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# Turning the Pyramid of Prenatal Care

Kypros H. Nicolaides[a, b]

[a]Harris Birthright Research Centre of Fetal Medicine, King's College Hospital, and [b]Department of Fetal Medicine, University College Hospital, London, UK

**Key Words**
First-trimester screening · Prenatal care · Preeclampsia · Preterm delivery · Gestational diabetes · Hypothyroidism · Small for gestational age · Macrosomia · Miscarriage · Stillbirth · Nuchal translucency

**Abstract**
The current approach to prenatal care, which involves visits at 16, 24, 28, 30, 32, 34 and 36 weeks and then weekly until delivery, was established 80 years ago. The high concentration of visits in the third trimester implies, firstly, that most complications occur at this late stage of pregnancy and, secondly, that most adverse outcomes are unpredictable during the first or even second trimester. This review presents evidence that many pregnancy complications can now be predicted at an integrated first hospital visit at 11–13 weeks by combining data from maternal characteristics and history with findings of biophysical and biochemical tests. It is therefore proposed that the traditional pyramid of care should be inverted with the main emphasis placed in the first rather than third trimester of pregnancy.

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## Introduction

In the 19th century, pregnancy care was confined to the time of delivery and reserved for the wealthy. In the beginning of the 20th century, high maternal and infant mortality stimulated the establishment of institutions for provision of prenatal care [1, 2]. In 1929, the Ministry of Health in the UK issued a Memorandum on Antenatal Clinics recommending that women should first be seen at 16 weeks, then at 24 and 28 weeks, fortnightly thereafter until 36 weeks and then weekly until delivery (fig. 1) [3]. Although no explicit rationale was offered for either the timing or clinical content of the visits, these guidelines established the pattern of antenatal care that is followed throughout the world even today. The high concentration of visits in the third trimester implies that, firstly, most complications occur at this late stage of pregnancy and, secondly, that most adverse outcomes are unpredictable during the first or even the second trimester.

In the last 20 years, it has become apparent that an integrated first hospital visit at 11–13 weeks combining data from maternal characteristics and history with findings of biophysical and biochemical tests can define the patient-specific risk for a wide spectrum of pregnancy complications, including fetal abnormalities, miscarriage and stillbirth, preeclampsia, preterm delivery, gestational diabetes, fetal growth restriction and macrosomia. Early estimation of patient-specific risks for these pregnancy complications would improve pregnancy outcome by shifting prenatal care from a series of routine visits to a more individualized patient- and disease-specific approach both in terms of the schedule and content of such visits. Each visit would have a predefined objective and the findings would generate likelihood ratios that can be used to modify the individual patient- and disease-specific estimated risk from the initial assessment at 11–13 weeks.

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Prof. K.H. Nicolaides
Harris Birthright Research Centre for Fetal Medicine, King's College Hospital
Denmark Hill
London SE5 9RS (UK)
Tel. +44 203 299 8256, E-Mail kypros@fetalmedicine.com

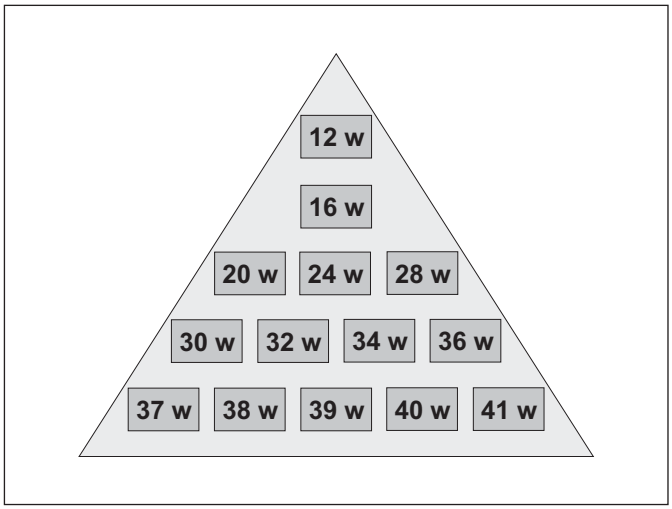


**Fig. 1.** Pyramid of traditional prenatal care established in 1929. w = Weeks.

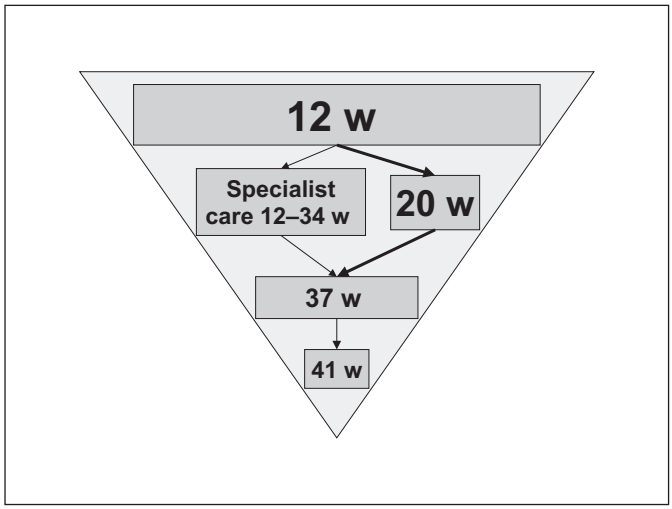


**Fig. 2.** Proposed new pyramid of prenatal care. w = Weeks.

At 11–13 weeks, the great majority of women would be classified as being at low-risk for pregnancy complications and a small proportion of women would be selected as being at high-risk (fig. 2). In the low-risk group, the number of medical visits could be substantially reduced to perhaps three. One visit at 20–22 weeks would re-evaluate fetal anatomy and growth, and reassess risk for such complications as preeclampsia and preterm delivery. Another visit at 37–38 weeks would assess maternal and fetal well-being and determine the best time and method of delivery, which would be repeated at 41 weeks for the few that remain pregnant at this stage. The high-risk group could have close surveillance in specialist clinics both in terms of the investigations to be performed and the personnel involved in the provision of care. In each of these visits, their risk would be reassessed and they would either remain high-risk or become low-risk, in which case the intensity of their care could be reduced.

This review summarizes the emerging evidence on the potential value of the 11 to 13 weeks' assessment and sets the basis for a challenge to invert the 80-year-old pyramid of prenatal care.

## Early Screening for Fetal Aneuploidies

Aneuploidies are major causes of perinatal death and childhood handicap. Consequently, the detection of chromosomal disorders constitutes the most frequent indication for invasive prenatal diagnosis. However, invasive testing, by amniocentesis or chorionic villus sampling, is associated with a risk of miscarriage; therefore, these tests are carried out only in pregnancies considered to be at high risk for aneuploidies.

*The Combined Test*

In the 1970s, the main method of screening for aneuploidies was by maternal age. In the 1980s, it was done by maternal serum biochemistry and detailed ultrasonographic examination in the second trimester. In the 1990s, the emphasis shifted to the first trimester when it was realized that the great majority of fetuses with major aneuploidies can be identified by a combination of maternal age, fetal nuchal translucency (NT) thickness, maternal serum-free β-hCG and PAPP-A [4–14]. Screening by this combined test can identify about 90% of fetuses with trisomy 21 and other major aneuploidies for a false-positive rate of 5%.

Studies in the last 10 years have shown that improvement in the performance of first-trimester screening can be achieved by (1) carrying out the biochemical test at 9–10 weeks and the ultrasound scan at 12 weeks and (2) inclusion in the ultrasound examination assessment of the nasal bone and flow in the ductus venosus, hepatic artery and across the tricuspid valve.

*Timing of Ultrasound and Biochemistry*

One option in first-trimester combined screening for trisomy 21 is to perform biochemical and ultrasonographic testing as well as counsel women in one-stop clin-

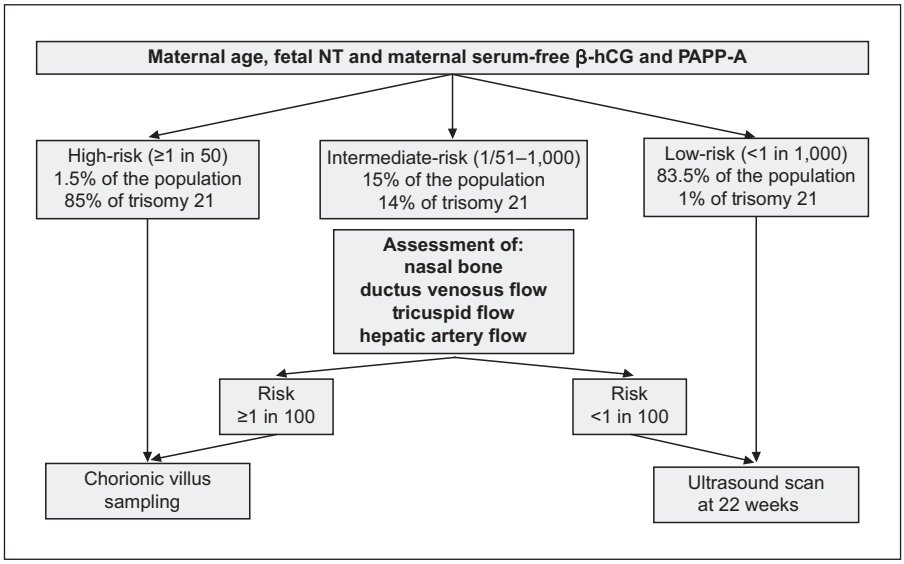


**Fig. 3.** Two-stage screening for fetal aneuploidies. In the first stage, all patients have screening using a combination of maternal age, fetal NT thickness and maternal serum-free β-hCG and PAPP-A; according to the results, they are classified into high-risk, intermediate-risk and low-risk groups. In the intermediate-risk group, second-stage screening is carried out by one or more sonographic markers, including nasal bone, blood flow in the ductus venosus, hepatic artery or across the tricuspid valve, and on the basis of these results, they are then classified as high-risk or low-risk.

ics for assessment of risk (OSCAR) [9, 10, 15]. The ideal gestation for OSCAR is 12 weeks because the aim of the first-trimester scan is not just to screen for trisomy 21 but also to diagnose an increasing number of fetal malformations. In this respect, the ability to visualize fetal anatomy is better at 12 weeks than at 10–11 or 13–14 weeks.

An alternative strategy for first-trimester combined screening is for biochemical testing and ultrasound scanning to be carried out on two separate visits, with the first done at 9–10 weeks and the second at 12 weeks [13, 14, 16]. It has been estimated that this approach would improve the detection rate from 90 to 93–94%. A third option would be to perform the scan at 12 weeks and optimize the performance of biochemical testing by measuring PAPP-A at 9 weeks and free β-hCG at the time of the scan at 12 weeks or even later, which would have an estimated detection rate of 95%. The cost and patient acceptability of the alternative policies of first-trimester testing will depend on the existing infrastructure of antenatal care. The potential advantage of two- or three-stage screening in terms of detection rate may be eroded by the likely increased noncompliance with the additional steps.

*Additional Ultrasound Markers*

At 11–13 weeks, absence of the fetal nasal bone, reversed a-wave in the ductus venosus, tricuspid regurgitation and increased peak systolic velocity in the hepatic artery are observed in about 60, 66, 55 and 80% of fetuses with trisomy 21 and in 2.5, 3.0, 1.0 and 5% of euploid fetuses, respectively [17–26].

In first-trimester combined screening, each of the additional ultrasound markers can be assessed in all patients resulting in an increase in detection rate to 93–96% and a decrease in the false-positive rate to 2.5% [19, 21, 24, 27]. A similar performance of screening can be achieved by a contingent policy in which first-stage screening by maternal age, fetal NT and serum-free β-hCG and PAPP-A is offered to all cases (fig. 3). Patients with a risk of 1 in 50 or more are considered to be screen-positive and those with a risk of less than 1 in 1,000 are screen-negative. Patients with the intermediate risk of 1 in 51 to 1 in 1,000, which constitutes 15–20% of the total population, have second-stage screening with nasal bone, ductus venosus or tricuspid blood flow, which modifies their first-stage risk. If the adjusted risk is 1 in 100 or more the patients are considered to be screen-positive and those with a risk of less than 1 in 100 are screen-negative.

## Early Diagnosis of Fetal Abnormalities

The 11 to 13 weeks' scan evolved over the last 20 years from essentially a scan for measurement of fetal NT and crown-rump length to one which includes a basic checklist for examination of the fetal anatomy with the intention of diagnosing major abnormalities which are either lethal or associated with severe handicap so that the parents can have the option of earlier and safer pregnancy termination.

Major fetal abnormalities fall into essentially three groups in relation to whether they can be detected at the 11 to 13 weeks' scan [28]. The first group consists of abnormalities which are always detectable, and include body stalk anomaly, anencephaly, alobar holoprosencephaly, exomphalos, gastroschisis and megacystis. The second group consists of undetectable abnormalities because they are manifested only during the second or third trimester of pregnancy, and include microcephaly, agenesis of the corpus callosum, semilobar holoprosencephaly, hypoplasia of the cerebellum or vermis, cystic adenomatoid malformation or pulmonary sequestration, and bowel obstruction. The third group includes abnormalities that are potentially detectable depending on, firstly, the objectives set for such a scan and, consequently, the time allocated for the fetal examination, the expertise of the sonographer and the quality of the equipment used. Additionally, the presence of an easily detectable marker for an underlying abnormality is also important for detection. A good example of such a marker in the first trimester is high NT, which is found in some fetuses with lethal skeletal dysplasias, diaphragmatic hernia and major cardiac defects.

*Major Cardiac Defects*

Abnormalities of the heart and great arteries are the most common congenital defects, accounting for about 20% of all stillbirths and 30% of neonatal deaths due to congenital defects [29]. Although most major cardiac defects are amenable to prenatal diagnosis by specialist fetal echocardiography, routine ultrasound screening in pregnancy fails to identify the majority of affected fetuses [30–32]. Consequently, effective population-based prenatal diagnosis necessitates improved methods of identifying the high-risk group for referral to specialists. The traditional method of screening for cardiac defects, which relies on family history of cardiac defects, maternal history of diabetes mellitus and maternal exposure to teratogens, identifies only about 10% of affected fetuses [33].

A major improvement in screening for cardiac defects came with the realization that the risk for cardiac defects increases with fetal NT thickness and is also increased in those with abnormal flow in the ductus venosus and across the tricuspid valve [34–40]. Reversed a-wave in the ductus venosus or tricuspid regurgitation, observed in about 2 and 1%, respectively, of normal fetuses is found in 30% of affected fetuses. Specialist fetal echocardiography for cases with NT above the 99th centile and those with reversed a-wave in the ductus venosus or tricuspid regurgitation, irrespective of NT, would require cardiac scanning in about 4% of the population and would detect about 50% of major cardiac defects.

*Open Spina Bifida*

In almost all cases of open spina bifida, there is an associated Arnold-Chiari malformation which is thought to be the consequence of leakage of cerebrospinal fluid into the amniotic cavity and hypotension in the subarachnoid spaces leading to caudal displacement of the brain and obstructive hydrocephalus. In the second trimester of pregnancy, the manifestations of the Arnold-Chiari malformation are the lemon and banana signs [41].

It has recently been realized that in open spina bifida, caudal displacement of the brain is apparent at 11–13 weeks in the same midsagittal view of the fetal face as for measurement of fetal NT and assessment of the nasal bone [42, 43]. In this view, the lower part of the fetal brain between the sphenoid bone anteriorly and the occipital bone posteriorly can be divided into the brain stem in the front and a combination of the fourth ventricle and cistern magna in the back (fig. 4). In fetuses with open spina bifida, the brain stem diameter is increased and the diameter of the fourth ventricle-cisterna magna complex is decreased.

It is possible that examination of the posterior fossa may also lead to the detection of at least some of the cases of cerebellar and vermian hypoplasia that are now missed in the first-trimester scan.

## Early Screening for Miscarriage and Stillbirth

The rates of miscarriage and stillbirth after demonstration of a live fetus at 11–13 weeks are about 1 and 0.4%, respectively [44]. Increased risk for miscarriage and stillbirth are associated with certain maternal characteristics, including increasing maternal age and maternal weight, previous miscarriage or stillbirth, and African racial origin. Miscarriage and stillbirth are also associated with abnormal results of first-trimester screening for aneuploidies, including increased fetal NT thickness, reversed a-wave in the fetal ductus venosus and low maternal serum PAPP-A [44].

Algorithms which combine maternal characteristics and biophysical and biochemical tests at 11–13 weeks could potentially identify about 35% of pregnancies that subsequently miscarry and 45 and 25% of stillbirths before and after 34 weeks, respectively, with a false-positive rate of 10% [44]. Such performance of screening is poor

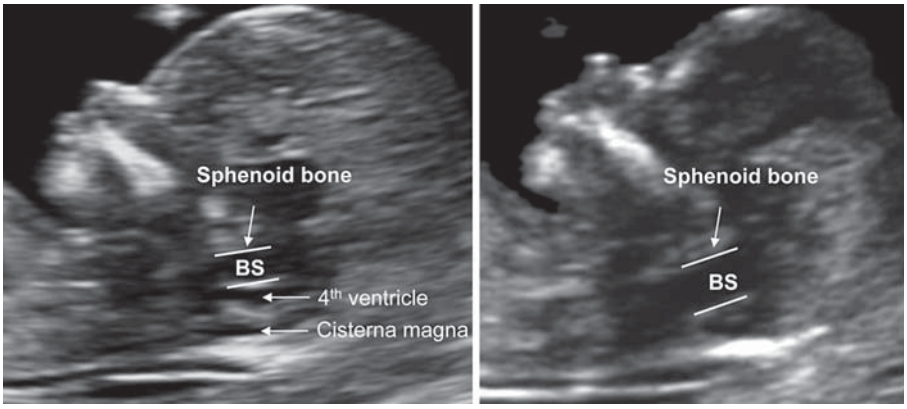


**Fig. 4.** Midsagittal view of the fetal brain in a normal (left) and a spina bifida (right) fetus at 12 weeks, demonstrating the measurement of brain stem (BS) diameter. In open spina bifida, the brain stem diameter is increased.

compared to combined testing for aneuploidies. However, unlike screening for aneuploidies where the endpoint is well defined, the heterogeneous etiology of miscarriage and stillbirth will hamper efforts to develop a high-performance screening test, unless the fetal losses are subdivided according to cause and we introduce disease-oriented biophysical and biochemical testing.

*Use of the Algorithm for Miscarriage*

The model for prediction of miscarriage can be used for the monitoring of risks from invasive antenatal interventions, such as chorionic villus sampling. The same risk factors leading to chorionic villus sampling, including increased maternal age, high fetal NT, reversed a-wave in the fetal ductus venosus and decreased serum PAPP-A, are also associated with increased risk for miscarriage. Consequently, these factors should be taken into account in monitoring the operator-dependent procedure-related risk of miscarriage.

*Use of the Algorithm for Stillbirth*

Early identification of the group at high risk for stillbirth could lead to a reduction of this complication through closer monitoring of fetal growth and well-being and appropriate timing of delivery.

## Early Screening for Preeclampsia

Preeclampsia, which affects 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality. There is evolving evidence that both the degree of impaired placentation and the incidence of adverse fetal and maternal short-term and long-term consequences of preeclampsia are inversely related to the gestational age at onset of the disease [45–50]. Consequently, the endpoint in screening for preeclampsia should not be total preeclampsia, but the condition should be subdivided according to gestational age at delivery.

Algorithms which combine maternal characteristics and biophysical and biochemical tests at 11–13 weeks could potentially identify about 90, 80 and 60% of pregnancies that subsequently develop early (before 34 weeks), intermediate (34–37 weeks) and late (after 37 weeks) preeclampsia, with a false-positive rate of 5% [51].

*Maternal Characteristics and History*

The risk for preeclampsia increases with maternal weight and decreases with height, is higher in women of African and South Asian racial origin than in Caucasians, and is increased in women conceiving after the use of ovulation induction drugs, in those with a personal or family history of preeclampsia and in those with pre-existing chronic hypertension or diabetes mellitus [51]. In general, the odds ratios for the factors in maternal history which define the risk for preeclampsia are inversely proportional to the gestation at delivery, with higher ratios for early disease compared to intermediate and late preeclampsia (fig. 5).

*Biophysical and Biochemical Markers*

The biophysical tests are uterine artery pulsatility index and mean arterial pressure. Increased uterine artery pulsatility index reflects the underlying mechanism for the development of preeclampsia which is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide nonmuscular channels independent of maternal vasomotor control [52–54].

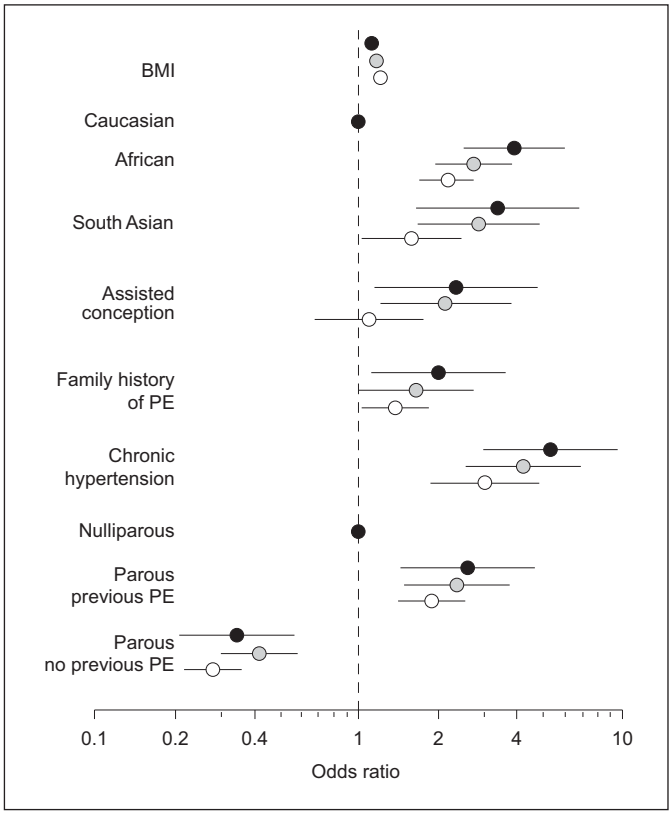


**Fig. 5.** Forest plot of odds ratios with 95% confidence interval of risk factors for development of early preeclampsia (PE; black circles), intermediate preeclampsia (grey circles) or late preeclampsia (open circles).

The biochemical tests are placental products thought to be involved in placentation or in the cascade of events leading from impaired placentation to placental ischemia and damage with release of inflammatory factors which cause platelet activation and endothelial dysfunction and consequent development of the clinical symptoms of the disease [55–57]. These include PAPP-A, placental growth factor, endoglin, activin-A and inhibin-A [51].

As in the case of maternal factors, the differences in biophysical and biochemical markers of impaired placentation between the affected and unaffected pregnancies are in general more pronounced in those developing early preeclampsia compared to intermediate or late disease (fig. 6) [51].

*Implications of Early Assessment of Patient-Specific Risk*

Effective early identification of the high-risk group for subsequent development of preeclampsia could potentially improve outcome by directing such patients to specialist clinics for close surveillance and would be the basis for future studies investigating the potential role of pharmacological interventions, such as aspirin, beginning in the first trimester to improve placentation and reduce the prevalence of the disease. Recent evidence suggests that the prophylactic use of low-dose aspirin started in early pregnancy can potentially halve the incidence of preeclampsia [58].

## Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is associated with increased risk of maternal and perinatal short-term and long-term complications [59–64]. The frequency of adverse pregnancy outcomes can be reduced by appropriate treatment of GDM [60, 65]. However, there is no internationally accepted method of screening. In the UK, it is recommended that an oral glucose tolerance test, which is the diagnostic test for gestational diabetes, should be offered to women with any of the following risk factors: BMI >30, previous history of GDM or macrosomic baby (>4.5 kg), or family history of diabetes or racial origin with a high prevalence of diabetes such as South Asian, African-Caribbean and Middle Eastern [66]. The performance of such screening is poor with a detection rate of about 60% and false-positive rate of 30–40% [67].

Algorithms combining maternal characteristics and biochemical tests at 11–13 weeks could potentially identify about 75% of pregnancies that subsequently develop GDM, with a false-positive rate of 20% [68].

*Maternal Characteristics and History*

The risk for the development of GDM increases with maternal age and BMI, is higher in women of African and South Asian racial origin than in Caucasians, and is increased in women with a family history of diabetes and previous pregnancies complicated by GDM and delivery of macrosomic neonates (fig. 7). The performance of screening by a regression model based on maternal factors with an estimated detection rate of about 60% and false-positive rate of 20% is superior to using each maternal factor as an independent screening test [66, 68, 69].

*Biochemical Markers*

In pregnancies that develop GDM, the maternal serum levels of adiponectin, an adipocyte-derived polypeptide, and sex hormone-binding globulin, a liver-derived glycoprotein, at 11–13 weeks are reduced by about

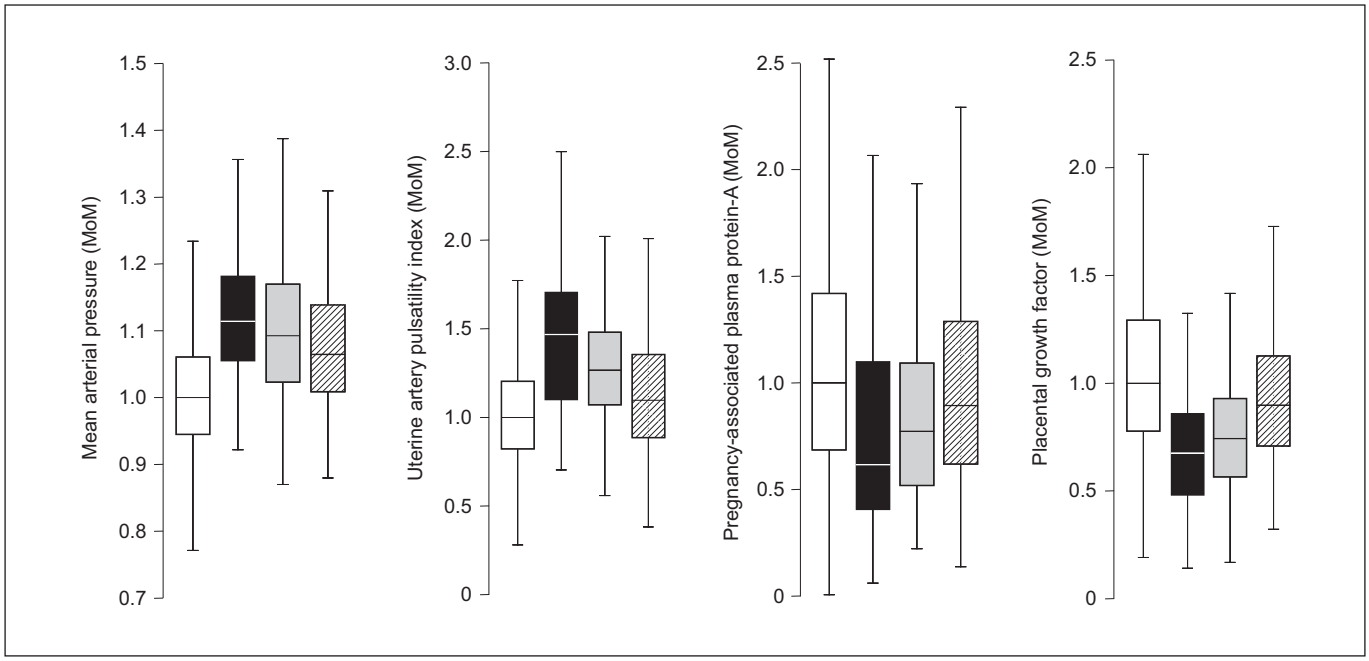


**Fig. 6.** Box and whisker plots (median, interquartile range and range) of biophysical and biochemical markers, expressed as the multiple of the normal median (MoM) in pregnancies that develop early preeclampsia (black boxes), intermediate preeclampsia (grey boxes) or late preeclampsia (hatched boxes) compared to pregnancies with normal outcome (white boxes).

30 and 20%, respectively [68]. In contrast, the concentration of visfatin, which is produced by adipose tissue, is increased by about 30% [70]. There is contradictory evidence that the serum concentration of follistatin-like-3 may also be reduced at 11–13 weeks [68, 71].

In women who had a previous pregnancy affected by GDM, the risk of recurrence is very high and such women can be automatically classified as screen-positive [72]. In nulliparous women and in those without a previous history of GDM, screening by a combination of maternal factors and serum adiponectin and sex hormone-binding globulin could identify about 65% of pregnancies that subsequently develop GDM, with a false-positive rate of 20%. A two-stage screening policy (screen positivity is defined by a history of previous GDM and the results of the combined test in those without such history) could identify about 75% of affected pregnancies at 11–13 weeks.

*Diagnosis of Gestational Diabetes at 11–13 Weeks*

The widely accepted gestation of 24–28 weeks for screening of GDM is based on an arbitrary recommendation which attempts to achieve a balance between two opposing factors: (1) the need to maximize the detection rate of GDM by testing as late in pregnancy as possible

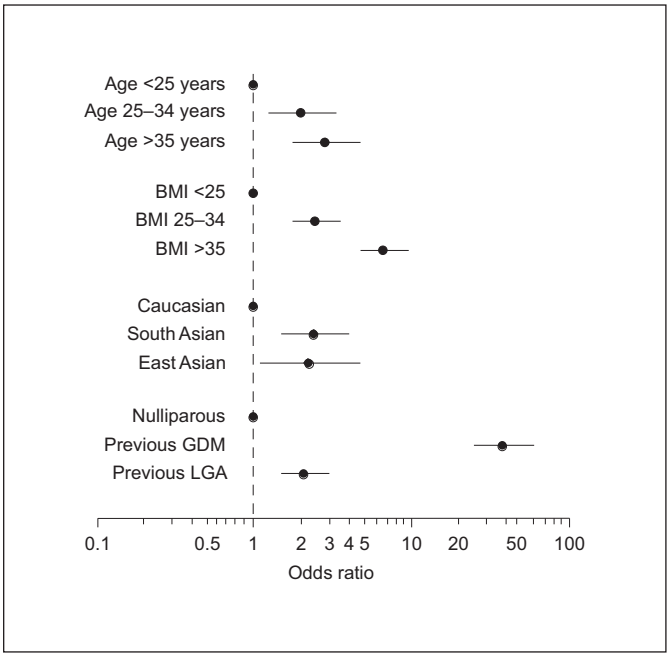


**Fig. 7.** Forest plot of odds ratios with 95% confidence interval of risk factors for development of GDM. LGA = Large for gestational age.

because the diabetogenic effect of pregnancy increases with gestation, and (2) to maximize the duration of therapeutic intervention for reduction in the maternal and perinatal complications associated with GDM.

The desire to diagnose GDM in the first trimester of pregnancy could be achieved by lowering the currently used second-trimester cutoffs in plasma glucose levels both for screening and diagnosis of the condition. In screening for GDM in the first trimester, the cutoff for the 1-hour plasma glucose level after the oral administration of 50 g of glucose should be 130 rather than 140 mg/dl. In the diagnosis of GDM, the cutoffs for the 1-, 2- and 3-hour blood glucose levels after the oral administration of 100 g of glucose should be 18–35% lower than the recommended cutoffs for the late second trimester of pregnancy [73].

*Implications of Early Assessment of Patient-Specific Risk*

Effective early identification of the high-risk group for subsequent development of GDM is likely to improve pregnancy outcome because appropriate dietary advice and pharmacological interventions, with such drugs as metformin, can reduce the incidence of the disease and associated fetal macrosomia.

## Small for Gestational Age Fetuses

Small for gestational age (SGA) fetuses with birth weight below the 5th centile for gestational age at delivery are at increased risk of perinatal death and handicap. These risks are substantially reduced in cases of SGA identified prenatally, compared to those detected after birth [74].

Screening for SGA in the absence of preeclampsia by a combination of maternal characteristics and obstetric history with a series of biophysical and biochemical markers at 11–13 weeks could potentially identify (at a false positive rate of 10%) about 75% of pregnancies delivering SGA neonates before 37 weeks and 45% of those delivering at term [75].

*Maternal Characteristics and History*

The risk for SGA increases with maternal age and decreases with maternal weight and height, is higher in women of African and Asian racial origin than in Caucasians, and is increased in cigarette smokers, those with a medical history of chronic hypertension, women with a previous SGA neonate and those who had assisted conception [76]. The estimated detection rate of SGA in the absence of preeclampsia with the use of the algorithm of maternal characteristics and obstetric history is about 35%, with a false-positive rate of 10%.

*Biophysical and Biochemical Markers*

The risk for SGA is inversely related to fetal NT at 11–13 weeks [76]. In pregnancies with SGA in the absence of preeclampsia, there is evidence of impaired placental perfusion and function from the first trimester of pregnancy. Uterine artery pulsatility index and mean arterial pressure are increased and placental volume and serum PAPP-A, free β-hCG, PLGF, PP13 and ADAM12 are decreased [75–77]. However, the magnitude of impairment in placental perfusion and function is considerably less than in preeclampsia. This is not surprising because, unlike preeclampsia which is a pathological disorder, SGA is a heterogeneous condition which includes constitutionally small fetuses, at no or minimally increased risk of perinatal death and handicap, and growth-restricted fetuses due to impaired placentation, genetic disease or environmental damage.

The impairment in placental function is greater for the subgroup of SGA delivering before 37 weeks than those delivering at or after 37 weeks [75]. Since the proportion of growth-restricted fetuses to constitutional SGA is likely to be higher in the preterm rather than term SGA, our findings imply that the early biophysical and biochemical markers could be identifying the growth-restricted subgroup amongst the SGA.

*Implications of Early Assessment of Patient-Specific Risk*

Effective early identification of the high-risk group for SGA could potentially improve pregnancy outcome by directing such patients to specialist clinics for regular monitoring of fetal growth and well-being. There is also evidence that the prophylactic use of low-dose aspirin started in early pregnancy can potentially halve the incidence of fetal growth restriction [58].

## Fetal Macrosomia

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 [78, 79].

Screening for macrosomia (birth weight above the 90th centile for gestational age at delivery) by a combination of maternal characteristics and obstetric history with fetal NT and maternal serum free β-hCG and PAPP-A at 11–13 weeks could potentially identify, at a false-positive rate of 10%, about 35% of women who deliver macrosomic neonates [80]. The detection rate is further improved to about 40% with the measurement of maternal serum adiponectin concentration at 11–13 weeks [81].

*Maternal Characteristics and History*

The risk for macrosomia increases with maternal weight and height, and is higher in parous women who had previously delivered a macrosomic infant and/or have a medical history of diabetes mellitus; however, the risk is lower in women of African and South Asian racial origins, in cigarette smokers and in those with a medical history of chronic hypertension [80].

*Biophysical and Biochemical Markers*

The risk for macrosomia increases with fetal NT, maternal serum-free β-hCG and PAPP-A, and is inversely related to serum adiponectin. A possible mechanism for the association between serum PAPP-A and macrosomia is related to the proteolytic properties of PAPP-A, which cleaves insulin-like growth factor-binding proteins, thereby increasing the bioavailability of insulin-like growth factor, which is thought to play a key role in the control of placental growth and transfer of nutrients to the fetus [82–84]. There are no obvious explanations for the associations of macrosomia with high serum-free β-hCG and fetal NT. The likely mechanism underlying the association between low maternal serum adiponectin and neonatal macrosomia is increased insulin resistance and glucose intolerance [81].

*Implications of Early Assessment of Patient-Specific Risk*

The performance of early screening for macrosomia is poor compared to that of screening for aneuploidies and preeclampsia. Future research should identify new biophysical and biochemical markers which could improve the performance of screening. Similarly, future studies should try to determine the extent to which knowledge of the individual patient-specific risk for macrosomia by first-trimester combined screening can improve antenatal surveillance and prevention of macrosomia itself or the intrapartum complications related to macrosomia.

**Preterm Delivery**

Preterm birth is the leading cause of perinatal death and handicap in children, with the vast majority of mortality and morbidity related to early delivery before 34 weeks [85, 86]. Delivery before 34 weeks occurs in about 2% of singleton pregnancies. In two thirds of the cases, this is due to spontaneous onset of labor or preterm prelabor rupture of membranes. In the other third, it is iatrogenic and mainly due to preeclampsia [87].

The rate of preterm delivery has not decreased in the last 30 years [88]. Although improvements in neonatal care have led to higher survival of very premature infants, a major impact on the associated mortality and morbidity will only be achieved through the development of a sensitive method to identify women at high risk of preterm delivery and an effective strategy for prevention of this complication.

The risk of spontaneous preterm birth is increased in women with a previous late miscarriage or preterm delivery and it is inversely related to cervical length measured by transvaginal sonography at 20–24 weeks' gestation [87, 89–92]. In women with a short cervix, administration of progesterone reduces the risk of spontaneous early preterm delivery by about 40% [93]. However, progesterone is not as effective in women with a cervical length less than 12 mm as in those with a length of 12–15 mm. An alternative treatment for women with a short cervix is cervical cerclage. This reduces the risk of spontaneous early preterm delivery by about 40% in women who had a previous preterm birth or second-trimester loss, but not in those without such history [94, 95].

There are two disadvantages of measuring cervical length at 20–24 weeks. First of all, there is the inevitable failure to identify cervical incompetence leading to miscarriage before this gestation. Secondly, the effectiveness of prophylactic administration of progesterone or cervical cerclage may be inversely related to the gestation at which treatment is initiated. Certainly in women who had a previous preterm birth or second-trimester loss, cervical cerclage is either carried out electively in the first trimester or is reserved for those where serial scans, beginning in the first trimester, demonstrate cervical shortening [96].

*Maternal Characteristics and History*

The patient-specific risk for spontaneous delivery before 34 weeks can be determined at 11–13 weeks by an algorithm combining maternal characteristics and obstetric history [97]. The risk for early delivery increases with maternal age and decreases with height, and is high-

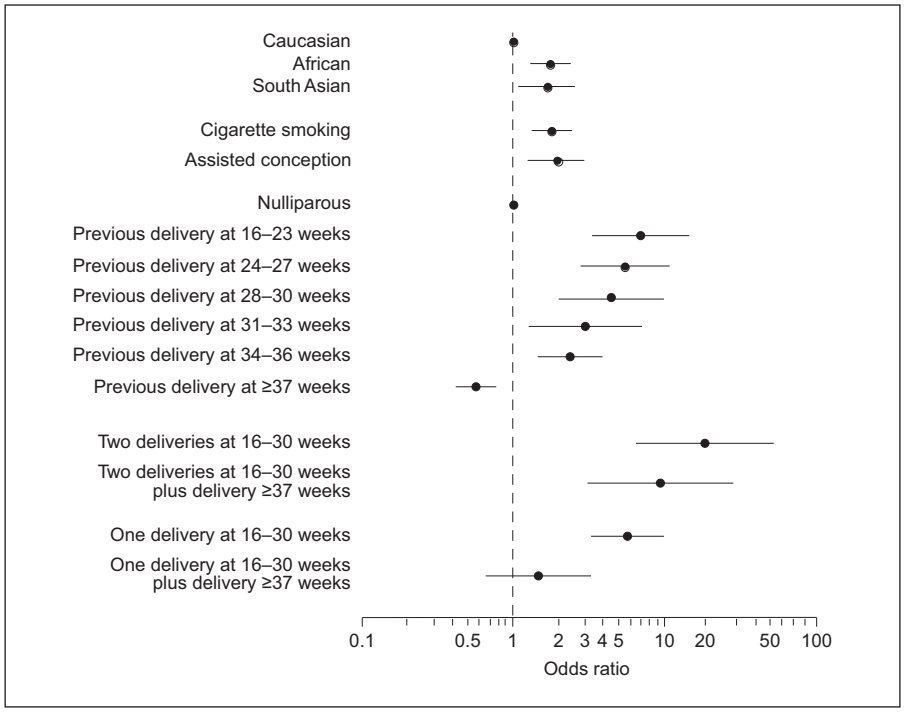


**Fig. 8.** Forest plot of odds ratios with 95% confidence interval of risk factors for spontaneous delivery before 34 weeks' gestation.

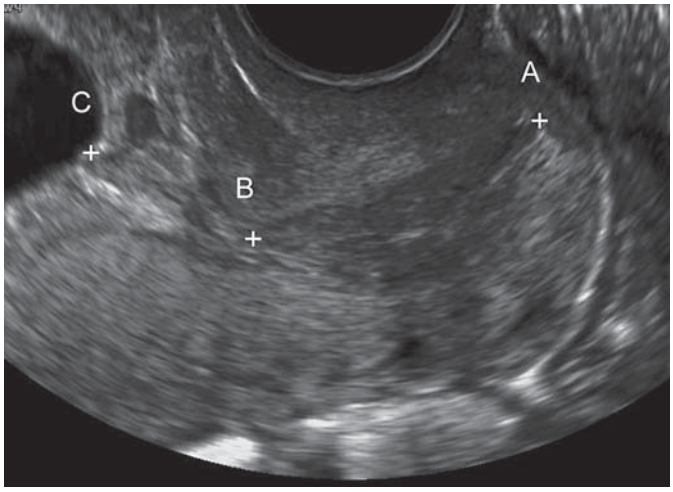


**Fig. 9.** Ultrasound picture illustrating the measurement of the length of the endocervix (A to B) and the isthmus (B to C).

er in women of African and South Asian racial origin than in Caucasians, in cigarette smokers, and in those conceiving after the use of ovulation induction drugs (fig. 8). The risk is substantially influenced by the outcome of previous pregnancies: it is inversely related to the gestation at previous spontaneous delivery, decreasing from about 7% if the gestation was 16–24 weeks to 3% if it was 31–33 weeks and 0.6% if all deliveries were at term. Additionally, the risk is affected by the number of previous spontaneous deliveries at 16–30 weeks and increases from about 6 to 19% if there were two rather than one such delivery. In women with previous preterm deliveries, there is a protective effect against recurrence if they also had a delivery at term. For women with one or two deliveries at 16–30 weeks, the risk of recurrence decreases from about 6 to 1.5% and from 19 to 10%, respectively.

The estimated detection rate of spontaneous early delivery with the use of the algorithm of maternal characteristics and obstetric history is 18% in nulliparous women and 38% in parous women, with a false-positive rate of 10%.

*Biophysical and Biochemical Markers*

Placental perfusion and function at 11–13 weeks are not altered in pregnancies resulting in spontaneous early delivery [97]. Consequently, the performance of screening provided by maternal characteristics and obstetric history is not improved by uterine artery pulsatility index and maternal serum or plasma concentration of PAPP-A, free β-hCG, placental growth factor, placental protein 13, a disintegrin and metalloprotease 12 (ADAM12), inhibin-A or activin-A.

Recent evidence suggests that at 11–13 weeks the cervical length in pregnancies complicated by subsequent spontaneous delivery before 34 weeks is shorter than in those delivering after 34 weeks, and the risk for early delivery is inversely related to cervical length [98]. In such an assessment, it is important to distinguish between the true cervix, characterized by the presence of the endocervical canal, which is bordered by the endocervical mucosa which is usually of decreased echogenicity compared to the surrounding tissues, and the isthmus (fig. 9). It is likely that the measurement of cervical length at 1–13 weeks will be combined with the algorithm derived from maternal characteristics and obstetric history to provide an effective method for identification of the group at high risk for subsequent early delivery.

*Implications of Early Assessment of Patient-Specific Risk*

Effective early identification of the high-risk group for subsequent spontaneous early delivery could potentially improve outcome by directing such patients to specialist clinics for regular monitoring of cervical length and stimulating research for identification of potentially useful biomarkers and the investigation of the potential role of earlier intervention with such measures as prophylactic use of progesterone or cervical cerclage.

## Conclusions

The scientific advances of the last 20 years raise the hope that many pregnancy complications can be detected as early as the 12th week of gestation. Future research will inevitably expand the number of conditions that can be identified in early pregnancy and define genetic markers of disease that will improve the accuracy of the a priori risk based on maternal characteristics and medical history. Similarly, new biophysical and biochemical markers will be described that may replace some of the current ones and modify the value of others. In the future, it will become necessary to re-evaluate and improve the timing and content of each visit and the likelihood ratios for each test. Early identification of high-risk groups will also stimulate further research that will define the best protocol for their follow-up and development of strategies for the prevention of disorders of pregnancy or their adverse consequences.

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