

ANTENATAL SCREENING FOR CHROMOSOMAL ABNORMALITIES

This is a continuation of application Ser. No. 08/256,320, filed Jun. 28, 1994 and now abandoned, which is hereby incorporated by reference which is a 371 of PCT/EP93/03296 filed Nov. 24, 1993.

This invention relates to a method for antenatal screening for chromosomal abnormalities and to an assay kit for performing the method and in particular to a method and kit for antenatal screening for Down's Syndrome.

The risk of Down's Syndrome and some other chromosomal abnormalities in a foetus is known to increase with the age of the mother and it is this knowledge which forms the basis for selection of pregnant women for further investigation. Further investigation for instance in the case of Down's Syndrome involves sampling of the amniotic fluid by amniocentesis, a procedure which itself carries a risk for the mother of the foetus, induction of a miscarriage being a recognised hazard of this procedure.

Maternal serum markers for Down's Syndrome are widely used for antenatal screening for this chromosomal abnormality, the most common of these markers being alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG)—either the intact molecule thereof or its beta subunit—and unconjugated estriol (uE). Disclosures relating to the use of these markers in antenatal screening for Down's Syndrome include U.S. Pat. No. 4,874,693, WO 89/00696 and WO 90/08325. U.S. Pat. No. 5,100,806 discloses the use of the beta subunit of hCG as a marker in antenatal screening for Edwards Syndrome.

Maternal serum screening is based on selecting a subgroup of women who are at the greatest risk of giving birth to a child with an abnormality, in whom the risks of an invasive diagnostic procedure are considered to be outweighed by the risk of the abnormality. The risk is calculated by multiplying the a priori age related risk by the likelihood ratio. The likelihood ratio is calculated from the relative heights of the multivariate Gaussian distribution functions of marker analytes in affected and unaffected pregnancies, corresponding to the value of the individual serum marker concentrations.

Since the concentrations of the various analytes vary normally with gestational age, the analyte concentrations must be corrected. Correction is performed by dividing the concentration of the analyte by the median concentration expected for that particular gestational age in women with unaffected pregnancies. This is termed the multiple of the median (MoM).

The use of two or more markers together in antenatal screening can be advantageous. For example the markers AFP, hCG and uE can be used together. The combination of marker analytes gives significantly more information than is given by any single marker alone, or by the group of markers when used sequentially. The use of likelihood ratios derived from a multivariate combination is an efficient means of deriving information relating to a woman's risk of carrying an affected child.

Present methods of antenatal screening using maternal serum markers which are in regular use, or are likely to come into regular use in the near future, rely on screening during the second trimester of pregnancy, that is approximately between 14 and 26 weeks.

However maternal serum screening in the first trimester of pregnancy, that is up to 14 weeks, offers considerable advantages over screening in the second trimester. In the first trimester the bonding between the mother and the foetus is

less strong than in the second trimester and hence there is less psychological impact should the foetus be affected. In addition the methods of pregnancy interruption are much less traumatic and are safer to the mother in the first trimester than are those available in the second trimester, particularly the late second trimester, that is approximately 18 to 25 or 26 weeks. It is in the late second trimester that several of the present methods for antenatal screening need to be performed.

Thus it is desirable to develop methods of antenatal screening for chromosomal abnormalities using two or more maternal serum markers together which can readily be performed in the first trimester of pregnancy.

According to the present invention we provide a method for antenatal screening for chromosomal abnormalities in which maternal blood from a pregnant woman is measured for levels of free beta hCG and at least a second serum marker and/or precursors and metabolites of these markers and the measured levels of these markers together with the gestational age of the pregnant woman are compared to reference values at various gestational ages of the levels for free beta hCG and the second serum marker in (a) pregnant women carrying foetuses having the abnormality(ies) subject to the screen and (b) pregnant women carrying normal foetuses, the comparison being indicative of the risk of the pregnant woman carrying a foetus with an abnormality subject to the screen characterised in that the second serum marker is pregnancy associated plasma protein A (PAPPA) and the screen is carried out by the end of the thirteenth (13th) completed week of pregnancy.

Further according to the present invention we provide an assay kit for performing a method for antenatal screening for chromosomal abnormalities comprising means for assaying a sample of maternal blood for levels of free beta hCG and at least a second serum marker and/or precursors and of these markers characterised in that the second serum marker is pregnancy associated plasma protein A (PAPPA) and the blood sample is taken by the end of the thirteenth (13th) completed week of pregnancy.

Further according to the present invention we provide an apparatus comprising means adapted for receiving measurements of a pregnant woman's maternal blood levels of free beta hCG and at least a second serum marker and/or precursors and metabolites of these markers and computer means for comparing the measurements of these levels to sets of reference data to determine fetal chromosomal abnormalities characterised in that the second serum marker is pregnancy associated plasma protein A (PAPPA) and the measurements are made on a blood sample taken by the end of the thirteenth (13th) completed week of pregnancy.

The method of the invention can be used for antenatal screening for a wide range of chromosomal abnormalities. The most significant and frequently occurring of these is Down's Syndrome (Trisomy 21). Other abnormalities which may be screened for using the invention include Edwards Syndrome (Trisomy 18), Patau Syndrome (Trisomy 13), Turner Syndrome, Monosomy X and Klinefelter's Syndrome. The method of the invention may be used to screen for individual abnormalities or to screen for groups of abnormalities together, for example it could be used to screen for both Down's Syndrome and Edwards Syndrome.

The method of the invention can be used to measure other serum markers in blood samples in addition to hCG and PAPPA. Such other markers include alpha-fetoprotein (AFP), unconjugated estriol (uE), inhibin (In), progesterone (Pr), 16-alpha-hydroxy-dehydroepiandrosterone sulphate (16-alpha-hydroxy-DHEAS) and dehydroepiandrosterone