Sonographic Maturation of the Placenta at 30 to 34 Weeks Is Not Associated With Second Trimester Markers of Placental Insufficiency in Low-risk Pregnancies

Melissa G. Walker, MSc,[1] Peter C. Hindmarsh, MBBS,[2] Michael Geary, MD,[3,4] John C.P. Kingdom, MD[1,3]

[1]Department of Obstetrics and Gynaecology, Mount Sinai Hospital, Toronto ON

[2]Developmental Endocrinology Research Group, Institute of Child Health, University College London, London, UK

[3]Department of Obstetrics and Gynaecology, University College London Hospitals, London, UK

[4]Department of Obstetrics and Gynaecology, Rotunda Hospital, Dublin, Ireland

Abstract

Objective: Advanced placental maturation (Grannum [G] grade 3) before term is associated with adverse perinatal outcomes associated with placental insufficiency. The nature and timing of the underlying pathology of this process is presently unclear. We hypothesized that advanced placental maturation at 30 to 34 weeks' gestation is not associated with established second trimester markers of severe placental dysfunction.

Methods: In a cohort study of 1238 low-risk Caucasian women with singleton pregnancies who had sonographic assessment of placental maturation and fetal growth at 34 weeks, the results of maternal serum screening (MSS) and uterine artery Doppler (UtAD) flow studies at 16 weeks were related to adverse perinatal outcomes associated with placental insufficiency: antepartum hemorrhage, preeclampsia, preterm birth < 37 weeks, small for gestational age (< 10th percentile), or postnatal evidence of intrauterine growth restriction (IUGR; ponderal index < 5th percentile).

Results: G1 was found in 127 women (10.3%), G2 was found in 18 women (1.5%), and no cases of G3 were observed. Advanced Grannum grading was significantly associated with IUGR (48 [4.4%] in G0, 9 [7.1%] in G1, 5 [27.8%] in G2; $P < 0.001$), but was dependent on smoking status. IUGR was not predicted by abnormal MSS or abnormal UtAD findings at either the second or third trimester ultrasounds.

Conclusion: G2 maturation at 30 to 34 weeks' gestation is associated with mild IUGR at delivery in low-risk women and with smoking. IUGR was not predicted by either second or third trimester markers of severe placental dysfunction. Future studies directly observing the placenta in the late third trimester may aid the elusive diagnosis of "late-onset" mild IUGR.

Key Words: Placental ultrasound, Grannum grading, maternal serum screening, intrauterine growth restriction, uterine artery Doppler, fetal growth

Competing Interests: None declared.

Received on June 29, 2010

Accepted on July 13, 2010

Résumé

Objectif : La maturation placentaire avancée (grade 3 de Grannum [G]) avant terme est associée à des issues périnatales indésirables liées à l'insuffisance placentaire. La nature et le moment de l'apparition de la pathologie qui sous-tend ce processus demeurent encore troubles. Nous avons émis l'hypothèse selon laquelle la maturation placentaire avancée à 30-34 semaines de gestation n'était pas associée aux marqueurs établis d'une dysfonction placentaire grave au deuxième trimestre.

Méthodes : Dans le cadre d'une étude de cohorte qui portait sur 1 238 femmes de race blanche n'étant exposées qu'à de faibles risques et présentant une grossesse monofœtale qui ont subi une évaluation échographique de la maturation placentaire et de la croissance fœtale à 34 semaines, les résultat du dépistage sérique maternel (DSM) et d'études Doppler de l'artère utérine (DAUt) à 16 semaines ont été mis en relation avec les issues périnatales indésirables associées à l'insuffisance placentaire : hémorragie antepartum, prééclampsie, accouchement préterme < 37 semaines, hypotrophie fœtale (< 10^{e} percentile) ou signes postnataux de retard de croissance intra-utérin (RCIU; indice pondéral < 5^{e} percentile).

Résultats : Un G1 a été constaté chez 127 femmes (10,3 %), un G2 a été constaté chez 18 femmes (1,5 %) et aucun cas de G3 n'a été constaté. La gradation Grannum avancée a été associée de façon significative au RCIU (48 [4,4 %] en G0, 9 [7,1 %] en G1, 5 [27,8 %] en G2; P < 0,001), mais dépendait du statut quant au tabagisme. Le RCIU n'a pas été prédit par l'obtention de résultats anormaux de DSM ou de DAUt au cours des échographies menées au deuxième ou au troisième trimestre.

Conclusion : Une maturation G2 à 30-34 semaines de gestation est associée au tabagisme et à un RCIU bénin à l'accouchement chez les femmes n'étant exposées qu'à de faibles risques. Le RCIU n'a pu être prédit par les marqueurs de la dysfonction placentaire

grave du deuxième ou du troisième trimestre. La tenue de futures études observant directement le placenta à la fin du troisième trimestre pourrait contribuer au diagnostic difficile à établir de RCIU bénin « d'apparition tardive ».

J Obstet Gynaecol Can 2010;32(12):1134–1139

INTRODUCTION

Sonographic maturational changes of the placenta reflected by the Grannum grading scale were first described by Grannum in 1979.[1] The scale, from G0 (least mature) to G3 (most mature), is often referred to as "placental calcification" because the placental tissue develops greater amounts of reflective (white) particles. The changes were originally proposed as a marker of fetal lung maturity in pregnant women in an era when uncertain gestational age assignment was common.[1] However, subsequent studies revealed that the association with lung maturity is too weak to be clinically useful[2] and is confounded by maternal smoking. Eventually the original potential of this ultrasound observation was supplanted by the move towards implementation of universal early pregnancy dating and nuchal translucency measurements at 12 weeks to derive a risk for trisomy 21,[3] while selective use of amniocentesis for lung maturation studies remains in place.[4]

Follow-up studies of pregnancies with advanced placental maturation remote from term demonstrated an association with a variety of adverse maternal and fetal outcomes, including IUGR, fetal distress in labour, and pregnancy-induced hypertension or preeclampsia.[1,5–10] At one stage, inclusion of the Grannum grade was proposed in an expanded six-variable biophysical profile,[11] but this concept has not gained wider acceptance.[12] In 1987, a randomized controlled clinical trial in 2000 women in the United Kingdom demonstrated a reduction in perinatal mortality arising from placental insufficiency when the observation of a mature placenta at 34 to 36 weeks was followed by weekly fetal surveillance and targeted delivery.[6] The timing of risk identified in this study suggests late-onset placental insufficiency, but the underlying mechanisms of advanced placental maturation remain unknown. The use of placental grading as part of fetal assessment therefore remains controversial in clinical practice.

One explanation is that the underlying pathologic basis of advanced placental maturation remote from term is not well understood. Smoking is an antecedent risk factor,[1,5,6,13] but since the incidence of smoking has greatly reduced,[14,15] it is important to understand the risk factors for advanced placental maturation in non-smoking women. Biochemical markers of placental dysfunction, including unexplained abnormalities in serum levels of AFP and hCG measured in the second trimester maternal serum screening, can predict adverse maternal and perinatal outcomes attributable to placental insufficiency,[16] especially when combined with abnormal UtAD velocimetry.[14,17]

We hypothesized that the phenomenon of advanced placental maturation at 30 to 34 weeks in low-risk women is not predicted by tests that associate with severe, early-onset placental insufficiency, specifically second trimester MSS biochemistry and UtAD flow studies, or with persistently abnormal UtAD alone (uteroplacental vascular insufficiency).

METHODS

We utilized the dataset from our previously published cohort of fetal growth at University College London Hospitals.[18,19] To control for ethnic and racial influences on birth weight,[20,21] only Caucasian women were included in the study since they represented approximately 60% of pregnant women at University College London Hospitals. Other entry criteria were having a single anatomically normal fetus, enrolling at ≤ 20 weeks' gestation, having normal health status with no chronic medical disorders and no current drug therapy (other than iron and pregnancy vitamin supplements), and having an uncomplicated obstetrical history. Of the 1790 women who fulfilled the entry criteria, 1650 chose to participate; 1238 women were ultimately included in this analysis because they had an ultrasound performed at 30 to 34 weeks' gestation and had detailed perinatal information available. There were no demographic differences between those who refused to join the study or did not have a third trimester ultrasound and those who were recruited and included. Participants provided written informed consent.

All participants had a dating ultrasound at ≤ 16 weeks' gestation to confirm fetal viability, and gestational age was reassigned if the ultrasound-derived estimated date of delivery disagreed with the menstrual date by more than seven days. A second trimester anatomical ultrasound was performed at 18 to 24 weeks. A third trimester research ultrasound was performed between 30 and 34 weeks by a single operator (M.G.); this examination included standard fetal biometry, amniotic fluid, and umbilical and UtAD flow studies. The

ABBREVIATIONS

AFP	alpha-fetoprotein
G	Grannum grade
IUGR	intrauterine growth restriction
MoM	multiples of median
MSS	maternal serum screening
UtAD	uterine artery Doppler

placenta was graded according to the system of grading placental maturity originally described by Grannum.[1] G0 or normal was assigned when the placenta had a smooth homogenous texture throughout. G1 referred to cases in which the placenta had random echogenic areas present. G2 referred to cases in which the placenta had basal echogenic areas and indentations in the chorionic plate. G3 referred to the placenta with the most severe evidence of maturational change involving a combination of echo-poor areas, irregular echogenic areas, and deep indentations in the chorionic plate. All ultrasounds were performed with the Acuson 128/Xp ultrasound machine (Mountain View, CA), using a 5 MHz curvilinear transducer.

A second trimester maternal serum sample was obtained (n = 926) to determine concentrations of AFP and hCG, which are reported in multiples of median. Abnormal biochemistry was defined as an elevation in AFP > 2.0 MoM in the absence of a related birth defect of the spine, head, or anterior abdominal wall and/or hCG > 2.5 MoM in the absence of trisomy 21.

Uterine artery Doppler measurements were obtained during the same examination as the second (n = 573) and third (n = 1232) trimester ultrasounds. The cross-over point of the uterine and external iliac arteries was identified to obtain the proximal uterine artery waveform by pulsed Doppler ultrasound. Uterine artery Doppler results were categorized as abnormal when the mean pulsatility index obtained from three consecutive waveforms was greater than 1.45 and/or bilateral early diastolic notches were observed.

Adverse pregnancy outcome was defined as development of any of the following: antepartum hemorrhage, preeclampsia, preterm delivery (< 37 weeks), small-for-gestational age (SGA; birth weight < 10th percentile), and intrauterine growth restriction (IUGR; ponderal index at birth < 5th percentile). Preeclampsia was defined by incremental blood pressure changes[22] together with significant proteinuria (> 0.3g/24 hours or dipstick 2+ or more on two separate specimens prior to delivery). The UK–WHO growth charts[23] were used for birth weight percentile classification of SGA infants. The fifth percentile for ponderal index at birth was determined using the ponderal indices of all infants born to mothers who were included in the study. Placental weight percentile was determined according to Kraus et al.[24]

Demographic data are presented as median and range. The relationship between variables was determined by a chi-square test. A *P* value of < 0.05 was considered statistically significant.

Ethics Committee Approval was obtained by the Research Ethics Committee of University College Hospitals London.

Table 1. Pregnancy outcomes in the cohort

Outcome	n (%)
Placental grade	
G0	1093 (88.3)
G1	127 (10.3)
G2	18 (1.5)
G3	0 (0)
UtAD study (second trimester) + MSS (n = 436)	
Both MSS and UtAD normal	394 (90.4)
Either MSS or UtAD abnormal	40 (9.2)
Both MSS and UtAD abnormal	2 (0.5)
UtAD study, third trimester (n = 1232)	
Normal	1195 (97.0)
Abnormal	38 (3.1)
Mode of delivery: Caesarean section	300 (24.2)

RESULTS

Of 1650 women recruited to the fetal growth cohort study, 1238 had the 30 to 34 week ultrasound examination and detailed pregnancy and perinatal outcome available. The median maternal age of participants in the study was 31 years (range 15 to 48). Median gestational age at the second ultrasound was 20 weeks (18 to 24) and at third trimester ultrasound was 32 weeks (30 to 34). Six hundred sixty-six women (53.8%) were nulliparous, and 232 (18.7%) were current smokers. No significant differences in pregnancy or perinatal outcomes were found between the 1238 patients with the 30 to 34 week ultrasound and the remainder who did not attend this examination. The reasons for not having the 30 to 34 week ultrasound included inability to arrange an appointment within the specified time period, failure to attend the examination, maternal refusal, and preterm delivery.

The MSS and UtAD data are summarized in Table 1 together with the perinatal outcomes of the cohort. A strong association was observed between placental grade and maternal smoking, as previously reported for this cohort,[19] as 127 (11.6%), 91 (71.7%), and 14 (77.8%) women with G0, G1, and G2 placentas, respectively, were smokers ($P < 0.001$).

The incidence of adverse outcomes, grouped by Grannum grade, is presented in Table 2. Advanced placental maturation

Table 2. Incidence of adverse outcomes in women with placental G0, G1, and G2

Variable	Cohort population (n = 1238) n (%)	G0 (n = 1093; 88.3%) n (%)	G1 (n = 127; 10.3%) n (%)	G2 (n = 18; 1.5%) n (%)	*P*
Antepartum hemorrhage	66 (5.3)	58 (5.3)	7 (5.5)	1 (5.6)	0.99
Preeclampsia	45 (3.6)	40 (3.7)	4 (3.1)	1 (5.6)	0.20
Preterm delivery < 37 weeks	48 (3.9)	38 (3.5)	9 (7.1)	1 (5.6)	0.13
SGA	104 (8.4)	80 (7.3)	21 (16.5)	3 (16.7)	0.001
IUGR	62 (5.0)	48 (4.4)	9 (7.1)	5 (27.8)	< 0.001

was significantly associated with IUGR and SGA at delivery. These relationships did not persist after adjustment for being a current smoker. No such differences were found for antepartum hemorrhage, preterm delivery (< 37 weeks), or preeclampsia.

The relationship between Grannum grading and tests of placental function in the second and third trimesters is summarized in Table 3. Fewer than 1% of women in the cohort had abnormalities in both MSS and second trimester UtAD. No significant association was found between placental grade and the number of abnormal tests. Similarly, just over 3% of the women in the cohort had abnormal UtAD findings in the third trimester, and no association was found between placental grade and UtAD abnormalities at 30 to 34 weeks. In addition, no differences in placental weight distribution by Grannum grade were observed (data not shown).

DISCUSSION

This analysis of our fetal growth cohort was designed to explore the timing and therefore the underlying pathological processes associated with advanced placental maturation. In this cohort, we found no association between Grannum grade and proxy markers of early severe placental dysfunction. In addition, no differences in placental weight or their percentiles were noted. These findings suggest that advanced placental maturation represents a mild pathologic process developing in the third trimester, distinct from the observations noted in severe, early-onset IUGR where abnormalities of placental size and shape, first and second trimester biochemistry, and UtAD studies are observed.[14,25]

We found no association between advanced placental maturation and measures of second trimester markers of placental function, including abnormal maternal biochemistry (AFP and hCG), abnormal UtAD flow studies, or abnormalities in both tests. This conclusion is helpful, since it indicates an underlying pathology that is very different from that of early-onset, severe growth restriction, where echogenic cystic lesions, infarcts, and "wobbly" placentas are observed and correlate with UtAD or maternal serum biochemistry abnormalities.[14,15] Advanced placental maturation in this cohort also did not associate with persistent UtAD abnormalities measured at 30 to 34 weeks' gestation. This finding is consistent with other reports describing normal uterine and umbilical artery indices in sonographically mature placentas,[26–28] suggesting adequate utero-placental blood flow to the placental villi. In the context of our study, these observations imply that neither early abnormalities in placental villus development nor subsequent placental ischemia mediate Grannum placental changes. An independent disease process arising in the third trimester likely mediates these changes, because advanced placental maturation segregates with late-onset IUGR characterized by normal umbilical artery Doppler measurements.[26]

An important limitation of our study design was the timing of the fetal growth window at 30 to 34 weeks. Perhaps for this reason, no cases of G3 placenta were seen.[29] In an Irish study, a G3 placenta was observed in 3.8% of low-risk women at 36 weeks.[5] In the randomized controlled trial reported by Proud and Grant, women were screened at 34 to 36 weeks to identify and randomize the subset with a G3 placenta to standard care or increased fetal surveillance.[6] Despite our earlier examination window, a G2 placenta did segregate with postnatal measurements of fetal growth restriction (IUGR; ponderal index < 5th percentile, and SGA fetus; birth weight < 10th percentile). Given the size of this low-risk cohort, it is not surprising that the mild nature of the IUGR process was not associated with antepartum stillbirth. Since the risk of IUGR in a woman with a G2 placenta was attributed to her current smoking history, the detection of advanced placental maturation in a third trimester ultrasound examination should prompt the

Table 3. Relationship between Grannum grading and tests of placental function in the second and third trimesters

	G0	G1	G2
Placental tests in the second trimester (n = 436)	(n = 370; 84.9%) n (%)	(n = 57; 13.1%) n (%)	(n = 9; 2.1%) n (%)
Both UtAD and MSS normal	336 (90.8)	51 (89.5)	7 (77.8)
Either UtAD or MSS abnormal	33 (8.9)	5 (8.8)	2 (22.2)
Both UtAD and MSS abnormal	1 (0.3)	1 (1.8)	0 (0)
Abnormal UtADin the third trimester (n = 1232)	(n = 1088; 88.3%) n (%)	(n = 126; 10.2%) n (%)	(n = 18; 1.5%) n (%)
No	1059 (97.3)	119 (94.4)	17 (94.4)
Yes	29 (2.7)	8 (6.3)	1 (5.6)

clinician to address the woman's current smoking status. Our data do not support the use of Grannum grading in current clinical practice.

Given the associations between advanced placental maturation and adverse outcomes, it is important to investigate the underlying placental pathology. In a stereologic analysis, Jauniaux and colleagues demonstrated adaptive changes in placental villi of G3 placentas at the time of delivery.[30] This is an attractive concept, since it is consistent with the general view that the placenta makes this type of adaptive or compensatory response in other circumstances such as chronic anemia, smoking,[31] or high altitude.[32] A more recent stereologic study found no relationship between the structure of placental villi and Grannum grading, although the placental ultrasound examination in this study was done between 31 to 34 weeks, i.e., several weeks in advance of delivery.[33]

These contrasting publications illustrate the importance of study design in advancing our understanding of placental maturation as expressed in Grannum grading. For example, an important confounding variable in this context, illustrated in our study, is smoking during pregnancy. Almost one in five women smoked in this urban London UK cohort in the mid-1990s. Over the subsequent decade, concerted efforts have been made to reduce the prevalence of smoking during pregnancy, albeit with limited success. For example, in a network study in the United States of 31 sites that had achieved a > 30% reduction in baseline smoking rates during pregnancy, the subsequent education period of 2000–2005 saw the prevalence still ranging from 5.2% to 35.7%.[34] The pathology of a G3 placenta may differ between smokers and non-smokers, and to date no pathology study has distinguished between smokers and non-smokers. Careful pathological studies in the future, including molecular data, may elucidate the mechanisms by which advanced placental maturation, noted by changes in Grannum grade, may predispose a low-risk fetus to stillbirth or asphyxia. The defect may reside at the level of the syncytiotrophoblast layer that regulates fetal growth via its expression of energy-dependent carrier systems.[35]

REFERENCES

1. Grannum PA, Berkowitz RL, Hobbins JC. The ultrasonic changes in the maturing placenta and their relation to fetal pulmonic maturity. Am J Obstet Gynecol 1979;133:915–22.
2. Quinlan RW, Cruz AC, Buhi WC, Martin M. Changes in placental ultrasonic appearance. I. Incidence of Grade III changes in the placenta in correlation to fetal pulmonary maturity. Am J Obstet Gynecol 1982;144:468–70.
3. Driscoll DA, Gross SJ. Screening for fetal aneuploidy and neural tube defects. Genet Med 2009;11:818–21.
4. Roiz-Hernández J, Navarro-Solis E, Carreón-Valdéz E. Lamellar bodies as a diagnostic test of fetal lung maturity. Int J Gynaecol Obstet 2002;77:217–21.
5. McKenna D, Tharmaratnam S, Mahsud S, Dornan J. Ultrasonic evidence of placental calcification at 36 weeks' gestation: maternal and fetal outcomes. Acta Obstet Gynecol Scand 2005;84:7–10.
6. Proud J, Grant AM. Third trimester placental grading by ultrasonography as a test of fetal wellbeing. Br Med J (Clin Res Ed) 1987;294:1641–4.
7. Chitlange SM, Hazari KT, Joshi JV, Shah RK, Mehta AC. Ultrasonographically observed preterm grade III placenta and perinatal outcome. Int J Gynaecol Obstet 1990;31:325–8.
8. Baeza Valenzuela A, García Méndez A. Premature aging of the placenta. Ultrasonic diagnosis [article in Spanish]. Ginecol Obstet Mex 1995;63:287–92.
9. Zhang LY, Yu YH, Hu ML. Association between ultrasonographic signs of placental premature aging and pregnancy outcome [article in Chinese]. Di Yi Jun Yi Da Xue Xue Bao 2005;25:318–20.

10. Vosmar MB, Jongsma HW, van Dongen PW. The value of ultrasonic placental grading: no correlation with intrauterine growth retardation or with maternal smoking. J Perinat Med 1989;17:137–43.

11. Vintzileos AM, Campbell WA, Ingardia CJ, Nochimson DJ. The fetal biophysical profile and its predictive value. Obstet Gynecol 1983;62:271–8.

12. Ashton SS, Russo MP, Simon NV, Shearer DM. Relationship between Grade III placentas and biparietal diameter determinations. J Ultrasound Med 1983;2:127–9.

13. Brown HL, Miller JM Jr., Khawli O, Gabert HA. Premature placental calcification in maternal cigarette smokers. Obstet Gynecol 1988;71:914–7.

14. Toal M, Chan C, Fallah S, Alkazaleh F, Chaddha V, Windrim RC, et al. Usefulness of a placental profile in high-risk pregnancies. Am J Obstet Gynecol 2007;196:363.e1–e7.

15. Toal M, Keating S, Machin G, Dodd J, Adamson SL, Windrim RC, et al. Determinants of adverse perinatal outcome in high-risk women with abnormal uterine artery Doppler images. Am J Obstet Gynecol 2008;198:330.e1–e7.

16. Gagnon A, Wilson RD, Audibert F, Allen VM, Blight C, Brock JA, et al. Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Obstetrical complications associated with abnormal maternal serum markers analytes. J Obstet Gynaecol Can 2008;30:918–49.

17. Toal M, Chaddha V, Windrim R, Kingdom J. Ultrasound detection of placental insufficiency in women with elevated second trimester serum alpha-fetoprotein or human chorionic gonadotropin. J Obstet Gynaecol Can 2008;30:198–206.

18. Hindmarsh PC, Geary MP, Rodeck CH, Kingdom JC, Cole TJ. Intrauterine growth and its relationship to size and shape at birth. Pediatr Res 2002;52:263–8.

19. Pringle PJ, Geary MP, Rodeck CH, Kingdom JC, Kayamba-Kay's S, Hindmarsh PC. The influence of cigarette smoking on antenatal growth, birth size, and the insulin-like growth factor axis. J Clin Endocrinol Metab 2005;90:2556–62.

20. Gruenwald P. Growth of the human fetus. I. Normal growth and its variation. Am J Obstet Gynecol 1966;94:1112–9.

21. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992;339:283–7.

22. Redman CW, Jefferies M. Revised definition of pre-eclampsia. Lancet 1988;1:809–12.

23. UK-WHO growth charts: early years, 2009/2010. Available at: http://www.rcpch.ac.uk/Research/UK-WHO-Growth-Charts. Accessed September 29, 2010.

24. Kraus FT, Redline RW, Gersell DJ, Nelson DM, Dicke JM. Placental pathology. Washington, DC: American Registry of Pathology; 2004.

25. Viero S, Chaddha V, Alkazaleh F, Simchen MJ, Malik A, Kelly E, et al. Prognostic value of placental ultrasound in pregnancies complicated by absent end-diastolic flow velocity in the umbilical arteries. Placenta 2004;25:735–41.

26. Hershkovitz R, Kingdom JC, Geary M, Rodeck CH. Fetal cerebral blood flow redistribution in late gestation: identification of compromise in small fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol 2000;15:209–12.

27. Kara SA, Toppare MF, Avsar F, Caydere M. Placental aging, fetal prognosis and fetomaternal Doppler indices. Eur J Obstet Gynecol Reprod Biol 1999;82:47–52.

28. Degani S, Paltieli Y, Lewinsky R, Abramovici D, Sharf M. Fetal and uteroplacental flow velocity waveforms and placental grading. Am J Perinatol 1991;8:47–9.

29. Hill LM, Breckle R, Ragozzino MW, Wolfgram KR, O'Brien PC. Grade 3 placentation: incidence and neonatal outcome. Obstet Gynecol 1983;61:728–32.

30. Burton GJ, Jauniaux E. Sonographic, stereological and Doppler flow velocimetric assessments of placental maturity. Br J Obstet Gynaecol 1995;102:818–25.

31. Pfarrer C, Macara L, Leiser R, Kingdom J. Adaptive angiogenesis in placentas of heavy smokers. Lancet 1999;354:303.

32. Kingdom J. Adriana and Luisa Castellucci Award Lecture 1997. Placental pathology in obstetrics: adaptation or failure of the villous tree? Placenta 1998;19:347–51.

33. Yin TT, Loughna P, Ong SS, Padfield J, Mayhew TM. No correlation between ultrasound placental grading at 31–34 weeks of gestation and a surrogate estimate of organ function at term obtained by stereological analysis. Placenta 2009;30:726–30.

34. Tong VT, Jones JR, Dietz PM, D'Angelo D, Bombard JM; Centers for Disease Control and Prevention. Trends in smoking before, during, and after pregnancy—Pregnancy Risk Assessment Monitoring System (PRAMS), United States, 31 sites, 2000–2005. MMWR Surveill Summ 2009;58:1–29.

35. Sibley CP. Understanding placental nutrient transfer—why bother? New biomarkers of fetal growth. J Physiol 2009;587:3431–40.