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Maternal serum adiponectin at 11 to 13 weeks of gestation in the prediction of macrosomia

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Objective To examine the potential role of maternal serum level of adiponectin in the first trimester of pregnancy in the prediction of neonatal macrosomia.

Methods Maternal serum adiponectin concentration was measured in a case–control study of singleton pregnancies at 11 to 13 weeks' gestation, which included 50 cases that subsequently delivered macrosomic neonates with birth weight above the 95th percentile for gestation at delivery and 300 controls who delivered appropriate for gestational age neonates. The median multiple of the median (MoM) serum adiponectin in the two outcome groups was compared and the bivariate Gaussian distributions were simulated in a screened population of 33 344 pregnancies to estimate the performance of screening for macrosomia by a combination of maternal characteristics and obstetric history with serum adiponectin.

Results In the macrosomic group the median serum adiponectin [0.82, interquartile range (IQR): 0.56–1.02 MoM] was significantly lower than in the non-macrosomic controls (1.02, IQR: 0.70–1.29 MoM; $p = 0.001$). The estimated detection rate of macrosomia, at fixed false positive rate of 10%, from maternal characteristics and obstetric history was 34.6% and this increased to 38.2% with the addition of serum adiponectin.

Conclusion Maternal serum adiponectin at 11 to 13 weeks is a useful biomarker for early prediction of macrosomia. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: adiponectin; macrosomia; biochemical markers; first-trimester screening; pyramid of prenatal care

INTRODUCTION

Fetal macrosomia is associated with increased risks for the mother, including cesarean section and trauma to the birth canal, and for the baby, including shoulder dystocia and consequent brachial plexus or facial nerve injuries, fractures of the humerus or clavicle and birth asphyxia (Ferber, 2000; Grassi and Giuliano, 2000; Henriksen, 2008). The risk for macrosomia increases with maternal weight and height and is higher in parous women with previous delivery of a macrosomic infant and in those with a medical history of diabetes mellitus, and the risk is lower in women of African racial origin and in cigarette smokers (Poon *et al*., 2011). Screening for macrosomia with a combination of maternal characteristics and obstetric history could potentially identify about one third of women who deliver macrosomic neonates, at a false positive rate of 10% (Poon *et al*., 2011).

The serum concentration of adiponectin, an adipocytokine released from adipose tissue, is inversely correlated with insulin resistance and is consequently reduced in obesity and type 2 diabetes mellitus (Arita *et al*., 1999; Hotta *et al*., 2000). Serum adiponectin is also reduced in pregnancies with gestational diabetes mellitus and this reduction is apparent from the first trimester of pregnancy (Williams *et al*., 2004; Paradisi *et al*., 2010; Nanda *et al*., 2011). It is therefore possible that maternal serum adiponectin in early pregnancy may be a biomarker of the common metabolic derangement observed in obesity and GDM causing fetal macrosomia.

The aim of this study was firstly, to investigate whether the maternal serum concentration of adiponectin at 11 to 13 weeks is reduced in pregnancies that subsequently deliver macrosomic neonates and secondly, to examine the potential value of this biomarker in combination with maternal characteristics and obstetric history in early screening for macrosomia.

METHODS

Screened population

The data for this study were drawn from a large prospective observational study for early prediction of pregnancy complications in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK. In this visit, which was held at week 11 to 13 weeks and 6 days of gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidies by measurement of the fetal crown-rump length (CRL) and nuchal translucency (NT) thickness and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG)

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(Robinson and Fleming, 1975; Snijders *et al*., 1998; Kagan *et al*., 2008). We stored serum and plasma at −80 °C for subsequent biochemical analysis from women agreeing to participate in the study that was approved by King's College Hospital ethics committee.

Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were recorded in our database. The neonate was considered to be macrosomic if the birth weight was more than 95th percentile for gestation at delivery, using a reference range derived from our population (Poon *et al*., 2011). Neonates with birth weight at or below 95th percentile were classified as non-macrosomic.

We have previously reported the development of an algorithm for the prediction of large for gestational age neonates with birth weight above the 90th percentile for gestational age at delivery (Poon *et al*., 2011). In this study we developed an algorithm for the prediction of macrosomia defined by birth weight above the 95th percentile for gestational age. During the study period (March 2006 to September 2009) first-trimester screening for aneuploidies was carried out in 36 743 singleton pregnancies. We excluded 3399 cases because they had missing outcome data ($n = 2005$), the pregnancies resulted in miscarriage before 24 weeks of gestation ($n = 354$), they were terminated for fetal abnormalities or maternal psychosocial indications or they resulted in the birth of babies with major defects ($n = 782$) and they had pre-existing diabetes mellitus ($n = 258$). Statistical analysis was performed in the remaining 33 344 pregnancies.

Case–control study

Maternal serum adiponectin concentration was measured in a case–control study of singleton pregnancies at 11 to 13 weeks' gestation which included 50 cases who subsequently delivered macrosomic neonates with birth weight above the 95th percentile for gestation at delivery and 300 controls who delivered phenotypically normal, appropriate for gestational age (AGA) neonates. Cases were selected at random from our database of stored samples and controls were matched for the length of storage of the serum samples. None of the samples in this study was previously thawed and refrozen.

Duplicate serum sample of 250 μL was used to measure adiponectin concentration by a quantitative ELISA technique using Quantikine Adiponectin ELISA kit (DRP300, R & D Systems Europe Ltd., Abingdon, UK). The lower limit of detection of the assay was 0.246 ng/mL and the between-batch coefficient of variation (CV) was 6.8% at an adiponectin concentration of 20.5 ng/mL, 5.8% at 74.4 ng/mL, and 6.9% at 10.8 ng/mL. All samples were analyzed in duplicate and those with a CV exceeding 10% were reanalyzed.

Statistical analysis

Comparisons between outcome groups were by χ^2-test or Fisher's exact test for categorical variables and by Mann–Whitney U-test for continuous variables.

In the screened population multivariate logistic regression analysis with backward stepwise elimination was used to determine which of the factors amongst the maternal characteristics and obstetric history had a significant contribution in predicting macrosomia. The patient-specific *a priori* risk for macrosomia was calculated from the formula: odds/(1+odds), where odds $= e^Y$ and Y was derived from the logistic regression analysis of maternal characteristics and obstetric history.

In the case–control study, the following steps were taken. First, the distribution of serum adiponectin was made Gaussian after square root (sqrt) transformation and the normality of distribution was assessed using probability plots and Kolmogorov–Smirnov test ($D = 0.03$, $p = 0.20$). Second, in the non-macrosomic control group, multiple regression analysis was used to determine which of the factors among maternal characteristics and gestation provided a significant contribution in predicting sqrt adiponectin and then the measured concentration of adiponectin in each case and control was converted into a multiple of the non-macrosomic median (MoM). Third, Mann–Whitney U-test was used to compare the median MoM value of serum adiponectin in the two outcome groups. Fourth, the means and SDs of the Gaussian distributions of sqrt adiponectin MoM in the macrosomic and the non-macrosomic group were estimated and from these bivariate distributions Monte–Carlo simulations were used to generate values of adiponectin in the screened population of 33 344 pregnancies. Fifth, likelihood ratios for delivery of a macrosomic neonate were calculated from the fitted bivariate Gaussian distributions of adiponectin MoMs in each group. Sixth, in each patient in the screened population the *a priori* odds for delivery of a macrosomic neonate based on maternal history and characteristics were multiplied by the likelihood ratio for adiponectin to derive the *a posteriori* odds. The *a posteriori* risks were used to calculate detection rates of macrosomia and false positive rates and the performance of screening was determined by the receiver operating characteristic (ROC) curves analysis. The performance of different methods of screening was compared with the areas under the receiver operating characteristic curves (AUROC) (Zweig and Campbell, 1993).

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) and MedCalc software package version.9.6.2.0 (MedCalc software, Mariakerke, Belgium) were used for data analyses.

RESULTS

Screened population

In 1636 (4.9%) of the neonates, the birth weight was above the 95th percentile corrected for gestational age. The maternal characteristics of the study population are shown in Table 1. Multiple regression analysis demonstrated that in the prediction of macrosomia there were significant contributions from maternal racial

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Table 1—Maternal and pregnancy characteristics in the screened population

Maternal characteristics	Control ($n = 31\,708$)	Macrosomia ($n = 1\,636$)
Maternal age in years, median (IQR)	32.2 (27.8–35.9)	33.4 (29.2–36.9)*
Maternal weight in kg, median (IQR)	65.0 (59.0–75.0)	74.0 (65.0–86.0)*
Maternal height in cm, median (IQR)	164 (160–168)	167 (163–171)*
Crown-rump length in mm, median (IQR)	64.0 (59.1–69.4)	65.2 (60.0–71.0)*
Racial origin		
Caucasian, *n* (%)	22 697 (71.6)	1 272 (77.8)
African, *n* (%)	6 020 (19.0)	264 (16.1)*
South Asian, *n* (%)	1 419 (4.5)	41 (2.5)*
East Asian, *n* (%)	640 (2.0)	21 (1.3)
Mixed, *n* (%)	932 (2.9)	38 (2.3)
Parity		
Nulliparous, *n* (%)	15 496 (48.9)	556 (34.0)
Parous, no previous macrosmia, *n* (%)	14 743 (46.5)	748 (45.7)
Parous, previous macrosomia, *n* (%)	1 469 (4.6)	332 (20.3)*
Cigarette smoker, *n* (%)	2 638 (8.3)	73 (4.5)*
Conception		
Spontaneous, *n* (%)	30 515 (96.2)	1 596 (96.3)
Assisted, *n* (%)	1 193 (3.8)	60 (3.7)
Birth weight in kg, median (IQR)	3.4 (3.1–3.7)	4.4 (4.1–4.6)*
Birth weight percentile, median (IQR)	49.0 (26.0–70.3)	97.5 (96.2–98.8)*

Comparisons between outcome groups (χ^2 test and Fisher's exact test for categorical variables and Mann–Whitney U-test for continuous variables):
* $p < 0.05$. IQR, interquartile range.

Table 2—Multivariate logistic regression analysis for the prediction of macrosomia in the screened population from factors in maternal characteristics and obstetric history

Independent variable	Odds ratio	95% CI	*p*
Maternal weight in kg	1.092	1.069–1.116	<0.0001
(Maternal weight in kg)^2	1.000	1.000–1.000	<0.0001
Maternal height in cm	1.027	1.019–1.035	<0.0001
Parity	—	—	<0.0001
Nulliparous (Reference)	1.000	—	—
Parous, no previous macrosomic baby	1.374	1.226–1.540	<0.0001
Parous, previous macrosomic baby	4.734	4.067–5.511	<0.0001
Cigarette smoking	0.473	0.371–0.604	<0.0001
Racial origin	—	—	<0.0001
Caucasian (Reference)	1.000	—	—
African	0.549	0.476–0.634	<0.0001
South Asian	0.830	0.599–1.148	0.260
East Asian	1.054	0.673–1.651	0.819
Mixed	0.738	0.526–1.036	0.079

CI, confidence intervals; p = significance value.

origin, weight, height, previous delivery of macosomic neonates, and smoking (Table 2).

Case–control study

The maternal characteristics in the macrosomic and non-macrosomic group are compared in Table 3. In the macrosomic group, the median maternal age and weight were higher, there were more women of South Asian racial origin and more women delivered macrosomic neonates in their previous pregnancies.

Multiple regression analysis in the non-macrosomic group demonstrated that for sqrt adiponectin significant independent contribution was provided by maternal age, weight, smoking status, African and South Asian racial origin but not by fetal CRL ($p = 0.459$), method of conception ($p = 0.637$), or parity (0.219):

Sqrt adiponectin expected = $130.19 + 0.74 \times$ maternal age in years + (-18.24 if the racial origin was African, -31.89 if South Asian, 0 if Caucasian, East Asian or Mixed) $-0.53 \times$ maternal weight in kg -10.38 if cigarette smoker; $R^2 = 0.223$, $p < 0.0001$.

The median maternal serum adiponectin MoM in the macrosomic group [0.82, interquartile range (IQR) 0.56–1.02] was significantly lower than in the non-macrosomic controls (1.02, IQR 0.70–1.29; $p = 0.001$).

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Table 3—Maternal and pregnancy characteristics in the case–control study

Maternal characteristics	Control ($n = 300$)	Macrosomia ($n = 50$)
Maternal age in years, median (IQR)	32.2 (26.9–35.6)	34.8 (31.3–37.9)*
Maternal weight in kg, median (IQR)	63.3 (57.0–70.0)	76.5 (66.5–89.3)*
Maternal height in cm, median (IQR)	162 (160–168)	166 (162–169)
Crown-rump length in mm, median (IQR)	64.0 (58.7–69.6)	67.2 (60.0–73.0)
Racial origin		
Caucasian, *n* (%)	189 (63.0)	28 (56.0)
African, *n* (%)	86 (28.7)	14 (28.0)
South Asian, *n* (%)	10 (3.3)	6 (12.0)*
East Asian, *n* (%)	6 (2.0)	0
Mixed, *n* (%)	9 (3.0)	2 (4.0)
Parity		
Nulliparous, *n* (%)	148 (49.3)	10 (20.0)
Parous, no previous macrosmia, *n* (%)	140 (46.7)	29 (58.0)
Parous, previous macrosomia, *n* (%)	12 (4.0)	11 (22.0)*
Cigarette smoker, *n* (%)	28 (9.3)	3 (6.0)
Conception		
Spontaneous, *n* (%)	296 (98.7)	48 (96.0)
Assisted, *n* (%)	4 (1.3)	2 (4.0)
Birth weight in kg, median (IQR)	3.4 (3.2–3.7)	4.7 (4.5–4.9)*
Birth weight percentile, median (IQR)	50.5 (32.6–68.7)	99.1 (98.7–99.7)*
Maternal serum adiponectin		
ng/mL, median (IQR)	12 035 (8 595–17 085)	8 257 (5 258–13 171)
Multiple of the median, median (IQR)	1.02 (0.70–1.29)	0.82 (0.56–1.02)*

Comparisons between outcome groups (χ^2 test and Fisher's exact test for categorical variables and Mann–Whitney U-test for continuous variables):
* $p < 0.05$. IQR, interquartile range.

Estimated performance of screening for macrosomia

In the simulated screened population the *a posteriori* odds for macrosomia were derived by multiplying the *a priori* odds by the likelihood ratio for adiponectin. The *a posteriori* risk was calculated using the formula: $\beta/(1+\beta)$, where β = *a posteriori* odds.

The AUROC for macrosomia in screening by maternal factors was 0.722 (95% CI 0.710–0.735) and the detection rate at false positive rate of 10% was 34.6%. There was a significant improvement in the AUROC for maternal factors by the addition of adiponectin (0.747, 95% CI 0.735–0.760, $p < 0.001$) and the detection rate, at false positive rate of 10%, was 38.2%.

DISCUSSION

The findings of this study demonstrate that in pregnancies delivering macrosomic neonates the maternal serum adiponectin concentration at 11 to 13 weeks' gestation is significantly lower than in pregnancies delivering non-macrosomic neonates. Additionally, combining maternal characteristics with serum adiponectin concentration can potentially detect in the first trimester about 40% of the pregnancies that subsequently deliver macrosomic neonates.

In normal pregnancy, the maternal serum adiponectin concentration increases with maternal age, decreases with weight and is lower in cigarette smokers and in women of African and South Asian racial origin than in Caucasians. Consequently, in the comparison between the macrosomic and non-macrosomic groups, the levels in maternal serum must be adjusted for these maternal characteristics. These findings are compatible with results of previous studies in non-pregnant individuals, which reported a poor adipocytokine profile in women of African and South Asian racial origin (Meilleur *et al*., 2010; Mente *et al*., 2010) and in cigarette smokers (Swarbrick and Havel, 2008; Bergmann and Siekmeier, 2009). Similarly, studies in pregnancy have also shown decreased adiponectin levels with smoking and in women of African, South Asian and East Asian racial origin (Retnakaran *et al*., 2004; Nien *et al*., 2007).

Our finding that in pregnancies which subsequently deliver macrosomic neonates, maternal serum adiponectin levels are reduced is compatible with the results of Wang *et al*. (2010) who reported lower levels of adiponectin in 30 pregnancies at 37 to 42 weeks' gestation that delivered macrosomic neonates compared to 40 that delivered AGA neonates. The likely mechanism underlying the association between low maternal serum adiponectin and neonatal macrosomia is increased insulin resistance and glucose intolerance. In the case of diabetes mellitus, where adiponectin is reduced (Arita *et al*., 1999; Hotta *et al*., 2000; Williams *et al*., 2004; Paradisi *et al*., 2010; Nanda *et al*., 2011), fetal macrosomia is thought to be the consequence of fetal pancreatic β–cell hyperplasia and hyperinsulinemia due to maternal and fetal hyperglycemia (Salvesen *et al*., 1993). The

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same may also be the mechanism for lesser degrees of maternal glucose intolerance. A study of pregnancies at 24 to 32 weeks' gestation, reported that in women with blood glucose levels below those diagnostic of diabetes the incidence of macrosomia increased with increasing glucose levels (Metzger *et al*., 2008) and was inversely related to maternal serum adiponectin levels (Lowe *et al*., 2010). Even in macrosomic fetuses of non-diabetic mothers there is evidence of pancreatic β−cell hyperplasia (Pinar *et al*., 2000). There is also some evidence that in addition to glucose intolerance the risk of macrosomia is related to lipid metabolism and dyslipidemia (Bo *et al*., 2004; Clausen *et al*., 2005; Ricart *et al*., 2005; Henriksen, 2008).

Adiponectin, circulates in oligomeric complexes including low-molecular-weight (LMW) trimers, medium-molecular-weight (MMW) hexamers and high-molecular-weight (HMW) isoforms and there is some evidence that the physiological activity of adiponectin is determined by the relative distribution of its isoforms (Waki *et al*., 2003; Hara *et al*., 2006; Ong *et al*., 2007; Mazaki-Tovi *et al*., 2008). The extent to which the concentration of different isoforms and their ratios would be better than total adiponectin in the prediction of neonatal macrosomia merits further investigation.

Maternal serum adiponectin level in early pregnancy may be a useful biomarker of the maternal metabolic derangements resulting in neonatal macrosomia. Screening at 11 to 13 weeks' gestation by a combination of maternal characteristics, obstetric history, and serum adiponectin could identify a high proportion of pregnancies delivering macrosomic neonates. Future studies will determine whether dietary and pharmacological interventions, with such drugs as metformin, in the high-risk group can potentially reduce the incidence of macrosomia and its associated maternal and perinatal complications.

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