A First Trimester Prediction Model for Large for Gestational Age Infants: A Preliminary Study

Francesca Monari
University Hospital Policlinico of Modena
Daniela Menichini (daniela.menichini91@gmail.com)
University of Modena and Reggio Emilia
Ludovica Spano' Bascio
University Hospital Policlinico of Modena
Giovanni Grandi
University Hospital Policlinico of Modena
Federico Banchelli
University of Modena and Reggio Emilia
Isabella Neri
University Hospital Policlinico of Modena
Roberto D'Amico
University of Modena and Reggio Emilia
Fabio Facchinetti
University Hospital Policlinico of Modena

Research Article

Keywords: Prediction model, LGA, first trimester, biochemical markers, biophysical markers

Posted Date: April 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-398307/v1

Abstract

Background: Large for gestational age infants (LGA) have increased risks of adverse short-term perinatal outcomes. This study aims to develop a multivariable prediction model for the risk of giving birth to a LGA baby, by using biochemical, biophysical, anamnestic, and clinical maternal characteristics available at first trimester.

Methods: Prospective study that included all singleton pregnancies attending the first trimester aneuploidy screening at the Obstetric Unit of the University Hospital of Modena, in Northern Italy, between June 2018 and December 2019.

Results: A total of 503 consecutive women were included in the analysis. The final prediction model for LGA, included multiparity (OR = 2.8, 95%; CI: 1.6 - 4.9, p=0.001), pre-pregnancy BMI (OR = 1.08. 95% CI 1.03 – 1.14, p=0,002) and PAPP-A MoM (OR = 1.43 95% CI 1.08 – 1.90, p=0.013). The area under the ROC curve was 70.5%, indicating a satisfactory predictive accuracy. The best predictive cut-off for this score was equal to -1.378, which corresponds to a 20.1% probability of having a LGA infant. By using such a cut-off, the risk of LGA can be predicted in our sample with sensitivity of 55.2% and specificity of 79.0%.

Conclusion: At first trimester, a model including multiparity, pre-pregnancy BMI and PAPP-A satisfactory predicted the risk of giving birth to a LGA infant. This promising tool, once applied early in pregnancy, would identify women for targeted interventions.

Trial registration: NCT04838431

Introduction

It is well recognized that large for gestational age infants (LGA), defined as a babies born with a birthweight above the 90th centile for gestational age and gender, have increased risks of adverse short-term perinatal outcomes i.e., induction of labor, instrumental vaginal delivery, caesarean section, shoulder dystocia, and perinatal asphyxia [1–4]. These neonates also face long-term excess risks of death, hospitalization as well as increased occurrence of obesity, hypertension and type 2 diabetes later in life [5,6].

LGA is usually a result of maternal diabetes, obesity, and an excessive weight gain during pregnancy. However, there are several other factors that interplay with fetal growth as the genetics, intrauterine environment, nutrition and placental function.

Among others, plasma protein A (PAPP-A), an enzyme produced by the placenta and by several maternal tissues [7] which releases insulin-like growth factor from its carrier protein have been related with size at birth [8]. Indeed, increased PAPP-A between the 9-12 weeks was associated with LGA babies, in normal weight women[9]. Also β human chorionic gonadotropin (β-hCG) which stimulates trophoblast invasion [10] has been involved since its concentrations correlated with both placental volume and birthweight [11,12].

Fetal growth seems to be affected by other biochemical factors as placental growth factor (PlGF), an angiogenic molecule also produced by the placenta [13]. Higher PlGF levels are related with a better vascular function, which in turn increases glucose transport leading to higher glucose and nutrients exposure to the offspring. An association of PlGF levels with LGA babies, namely in women with preexisting diabetes, has been reported [14]. Furthermore, abnormal levels of inhibin-A were associated to adverse perinatal outcomes, also impacting on fetal growth [15].

Previous prediction models for LGA did not take into account the above reported factors[12] and have been developed either in obese mothers[16] or in women with gestational diabetes mellitus (GDM)[17,18]. Although PAPP-A, free β hCG, lipid[19] and inflammatory (interleukin-6, IL-6)[20] markers have all been included in those models, we have to remember that GDM is only a proxy of LGA. Thus, the objective of our prospective study is to develop a multivariable prediction model for the risk of having a LGA infant, by using biochemical, biophysical, anamnestic, and clinical maternal characteristics, all available at first trimester.

Materials And Methods

Singleton pregnancies between June 2018 and December 2019 were included in the study among women attending the first trimester Down syndrome screening at the University Hospital of Modena, in the North of Italy (tertiary Hospital).

The study was approved by the Ethical Committee of the Area Vasta Emilia Nord (AVEN, protocol AOU: 0001395/20) and written informed consent was obtained. Women were included if crown–rump length ranged 45–80 mm and no signs of miscarriage were present. Pregnancies with major fetal abnormalities were excluded from the study.

For each subject, blood sample was collected in fasting conditions, then centrifuged, and the serum stored at minus 80° C, for subsequent biochemical analyses. PAPP-A, PlGF and Inibin A have been measured with the automated DELFIA EXPRESS system (Thermo Fisher Scientific, Perkin Elmer ®). Insulin, high density lipoproteins (HDL) and triglycerides (TG) were measured through routine laboratory methods.

The mean arterial pressure (MAP) was measured with validated automated devices (Dinamap, BLTV6XX). After the women were seated and allowed to rest for 3–5 min, normal (22 to 32 cm) adult cuffs were fitted to their both arms. This was repeated two times with 1 min break in between. The MAP was calculated with the formula MAP = DBP + 1/3(SBP – DBP) [21], where DBP represents diastolic blood pressure and SBP, systolic blood pressure. We calculated the final MAP as the average of all four measurements. Uterine artery Doppler studies including pulsatility index were measured through trans-abdominal ultrasound (Voluson E8 or Voluson E10) examinations. As indicated in Fetal Medicine Foundation (FMF), when carrying out Doppler studies, color flow mapping was used to identify each uterine artery along the side of the cervix and uterus at the level of internal os. Pulsed wave Doppler

imaging was used with the sampling gate set at 2 mm to cover the whole vessel, and care was taken to ensure that the angle of insonation was less than 30°. When three to five similar consecutive waveforms had been obtained, PI was measured. The uterine artery mPI was calculated by adding the right and left pulsatility index together, divided by two. All ultrasound and Doppler studies were carried out by a physician who had received the appropriate certificate of competence in the 11–13 + 6 week scans and Doppler study from the FMF [22].

Data on pregnancy outcome were collected from the hospital maternity records or directly from women if delivered elsewhere.

Medical records were reviewed by research associates to obtain anonymized data on mothers (i.e maternal demographics, BMI, age…) and their newborns (birthweight, gender, Apgar score, admission to the neonatal intensive care unit (NICU) and length of stay, neonatal morbidities, and mortality), and were organized in a password protected database.

Statistical analysis

Quantitative variables were described as the mean ± standard deviation (SD), whereas qualitative variables were described as the absolute and percentage frequencies. The multivariable prediction model was developed by carrying out the following steps. Firstly, univariate logistic regression models were used to assess the relationship among each relevant independent variable and the risk of having a LGA infant. During this step, several alternative parameterizations were used for quantitative variables, including linear effect; step effect based on median or first / third quartile; step effect based on clinically meaningful values; linear effect on multiples of median (MoM). The metabolic syndrome was defined as the presence of at least three of the following variables: HDL < 50 mg/dl, TG ≥ 150 mg/dl, SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, BMI ≥ 30 kg/m2 [23].

The variables that were associated to LGA risk with p-value < 0.10 in the univariate analyses were considered for inclusion in a multivariable logistic model. The final prediction model was determined by a stepwise backward selection procedure in which only independent variables associated to LGA risk with p-value < 0.05 were retained. Results of logistic models were reported as the Odds Ratio (OR) with 95% confidence interval and Wald p-value. The overall accuracy of the estimated prediction model was assessed by using the area under the ROC curve with 95% confidence interval. The formula for the predictive score for LGA was equal to the linear predictor of the final model, in which each independent variable was weighted proportionally to its log OR. The predicted probability of having a LGA infant can be calculated as exp(score) / [1 + exp(score)]. Furthermore, we calculated the best score threshold by using the Youden's rule and we reported the associated values for sensitivity and specificity. Statistical analyses were performed by using R 3.6.3 software (The R Foundation for Statistical Computing, Wien).

Results

Five-hundred fifteen women agreed to participate in this prospective study. Of them, 2 had spontaneous miscarriage in the second trimester, 2 underwent a therapeutic termination of pregnancy (one for trisomy 21 and one for fetal congenital heart disease detected at ultrasound) while 8 women not delivering at our center were lost to follow-up. Therefore, a total of 503 women were included in the final analysis.

The maternal baseline characteristics were compared between those giving birth to a LGA neonate was (87, 17.3%) and the remnants (416) delivering normal weight infants (Table 1).

Table 1
Maternal baseline characteristics.

	Non LGA (N = 416)	**LGA (N = 87)**
Maternal age (mean ± SD)	32.4 ± 4.5	33.0 ± 4.8
Low Education level (≤ 8 years)	52 (12.5)	13 (14.9)
Foreign women	52 (12.5)	18 (20.7)*
Smoking habits	27 (6.4)	4 (4.6)
BMI classes	19 (4.5)	0
Underweight	266 (63.9)	36 (41.4)*
Normal weight	67 (16.1)	29 (33.3)
Overweight	56 (13.5)	19 (21.8)
Obese	8 (1.9)	3 (3.5)
Morbidly Obese		
Nulliparity	263 (63.2)	36 (41.4)*
Assisted reproductive conception	15 (3.7)	2 (2.3)
Preexisting Diabetes Mellitus	3 (0.7)	3 (3.4)*
Chronic Hypertension	15 (3.5)	3 (3.4)
Metabolic Syndrome [a]	21 (5.0)	7 (8.0)
Data are reported as numbers with percentage in brackets.		
* p value < 0.05		
[a] Metabolic syndrome is defined as the presence of at least 3 of the 5 following variables:		
− HDL < 50 mg/dl		
− TG >/= 150 mg/dl − SBP >/= 130 mmHg − DBP >/= 85 mmHg − BMI >/= 30 kg/m^2		

The two groups were similar for maternal age and education level, while the rate of foreign women was higher in the LGA group. Moreover, the LGA group included less normal weight while more multiparous

women. A higher rate of women with preexisting diabetes mellitus was also found in the LGA group, while metabolic syndrome was similarly represented in the two groups.

Table 2 summarizes the biochemical and biophysical markers for LGA at first trimester enrollment.

Mean arterial pressure > 90 mmHg and the mean pulsatility index of the uterine artery doppler > 90th centile, were similar between the two groups as well as plasma insulin, triglycerides, and HDL. Placental and vascular markers as PlGF, inhibin A and IL-6 mean values were comparable while the MoM of PAPP-A significantly differed between groups.

Table 2
Biochemical and biophysical markers under evaluation.

	Non LGA (N = 416)	**LGA (N = 87)**
MAP > 90 mmHg	116 (27.1)	32 (36.8)
Uterine Doppler PI > 90th centile	44 (10.3)	7 (8.0)
Insulin (µUI/mL)	11.7 ± 1.47	15.0 ± 4.35
Triglycerides (mg/dL)	107.32 ± 4.21	116.00 ± 9.94
HDL (mg/dL)	64.38 ± 1.1	62.48 ± 2.5
Inhibin A (pg/mL)	322.13 ± 16.6	342.92 ± 46.8
Interleukin-6 (pg/mL)	1151.05 ± 191.6	986.18 ± 391.7
PAPP-A (MoM)	1.40 ± 0.75	1.53 ± 0.86*
Free Beta hCG (MoM)	1.12 ± 0.60	1.01 ± 0.58
PlGF (MoM)	1.23 ± 0.50	1.28 ± 0.55
Fetal cardiac frequency > 162 bpm	191 (44.6)	31 (35.6)
Mean values ± SD and numbers with percentage in brackets are reported.		
* p value < 0.05		
MAP: mean arterial pressure; MoM: Multiple of the median		

Pregnancy outcomes are reported in Table 3. No significant differences were detected as far as GDM, pregnancy induced hypertension (PIH) or preeclampsia (PE). Interestingly, the number of women who gained more weight than recommended by the Institute of Medicine (IOM) (47.1% vs 20.9%) were increased in LGA group (Table 3).

Table 3
Pregnancy Outcomes

	Non LGA (N = 416)	LGA (N = 87)
GDM	46 (10.7%)	12 (13.7%)
Dietary treatment	11 (2.6%)	7 (8.0%)
Insulin treatment		
Pregnancy induced Hypertension	23 (5.3%)	4 (4.6%)
Pre-eclampsia	6 (1.4%)	1 (1.1%)
Weight gain above IOM recommendations	87 (20.9%)	41 (47.1%)
Abruptio Placentae	3 (0.7%)	1 (1.1%)
Fetal Growth Restriction	6 (0.7%)	0 (0.0%)

Table 4 showed the main perinatal outcomes. While a significantly higher percentage of women with a LGA baby underwent induction of labor, the rate of cesarean section and vaginal operative deliveries was similar between the two groups. Neonatal adverse outcomes, as NICU admission, acidosis at birth or Apgar score < 7 at 5th minute were comparable.

Table 4
Perinatal Outcomes

	Non LGA (N = 428)	LGA (N = 87)
Mode of Labour	303 (70.8%)	52 (59.7%)*
Spontaneous	101 (23.6%)	35 (40.2%)*
Induced		
Delivery	302 (70.6%)	61 (70.1%)
Vaginal	28 (6.5%)	3 (3.4%)
Vaginal Operative	98 (22.9%)	23 (26.4%)
Cesarean Section		
Male gender	214 (50.0%)	49 (56.3%)
NICU admission	14 (3.3%)	1 (1.1%)
Umbilical a. pH < 7.2	23 (5.4%)	6 (3.4%)
5th min. Apgar < 7	6 (1.4%)	1 (1.1%)
* p value < 0.05		

Early prediction model of LGA risk

Based on parameters available in at first trimester, a backward stepwise logistic regression was performed to identify potential predictors of LGA among 13 relevant independent variables (age, parity, pre-pregnancy BMI, preexisting diabetes mellitus, HDL, TG, insulin, PAPP-A, PlGF, IL-6, inhibin A, fetal cardiac frequency, and metabolic syndrome). The results of both univariate and multivariable analyses were reported in Table 5. At univariate analysis LGA babies were associated with multiparity (OR = 2.41, 95%CI 1.51–3.86, p = 0.001), pre-pregnancy BMI (OR = 1.08, 95%CI 1.04–1.12, p = 0.001), pre-existing diabetes (OR = 5.04, 95%CI 1.00–25.38, p = 0.050) and PAPP-A MoM (OR = 1.30, 95%CI 1.00–1.70, p = 0.051).

The final prediction model for LGA at multivariable analysis included the following independent variables: multiparity (OR = 2.8, 95% CI = 1.6–4.9, p = 0.001), pre-pregnancy BMI (OR = 1.08, 95%CI 1.03–1.14, p = 0.002) and PAPP-A MoM (OR = 1.43, 95%CI 1.08–1.90, p = 0.013) (Table 5).

Table 5
Development of the prediction model for LGA risk

	Univariate analysis (n = 503)				Multivariable prediction model (n = 434)			
	OR	95% CI		p	OR	95% CI		p
Maternal Age (+ 1 year)	1.03	0.98	1.08	0.283				
Multiparity	**2.41**	**1.51**	**3.86**	**0.001**	**2.80**	**1.61**	**4.87**	**0.001**
Pre-pregnancy BMI	**1.08**	**1.04**	**1.12**	**0.001**	**1.08**	**1.03**	**1.14**	**0.002**
Pre-existing diabetes	**5.04**	**1.00**	**25.38**	**0.050**				
HDL ≥ 50	0.63	0.30	1.29	0.206				
TG ≥ 150	1.76	0.96	3.23	0.068				
Insulin ≥ 24	1.74	0.92	3.29	0.091				
PAPP-A MoM	**1.30**	**1.00**	**1.70**	**0.051**	**1.43**	**1.08**	**1.90**	**0.013**
PLGF MoM	1.21	0.75	1.97	0.432				
IL-6	1.00	1.00	1.00	0.477				
Inhibin A	1.00	1.00	1.00	0.338				
FCF ≥ 162	0.69	0.41	1.16	0.157				
Metabolic Syndrome	1.70	0.70	4.12	0.244				

The area under the ROC curve was 70.5%, indicating a satisfactory predictive accuracy (Fig. 1).

The prediction score for LGA risk was as follows:

Score = -4.565 + 1.030 * multiparous + 0.079 * BMI + 0.358 * PAPP-A MoM.

The best predictive cut-off for this score was equal to -1.378, which corresponds to a 20.1% probability of having a LGA infant. By using such a cut-off, the risk of LGA can be predicted in our sample with sensitivity of 55.2% and specificity of 79.0%.

Discussion

This prospective study developed a tool for the early pregnancy prediction of a LGA baby in a non-selected population. Previous prediction models for LGA have been build-up in larger, although selected populations, i.e. within obese subjects [16] or in women with a diagnosis of GDM [17,18]. In our small series, we included all classes of pre-pregnancy BMI, women with different ethnicity, parity and with heterogenous obstetric history.

This study thus confirms and enlarges the observation that there is a linear association between MoM of PAPP-A levels and LGA, as firstly reported in a cohort of GDM women [24] and later found also in pre-pregnancy obese mothers[16]. This finding is compatible with the observations that glucose levels affect placentation by influencing trophoblast invasion[25]. Indeed, low levels of PAPP-A were reported to be associated with poor early placentation resulting in perinatal complications such as fetal growth restriction, fetal demise, preterm birth, and pre-eclampsia [26].

Moreover, we confirmed that either multiparity and maternal pre-pregnancy BMI are good predictors of increased birthweight and LGA infants [27–29], possibly due to the faster fetal growth transfer in those conditions [30]. On the other hand, it is now assessed that the levels of placental growth factor in maternal blood, as well as the measures of uterine artery pulsatility index, should be excluded among possible markers for LGA [12]. Despite promising, also the other new markers we tested, Inhibin A and Interleukin 6 did not enter in the equation.

The early pregnancy prediction model we obtained is mathematically worth of note, with a satisfactory specificity and an AUC of 0.705. This tool, in line with the concept of “Inverted Pyramid of Care” [31], adds LGA among those pregnancy complications that could be predicted, hence prevented through timely interventions.

Several studies focused attention on the excessive gestational weight gain which is a well-recognized factor contributing to LGA infant and standards for appropriate increase have been defined[32]. Moreover, also interpregnancy weight increase has found to be associated with LGA [33]. Therefore, we and others previously demonstrated that implementing an early customized low glycemic index, low fat diet together with the stimulation of physical activity has the potential to reduce the risk of LGA baby in some populations[34,35]. Unfortunately, quality, timing and adherence to intervention are factors significantly affecting success[42]. A big individual patient data meta-analysis reported that diet and/or physical activity prescription induced a significant reduction of cesarean section rate being however unable to demonstrate a large-scale reduction in the rate of LGA babies [36,37]. It is possible that in many studies the window for intervention was too small to effectively change women lifestyle and/or it could be too late since the fetal metabolic “programming” is already set [38]. Indeed, timing of intervention seems crucial to prevents disorders, such as preeclampsia which is effectively reduced only when the prophylactic aspirin administration is instituted early in pregnancy [39,40].

In summary, multiparity, increased maternal pre-pregnancy BMI and high PAPP-A levels measured at first trimester can predict the increasing risk of having a LGA infant, with a good specificity. This helps target the population which deserves early interventions. We hope this formula will undergo validation in further, larger populations.

Declarations

Ethics approval and consent to participate

The study was approved by Ethical Committee of the Area Vasta Emilia Nord (AVEN, protocol AOU: 0001395/20) and written informed consent was obtained. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

A consent for anonymized data publication was obtained.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no competing interests.

Funding

There were no funding for this study.

Authors' contributions

F.M., D.M. and L.S.B. wrote the main manuscript text and collected the study data. F.B. and R.D. followed the statistical analysis. G.G. collected the data. I.N. and F.F. supervised and conceived the idea of this work. All authors reviewed the manuscript.

Acknowledgements

We acknowledge the support of the Laboratory “Test” of Modena (Italy), that performed the biochemical analyses and for storage serum for subsequent metabolic evaluation We also thank Perkin Elmer ® which offered the biochemical analysis of Inhibin A.

We are moreover in debt with Dr. Claudia Re, Dr. Francesca Ferrari and Dr Emma Bertucci who contributed to perform both the Down syndrome screening and uterine artery Doppler study.

References

1. Weissmann-Brenner A, Simchen MJ, Zilberberg E, et al. Maternal and neonatal outcomes of large for gestational age pregnancies. *Acta Obstet Gynecol Scand*. 2012;91(7):844-849. doi:10.1111/j.1600-0412.2012.01412.x
2. Mendez-Figueroa H, Truong V, Pedroza C, Chauhan S. Large for Gestational Age Infants and Adverse Outcomes among Uncomplicated Pregnancies at Term. *Am J Perinatol*. 2016;34(07):655-662.

doi:10.1055/s-0036-1597325

3. Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S. Risk factors for macrosomia and its clinical consequences: A study of 350,311 pregnancies. *Eur J Obstet Gynecol Reprod Biol*. 2003;111(1):9-14. doi:10.1016/S0301-2115(03)00154-4
4. Chavkin U, Wainstock T, Sheiner E, Sergienko R, Walfisch A. Perinatal outcome of pregnancies complicated with extreme birth weights at term. *J Matern Neonatal Med*. 2019;32(2):198-202. doi:10.1080/14767058.2017.1376048
5. Johnsson IW, Haglund B, Ahlsson F, Gustafsson J. A high birth weight is associated with increased risk of type 2 diabetes and obesity. *Pediatr Obes*. 2015;10(2):77-83. doi:10.1111/ijpo.230
6. Kuciene R, Dulskiene V, Medzioniene J. Associations between high birth weight, being large for gestational age, and high blood pressure among adolescents: a cross-sectional study. *Eur J Nutr*. 2018;57(1):373-381. doi:10.1007/s00394-016-1372-0
7. Boldt HB, Conover CA. Pregnancy-associated plasma protein-A (PAPP-A): A local regulator of IGF bioavailability through cleavage of IGFBPs. *Growth Horm IGF Res*. 2007;17(1):10-18. doi:10.1016/j.ghir.2006.11.003
8. Agrogiannis G, Sifakis S, Patsouris E, Konstantinidou O. Insulin-like growth factors in embryonic and fetal growth and skeletal development (Review). *Mol Med Rep*. 2014;10(2):579-584. doi:10.3892/mmr.2014.2258
9. Baer RJ, Lyell DJ, Norton ME, Currier RJ, Jelliffe-Pawlowski LL. First trimester pregnancy-associated plasma protein-A and birth weight. *Eur J Obstet Gynecol Reprod Biol*. 2016;198:1-6. doi:10.1016/j.ejogrb.2015.12.019
10. Heidegger H, Jeschke U. Human Chorionic Gonadotropin (hCG)—An Endocrine, Regulator of Gestation and Cancer. *Int J Mol Sci*. 2018;19(5):1502. doi:10.3390/ijms19051502
11. Metzenbauer M, Hafner E, Hoefinger D, et al. Three-dimensional ultrasound measurement of the placental volume in early pregnancy: Method and correlation with biochemical placenta parameters. *Placenta*. 2001;22(6):602-605. doi:10.1053/plac.2001.0684
12. Frick AP, Syngelaki A, Zheng M, Poon LC, Nicolaides KH. Prediction of large-for-gestational-age neonates: Screening by maternal factors and biomarkers in the three trimesters of pregnancy. *Ultrasound Obstet Gynecol*. 2016;47(3):332-339. doi:10.1002/uog.15780
13. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111(5):649-658. doi:10.1172/JCI17189
14. Kuc S, Wortelboer EJ, Koster MPH, De Valk HW, Schielen PCJI, Visser GHA. Prediction of macrosomia at birth in type-1 and 2 diabetic pregnancies with biomarkers of early placentation. *BJOG An Int J Obstet Gynaecol*. 2011;118(6):748-754. doi:10.1111/j.1471-0528.2011.02904.x
15. Singnoi W, Wanapirak C, Sekararithi R, Tongsong T. A cohort study of the association between maternal serum Inhibin-A and adverse pregnancy outcomes: a population-based study. *BMC Pregnancy Childbirth*. 2019;19(1):124. doi:10.1186/s12884-019-2266-y

16. Åmark H, Westgren M, Persson M. Prediction of large-for-gestational-age infants in pregnancies complicated by obesity: A population-based cohort study. *Acta Obstet Gynecol Scand*. 2019;98(6):769-776. doi:10.1111/aogs.13546
17. Nelson L, Wharton B, Grobman WA. Prediction of Large for Gestational Age Birth Weights in Diabetic Mothers Based on Early Third-Trimester Sonography. *J Ultrasound Med*. 2011;30(12):1625-1628. doi:10.7863/jum.2011.30.12.1625
18. Boriboonhirunsarn D, Kasempipatchai V. Incidence of large for gestational age infants when gestational diabetes mellitus is diagnosed early and late in pregnancy. *J Obstet Gynaecol Res*. 2016;42(3):273-278. doi:10.1111/jog.12914
19. Sweeting AN, Wong J, Appelblom H, et al. A Novel Early Pregnancy Risk Prediction Model for Gestational Diabetes Mellitus. *Fetal Diagn Ther*. 2019;45(2):76-84. doi:10.1159/000486853
20. Hassiakos D, Eleftheriades M, Papastefanou I, et al. Increased Maternal Serum Interleukin-6 Concentrations at 11 to 14 Weeks of Gestation in Low Risk Pregnancies Complicated with Gestational Diabetes Mellitus: Development of a Prediction Model. *Horm Metab Res*. 2015;48(1):35-41. doi:10.1055/s-0034-1395659
21. DeMers D, Wachs D. *Physiology, Mean Arterial Pressure*.; 2019.
22. Lai J, Poon LCY, Bakalis S, Chiriac R, Nicolaides KH. Systolic, diastolic and mean arterial pressure at 30-33 weeks in the prediction of preeclampsia. *Fetal Diagn Ther*. 2013;33(3):173-181. doi:10.1159/000345950
23. Bloomgarden ZT. American Association of Clinical Endocrinologists (AACE) Consensus Conference on the Insulin Resistance Syndrome: 25-26 August 2002, Washington, DC. *Diabetes Care*. 2003;26(3):933-939. doi:10.2337/diacare.26.3.933
24. Wells G, Bleicher K, Han X, et al. Maternal Diabetes, Large-for-Gestational-Age Births, and First Trimester Pregnancy–Associated Plasma Protein-A. *J Clin Endocrinol Metab*. 2015;100(6):2372-2379. doi:10.1210/jc.2014-4103
25. Jensen DM, Korsholm L, Ovesen P, et al. Peri-Conceptional A1C and Risk of Serious Adverse Pregnancy Outcome in 933 Women With Type 1 Diabetes. *Diabetes Care*. 2009;32(6):1046-1048. doi:10.2337/dc08-2061
26. Patil M, Panchanadikar TM, Wagh G. Variation of Papp-A Level in the First Trimester of Pregnancy and Its Clinical Outcome. *J Obstet Gynecol India*. 2014;64(2):116-119. doi:10.1007/s13224-013-0481-4
27. McDonnold M, Mele L, Myatt L, et al. Waist-to-Hip Ratio versus Body Mass Index as Predictor of Obesity-Related Pregnancy Outcomes. *Am J Perinatol*. 2016;33(06):618-624. doi:10.1055/s-0035-1569986
28. Stogianni A, Lendahls L, Landin-Olsson M, Thunander M. Obstetric and perinatal outcomes in pregnancies complicated by diabetes, and control pregnancies, in Kronoberg, Sweden. *BMC Pregnancy Childbirth*. 2019;19(1):159. doi:10.1186/s12884-019-2269-8

29. Boubred F, Pauly V, Romain F, Fond G, Boyer L. The role of neighbourhood socioeconomic status in large for gestational age. Farrar D, ed. *PLoS One*. 2020;15(6):e0233416. doi:10.1371/journal.pone.0233416
30. Scott A, Moar V, Ounsted M. The relative contribution of different maternal factors in large-for-gestational-age pregnancies. *Eur J Obstet Gynecol Reprod Biol*. 1982;13(5):269-277. doi:10.1016/0028-2243(82)90049-1
31. Sonek JD, Kagan KO, Nicolaides KH. Inverted Pyramid of Care. *Clin Lab Med*. 2016;36(2):305-317. doi:10.1016/j.cll.2016.01.009
32. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. *Weight Gain During Pregnancy*. (Rasmussen K, Yaktine A, eds.). National Academies Press; 2009. doi:10.17226/12584
33. Teulings NEWD, Masconi KL, Ozanne SE, Aiken CE, Wood AM. Effect of interpregnancy weight change on perinatal outcomes: systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2019;19(1):386. doi:10.1186/s12884-019-2566-2
34. Menichini D, Petrella E, Dipace V, Di Monte A, Neri I, Facchinetti F. The impact of an early lifestyle intervention on pregnancy outcomes in a cohort of insulin-resistant overweight and obese women. *Nutrients*. 2020;12(5). doi:10.3390/nu12051496
35. Englund-Ögge L, Brantsæter AL, Juodakis J, et al. Associations between maternal dietary patterns and infant birth weight, small and large for gestational age in the Norwegian Mother and Child Cohort Study. *Eur J Clin Nutr*. 2019;73(9):1270-1282. doi:10.1038/s41430-018-0356-y
36. The International Weight Management in Pregnancy (i-WIP) Collaborative Group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ*. 2017;358:j3119. doi:10.1136/bmj.j3119
37. O'Brien EC, Segurado R, Geraghty AA, et al. Impact of maternal education on response to lifestyle interventions to reduce gestational weight gain: individual participant data meta-analysis. *BMJ Open*. 2019;9(8):e025620. doi:10.1136/bmjopen-2018-025620
38. Barker D. Maternal nutrition, fetal nutrition, and disease in later life. *Nutrition*. 1997;13:807–813.
39. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161(11):819-826. doi:10.7326/M14-1884
40. American College of Obstetricians and Gynecologists. Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obs Gynecol*. 2019;133(1):e1-e25.

Figures

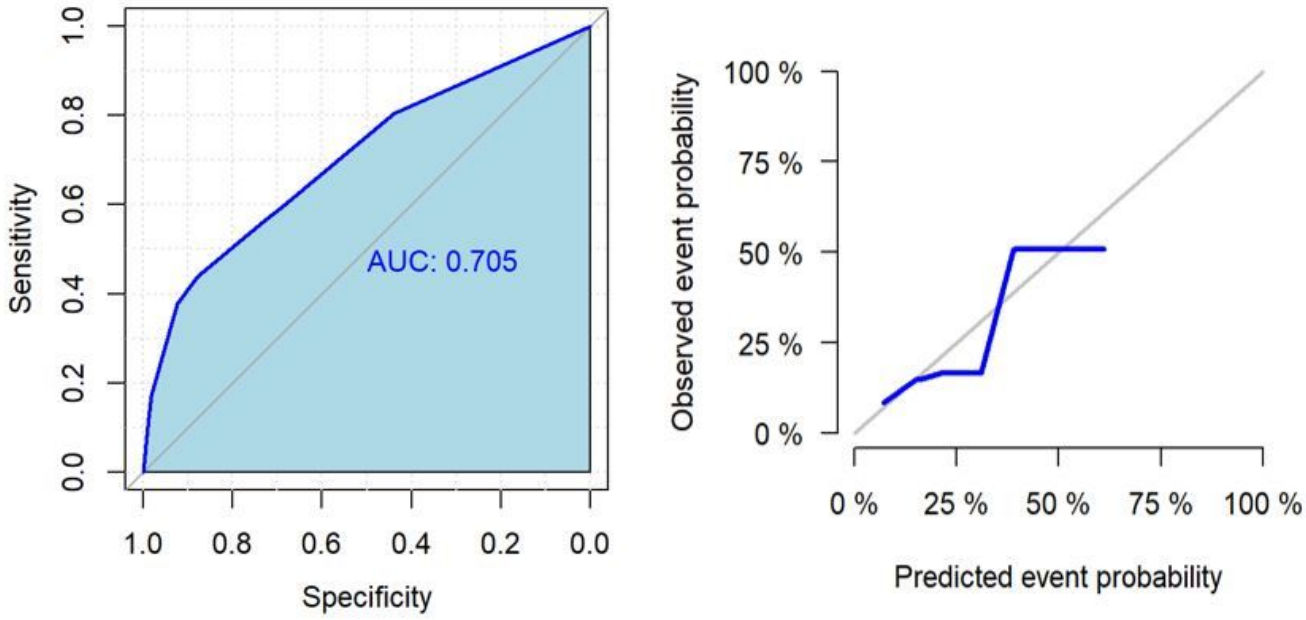

Figure 1

ROC curve and predicted event probability