# Prenatal care in the new era: 2014 - 15 update on earlier and less invasive individualized risk assessment


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Prenatal care is the most widely used preventive service in the western world due to the recognition of its fundamental role in improving pregnancy outcome. The preventive nature of antenatal care, inspired by the teachings of Hippocrates, was re - introduced by John William Ballantyne in Edinburgh at the end of the 19th century, who focused on congenital anomalies, and later, during the first three decades of the 1900s, by John Whitridge Williams at the Johns Hopkins Hospital in Baltimore who championed the potential benefits of prenatal care for the diminution of neonatal deaths due to prematurity.

In 1929, the United Kingdom Department of Health published the first official recommendations on antenatal care, these stressing the need for a high concentration of visits during the last trimester of pregnancy when the complications of pregnancy were considered to be more likely to occur. However, scientific advances during the last few decades have enabled detection, and thus potential prevention, of many pregnancy complications from much earlier, i.e. before the end of the first trimester of gestation.

The past 40 years have thus witnessed such important developments as: maternal age - based prenatal screening for chromosomal abnormalities in the 1970s, the nuchal translucency screening test in 2003 and, towards the end of that decade, the combined test with maternal serum β - hCG and PAPP - A in the first trimester (11 - 13 weeks). This last was in particular a major breakthrough, resulting in a marked improvement in screening results, with the detection rate rising from 30% to 90%. Finally, the past three years have seen the introduction of an extremely high - performance screening test, massively parallel sequencing of maternal plasma cell - free fetal DNA (cffDNA testing). In a series of clinical implementation and validation studies, the latter method proved capable of accurately detecting fetal autosomal aneuploidy in 99% of the cases of Down syndrome, 97% of trisomy 18 and about 92% of trisomy 13, at an overall false positive rate or unnecessary invasive testing rate of 0.4%. The outcome has been the successful completion of screening for aneuploidies by the end of the first trimester of pregnancy. The information obtained from the combined test can with great precision identify those women who should have an invasive diagnostic procedure in the second trimester (chorionic villus sampling or amniocentesis), those who will be classified as having a high risk of

trisomy, namely higher than 1/300, which is the expected risk for amniocentesis or CVS - related miscarriage. Meanwhile, women classified as having an intermediate risk (1/1,000 to 1/300) could be offered cff DNA testing before a final decision on an invasive procedure is made.

Furthermore, thanks to the 11 - 13 weeks' gestation ultrasound screening, it is possible to diagnose the majority of severe fetal structural abnormalities in order to achieve an early as possible diagnosis, complementing the ultrasound scan performed in the second trimester (20 - 22 weeks). The early identification of such disorders enables couples to make a timely informed choice as to whether they wish to continue with the pregnancy or have a termination.

Preeclampsia complicates approximately 10,000,000 pregnancies each year around the world. Up to 15% of the over half a million women who die annually from pregnancy related causes, as well as at least 15% of premature births, are associated with hypertensive disorders of pregnancy. Although in most countries there are currently no official guidelines, there is evidence that mathematical models which combine maternal characteristics, mean arterial pressure, uterine artery pulsatility index and biochemical tests including the measurement of PAPP - A and PlGF (placental growth factor) at 11 to 13 weeks could potentially identify about 90% and 60% of pregnancies that subsequently develop into early (before 34 weeks) or late (after 37 weeks) preeclampsia, respectively, at a false positive rate of 5%. Interestingly, research has reported that even simple information easily obtained from the woman's history could be extremely helpful: for example, being overweight or obese is alone responsible for almost two thirds of total preeclampsia cases. First trimester screening combined with the results from the uterine artery Doppler at 20 - 24 weeks and a series of new biochemical tests, including PlGF and sFlt - 1 (soluble fms - like tyrosine kinase - 1), can identify virtually all women who will develop the disorder. However, while identification of high - risk women in the second trimester could potentially improve the pregnancy outcome by means of intensive maternal and fetal monitoring, first trimester screening is now considered more valuable because there is evidence that the rate of preeclampsia as well as the rate of intrauterine growth restriction linked to impaired placentation in these women can be reduced by more than 50% if aspirin therapy is initiated at less than 16 weeks of gestation.

Preterm birth is a major cause of neonatal mortality and morbidity, has important long - term consequences in the offspring's later life and is associated with a devastating economic impact. It is estimated that globally 15,000,000 neonates are born before 37 completed weeks of gestation, with preterm birth rates increasing in most countries. Prematurity is directly linked to more than 1,000,000 neonatal deaths each year, more than one third of the total burden of neonatal deaths worldwide, while it is also the leading cause of child death in the high- and middle - income countries of the world. Preterm birth is also a major public health concern in Greece, which in 2010 registered the highest preterm birth rate among European countries. Spontaneous preterm birth is a syndrome of multifactorial and mostly unknown etiology. Patient - specific risk of preterm delivery provided by maternal characteristics and obstetric history can predict only about a third of prematurity cases before 34 weeks. Secondary prevention focuses on recurrent preterm birth, which is the most important risk factor. In the high - risk group of women, measurement of cervical length in the second trimester could increase the identification rate to almost 65% and these women should be closely monitored as pregnancy proceeds. Recommended options based on individualized risk are elective cerclage at 13 to 16 weeks of gestation for high - risk patients after the first trimester assessment, and progesterone therapy for those classified as high - risk in the second trimester.

Gestational diabetes is a silent epidemic closely linked to the concurrent growing prevalence of obe-


The current approach to prenatal care places emphasis on early detection of high - risk pregnancies and less use of invasive diagnostic procedures for low - risk pregnancies. The recently issued Hellenic Society of Obstetrics and Gynecology (HSOG) Guideline "Prenatal care: surveillance of low - risk pregnancy" is published in Greek, but is also available at http://www.hsog.gr/ and can be downloaded as an application for tablets and smartphones. Users, both health professionals and the lay public, can access evidence - based information and find answers to their clinical questions just one click away on their mobile devices

sity worldwide. It has been estimated that almost half of gestational diabetes cases are attributable to the increased body mass index (BMI of 25 kg/m$^2$ or above) at the beginning of pregnancy. Unfortunately, the current prognostic models for gestational diabetes recommended for the first trimester attain relatively low detection rates. These models, combining certain maternal characteristics and history information (including pre - pregnancy body mass index, maternal age, personal or family history of diabetes and birth - weight in previous pregnancies) with certain biochemical parameters (such as adiponectin and sex hormone binding globulin), are potentially able to identify up to 75% of the subsequent cases of gestational diabetes - however, with a high false positive rate of more than 20%. This is explained by the existence of other factors that play an important role in the pathogenesis of the disorder and which occur later in pregnancy, particularly gestational weight gain, which has been shown to be an important independent risk factor for the disorder. Currently, the identification of high - risk preg-

nancies by the oral glucose tolerance test at the end of the second trimester and the subsequent treatment has been shown to be effective in reducing many important adverse pregnancy outcomes associated with gestational diabetes, including macrosomia, shoulder dystocia and gestational hypertension. Nevertheless, the results are disappointing for the long - term metabolic outcomes of offspring, which are typically associated with fetal pancreatic hyperplasia that occur during the second trimester. The objective thus appears to be the integration of the abovementioned model with a modified oral glucose tolerance test performed 10 weeks earlier than the current one in order to identify the high-risk group at the beginning of the second trimester and, through interventions, to promptly prevent occurrence of pancreatic hyperplasia in the fetus. Of note, with regard to the pharmacotherapy of gestational diabetes, there is a trend towards replacing the traditional insulin therapy with oral hypoglycemic agents. Already, over the past decade in the United States, glyburide has replaced insulin as the more common medication for gestational diabetes, especially among younger women.

Similar algorithmic approaches are also being developed for the early detection of women at risk for other pregnancy complications such as stillbirth and intrauterine growth restriction. Although currently there is no clinically useful first - trimester test to predict stillbirth and intrauterine growth restriction, risk assessment based on the uterine artery pulsatility index and maternal serum PAPP - A levels appears to be a good predictor of these disorders in cases where they are related to placental dysfunction disorders.

The philosophy of the new era in prenatal care translates as utilization of appropriate risk - as sessment algorithms from universal screening in the first trimester, followed by a final evaluation of women of intermediate risk in the second trimester. Application of the above will lead to the highest yield of high - risk pregnancies, these women subsequently being offered interventional diagnostic procedures and close monitoring with cost and side - effects minimization.