

The relationship between umbilical cord components, HbA1c, and fetal macrosomia was evaluated at 27-28 gestational weeks. Macrosomic fetuses were compared to non-macrosomic fetuses. Umbilical cord area and Wharton's jelly values were statistically different for each group. Cord diameter, umbilical artery and vein area values were not statistically different between groups at this gestational time point. However, at 36-37 gestational weeks at the second examination, an assessment of the relationship between umbilical cord components and fetal macrosomia revealed that all umbilical cord parameters were statistically different for both groups when macrosomic fetuses compared to non-macrosomic ones. As regards the glycated hemoglobin, both groups did not differ significantly when compared the levels measured at 27-28 weeks of gestation. While, at 36-37 weeks of gestation, the macrosomic group had a higher HbA1c than group 2, which was statistically significant. The previously

mentioned results were in agreement with those of a published research, at which the authors found a positive correlation between the umbilical cord area and the birth weight (g), especially when estimated at the beginning of the third trimester *Birol et al. (2012)* assessed umbilical cord components to predict fetal weight, and showed that there was a correlation between umbilical cord diameter area and fetal biometric parameters. In addition, some suggested that combination of these two methods should give more reliable results for estimating macrosomic fetuses. The study found that the relationship between umbilical cord thickness and fetal macrosomia was specific for diabetic patients, as it was non-significant in the non-macrosomic fetuses' subgroup. These data disagreed with the reported data of *Birol et al. (2012)* where the correlation was also significant for the control group. However, this might be due to the fact that their study design was based on cases controls design, while ours was including all as patients, no controls.

In addition, some other studies have shown that the presence of a lean umbilical cord in the second trimester may cause low birth weight and results in more fetal distress in labor. Besides, they showed that umbilical cord diameter and area measurements are associated with increased fetal macrosomia (*Proctor et al., 2013*). Hadlock formula based on fetal biometric measurements that are still in use and maintains its importance. For all that, ultrasound-based fetal weight prediction is still insufficient. The positive predictive value of estimated fetal weight (EFW) varies between 60 and 79% (*Proctor et al., 2013*). They suggested that when EFW and umbilical cord area are combined together, the positive predictive value for macrosomic fetuses is significantly improved. In addition, the assessment of the umbilical cord area and its components does not seem to be influenced by gestational age or amniotic fluid volume. They reported through a period of approximately 2 weeks from ultrasound examination till delivery a results that were similar to our study.

In addition, *Kamana et al. (2015)* showed that delivery by cesarean section was higher in mother with macrosomic fetuses than non-macrosomic fetuses, which in turn is in agreement with our currently reported data. In the literature, postprandial blood glucose levels have been shown to be correlated with macrosomia.

CONCLUSION

Macrosomia is a cause of worst obstetric emergencies such as shoulder dystocia, birth asphyxia and postpartum haemorrhage. Shoulder dystocia cannot always be predicted accurately. However,

predicting macrosomia can help to identify the population at risk of such complications. Several studies of sonographic measurement for predicting of fetal macrosomia were established. Umbilical cord thickness and fetal fat layer are good predictors of fetal macrosomia.

In the assessment of risk of macrosomia in addition to the ultrasonographic measurements the clinical risk factors must be considered. Further studies are needed to evaluate the clinical value of incorporating these soft tissue measurements in formulas for estimation of fetal weight.

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دور قطر الحبل السرى ومستوي الهيموجلوبين السكرى فى التنبؤ بضخامه جسم الجنين فى مرضى سكري الحمل

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خلفية البحث: مرض السكرى مع الحمل هو عامل خطر سريري معروف يرتبط بعملاقة الجنين يتضمن الأساس المنطقى لإجراء ولادة قيصرية إختيارية انخفاضاً محتملاً فى مضاعفات الفترة المحيطة بالولادة خاصة تلك المتعلقة بعملاقة الاجنة.

الهدف من البحث: تقييم دقة تحليل السكر التراكمي وسمك الحبل السري في التنبؤ بعملاقة الجنين في النساء الحوامل المصابات بالسكري.

المريضات وطرق البحث: شملت هذه الدراسة (100) امرأة حامل مصابة بمرض السكري، 27 - 28 أسبوعاً من الحمل، تم جمعها من المرضى الداخليين والعيادة الخارجية التوليدية بمستشفى باب الشعرية الجامعي اللاتى يقمن بزيارات منتظمه لمتابعه حملهن قبل الولادة من نوفمبر 2018 إلى اغسطس 2019 و تم تقييم جميع المرضى عن طريق أخذ بيانات كاملة، والفحص الطبي الكامل، هذا وقد تضمنت الدراسه الفحص بالموجات فوق الصوتية وفق معايير القياسات البشرية الجنين، والقطر بين الجداريين، وطول عظم الفخذ ووزن الجنين المقدر والذي تم حسابه تلقائياً وفقاً لمعادله هادلوك.

نتائج البحث: عند معيار 211 مم 2، كانت منطقة الحبل السري التي تم قياسها عند 27 - 28 أسبوعاً من الحمل قادرة على التنبؤ بوزن المواليد المرتفع (عملاقة) ، بحساسية 90.5% وخصوصية 91.7%. كانت المنطقة تحت المنحنى لخاصية تشغيل جهاز الاستقبال 0.9294 (ROC)، مع فاصل ثقة 95% من 0.8608 إلى 0.9702، والتي وجد أنها ذات دلالة إحصائية عالية (p = 0.0001). عند مقارنة منحنيات ROC لكل من منطقة الحبل

السري والهيموجلوبين السكري، فقد وجد أن منطقة الحبل السري أكثر موثوقية في التنبؤ بعملقة الجنين بالمعيار الصحيح، وقد وجد أن الفرق بين الكفاءة التنبؤية لكلا المعلمتين مرتفع إحصائياً.

الإستنتاج: مساحة الحبل السري أكثر موثوقية في التنبؤ بعملقة الجنين بالمعيار الصحيح، والفرق بين الكفاءة التنبؤية لكلا المعيارين مرتفع للغاية من الناحية الإحصائية. هذا بالإضافة إلى قيم مساحة الحبل السري ومنطقة الحبل السري (منطقة جيلي وارتون) كانت أكبر من الناحية الإحصائية في الثلاثه اشهر الأولي عند مقارنة الأجنة المعملقة مع الأجنة غير المعملقة. لذلك، توصلت الدراسة إلى أن منطقة جيلي وارتون هي العامل الرئيسي لسماك السرة المرتبط بتضخم الجنين.