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EDITORIAL

A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment

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One century ago it was recognized that with the methods and material at our disposal we were not making all the progress possible toward solving many problems of prenatal diagnosis and treatment (Ballantyne, 1901, 1921). In order to achieve these objectives it was urged that a new means of investigation should be undertaken which had not yet been tried, at least not yet attempted on a large scale and in a systematic fashion. This led to the introduction of prenatal care which constituted a major advance in the care of pregnant women and played a pivotal role in the substantial reduction in maternal and perinatal mortality achieved during the last century.

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 (Figure 1) (Ministry of Health Report, 1929). No explicit rationale was offered for either the timing or clinical content of visits, yet these guidelines established the pattern of prenatal care to be followed throughout the world until now. The high concentration of visits in the late third trimester implies that most complications occur toward the end of pregnancy and most adverse outcomes cannot be predicted from the first trimester. However, is this really the case? Scientific advances in the last 20 years have raised the hope that many pregnancy complications are potentially detectable from at least as early as the 12th week of gestation. It has become apparent that most major aneuploidies can be identified at 11 to 13 weeks' gestation by a combination of maternal characteristics, ultrasound findings and biochemical testing of maternal blood. It is also becoming increasingly apparent that an integrated first hospital visit at 11 to 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 miscarriage and fetal death, preterm delivery, preeclampsia, gestational diabetes, fetal growth restriction and macrosomia.

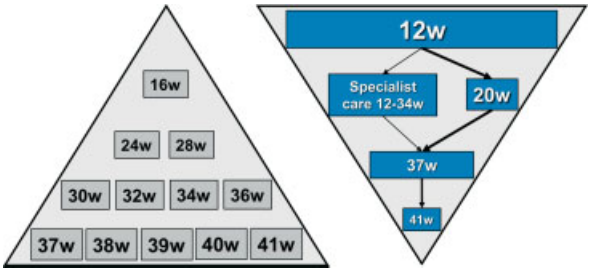

Figure 1—Pyramid of prenatal care: past (left) and future (right)

FETAL ANEUPLOIDIES

We have learnt that about 90% of fetuses with major aneuploidies can be identified by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum-free ß-hCG and PAPP-A at 11 to 13 weeks (Nicolaides, 2011). Improvement in the performance of first-trimester screening can be achieved by first carrying out the biochemical test at 9 to 10 weeks and the ultrasound scan at 12 weeks and second, inclusion in the ultrasound examination assessment of the nasal bone and flow in the ductus venosus, hepatic artery and across the tricuspid valve. A similar performance of screening can be achieved by examining the additional ultrasound markers in all cases and by a contingent policy in which first-stage combined screening classifies the patients as high-, intermediate- and low-risk and the new markers are examined only in the intermediate-risk group which is then reclassified as low- or high-risk.

FETAL STRUCTURAL ABNORMALITIES

We have learnt that at the 11 to 13 weeks' scan it is possible to diagnose or suspect the presence of most 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 (Syngelaki *et al.*, 2011): first, those which are always detectable abnormalities, including body stalk anomaly, anencephaly,

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alobar holoprosencephaly, exomphalos, gastroschisis and megacystis and second, undetectable abnormalities because sonographic signs are only manifest during the second or third trimester of pregnancy, including some brain abnormalities, such as microcephaly, hypoplasia of the cerebellum or vermis, hydrocephalus and agenesis of the corpus callosum, achondroplasia, echogenic lung lesions, many renal anomalies and bowel obstruction. A third group includes abnormalities that are potentially detectable depending on first 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 and second, the presence of an easily detectable marker for an underlying abnormality. Good examples of such markers in the first trimester include high NT in some fetuses with lethal skeletal dysplasias (Khalil *et al*., 2011) and diaphragmatic hernia, high NT and abnormal flow in the ductus venosus and across the tricuspid valve in major cardiac defects (Chelemen *et al*., 2011) and increase in brain stem diameter with decrease in the diameter of the fourth ventricle-cisterna magna complex in open spina bifida (Lachmann *et al*., 2011).

MISCARRIAGE AND STILLBIRTH

We have learnt that the rates of miscarriage and stillbirth after demonstration of a live fetus at 11 to 13 weeks are about 1 and 0.4%, respectively. 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 (Akolekar *et al*., 2011a). At present there is no useful intervention for avoidance of miscarriage and so the use of this algorithm in clinical practice is debatable (van Ravenswaaij *et al*., 2011). In contrast, 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 wellbeing and appropriate timing of delivery.

PRETERM DELIVERY

We have learnt that preterm birth is the leading cause of perinatal death and handicap in children and the vast majority of mortality and morbidity relates to early delivery before 34 weeks which 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 and in the other one-third it is iatrogenic, mainly due to preeclampsia. The patient-specific risk for spontaneous delivery before 34 weeks can be determined by an algorithm combining maternal characteristics and obstetric history (Beta *et al*., 2011). This *a priori* risk can be modified by the sonographic measurement of cervical length at 11 to 13 weeks which is inversely related to the likelihood for subsequent spontaneous early delivery (Greco *et al*., 2011). At present there are no other useful biophysical or biochemical markers of spontaneous early delivery (Beta *et al*., 2011). Future research will determine whether early intervention with such measures as prophylactic use of progesterone or cervical cerclage will be effective in reducing spontaneous preterm delivery.

PREECLAMPSIA

We have learnt that in preeclampsia, which is a major cause of maternal and perinatal morbidity and mortality, both the degree of impaired placentation and the incidence of adverse fetal and maternal short-term and long-term consequences are inversely related to the gestational age at the onset of the disease. Consequently, in screening for preeclampsia the condition should be subdivided according to gestational age at delivery. Algorithms which combine maternal characteristics, mean arterial pressure, uterine artery Doppler and biochemical tests at 11 to 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, for a false positive rate of 5% (Akolekar *et al*., 2011b). Further investigations will determine whether in the high-risk group pharmacological interventions, such as low-dose aspirin, starting from the first trimester could improve placentation and reduce the prevalence of the disease.

GESTATIONAL DIABETES MELLITUS

We have learnt that in gestational diabetes mellitus (GDM), which is associated with increased risk of maternal and perinatal short-term and long-term complications, the performance of traditional screening at the end of the second trimester by a series of independent maternal characteristics is poor with a detection rate of about 60%, at a false positive rate of 30 to 40% (Waugh *et al*., 2007). Algorithms which combine maternal characteristics and maternal serum levels of adiponectin, an adipocyte-derived polypeptide, and sex hormone binding globulin, a liver-derived glycoprotein, at 11 to 13 weeks could potentially identify about 75% of pregnancies that subsequently develop GDM, for a false positive rate of 20% (Nanda *et al*., 2011). Additionally, the diagnosis of GDM can be made in the first trimester by appropriate adjustments to the traditional criteria of the oral glucose tolerance test (Plasencia *et al*., 2011). Future research will determine whether in the high-risk group appropriate dietary advice and pharmacological interventions, such as metformin, could reduce the incidence of GDM and associated fetal macrosomia.

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SMALL FOR GESTATIONAL AGE FETUSES

We have learnt that small for gestational age (SGA) fetuses may be constitutionally small or growth restricted due to impaired placentation, genetic disease or environmental damage. In the growth-restricted group the risks of perinatal death and handicap are substantially increased but these risks can be reduced if the condition is detected prenatally allowing appropriate monitoring and delivery. Algorithms which combine maternal characteristics, mean arterial pressure, uterine artery Doppler and the measurement of various placental products in maternal blood at 11 to 13 weeks could potentially identify, at a false positive rate of 10%, about 75% of pregnancies without preeclampsia delivering SGA neonates before 37 weeks and 45% of those delivering at term (Karagiannis *et al*., 2011). Since the proportion of growth restricted to constitutional small fetuses is higher in the preterm rather than term SGA, it is likely that the early biophysical and biochemical markers identify the growth-restricted subgroup among the SGA.

FETAL MACROSOMIA

We have learnt that 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. 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 ß-hCG and PAPP-A at 11 to 13 weeks could potentially identify, at a false positive rate of 10%, about 35% of women who deliver macrosomic neonates (Poon *et al*., 2011). Future research would identify new biophysical and biochemical markers which could improve the performance of screening and determine the extent to which early identification of the high-risk group can improve prenatal surveillance and prevention of macrosomia itself or the intrapartum complications related to the condition.

THE NEW PYRAMID OF CARE

Early estimation of patient-specific risks for 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 will generate likelihood ratios that can be used to modify the individual patient and disease-specific estimated risk from the initial assessment at 11 to 13 weeks. Such sequential screening is now well established in screening for aneuploidies whereby the patient-specific risk based on maternal age is modified by the sonographic findings and results of biochemical testing both in the first and second trimesters of pregnancy. The new approach will adhere to the teachings of Hippocrates, that we should learn the past and research the present to predict the future, and the pronouncements of Galileo Galilei, that the language of God is mathematics and that we should measure everything that is measurable and make measurable everything that is not so.

At 11 to 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 (Figure 1). In the low-risk group the number of medical visits can be substantially reduced to perhaps three. One visit at around 20 weeks will re-evaluate fetal anatomy and growth and reassess risk for such complications as preeclampsia and preterm delivery. Another visit at 37 weeks will assess maternal and fetal wellbeing and determine the best time and method of delivery and this will be repeated at 41 weeks for the few that remain pregnant at this stage. The high-risk group can 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 will be reassessed and they will either remain high-risk or they will become low-risk in which case the intensity of their care can be reduced.

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. As the years pass, 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.

It is likely that the new challenge for improvement of pregnancy outcome will be met by inverting the pyramid of prenatal care (Figure 1) to introduce on a large scale and in a systematic fashion a new model of prenatal care which will be based on the results of a comprehensive assessment at 11 to 13 weeks.

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