A 'Normal' Baby for Every Pregnancy: Dream or Reality?

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Childbearing is one of the most stressful events in a woman's life. Stress may originate from the physical discomfort of pregnancy, labour and delivery. It can also arise from negative expectations over the baby's health. It is common for pregnant women to feel uncertain or anxious about her baby's condition at birth. However, with a better understanding of periconceptional care, and the availability of various prenatal screening and diagnostic techniques, expectant mothers may be more reliably assured of the 'normality' of her baby. In this article, 'normality' is used in the context of chromosomal and structural normality.

PERICONCEPTIONAL MEASURES TO ENSURE 'NORMALITY'

The protective effect of folate supplementation against neural tube defects has been confirmed by randomised controlled trials. Women whose previous pregnancies were affected by neural tube defects are at increased risk in subsequent pregnancies. However, periconceptual folate therapy (4 mg/day) can reduce the risk of recurrence by 72%.[1] Multivitamin preparations that include small amounts of folate (0.8 mg) also significantly reduce the occurrence of neural tube defects in women whose pregnancies have not yet been affected.[2] The protective effects of folate against other congenital malformations such as cleft lip and congenital heart disease are less clear.[2,3] Nevertheless, folate supplementation has no known harmful effects on either the mother or foetus.[1,2] In localities where neural tube defects are prevalent, pregnant women should be given folate. Whether folate supplementation should be recommended in areas with a low incidence of neural tube defects has yet to be determined.

There is strong evidence that cigarettes and alcohol are harmful to the foetus. Intensive prenatal anti-smoking programmes that use self-help manuals, letters, telephone contacts and dedicated antenatal visits have achieved a 50% increase in smoking cessation and a reduced incidence of low birth weight neonates.[4] Midwives can effectively run such programmes.[5] Motivational interviews may also be effective in reducing alcohol consumption among heavy drinkers.[6] Data suggest that anti-smoking and drinking programmes should be instituted before conception.[7]

PRENATAL SCREENING AND DIAGNOSTIC TESTS

Numerous prenatal screening and diagnostic tests are available to detect foetal abnormalities. It is important to distinguish between screening and diagnostic examinations since they are often performed on different populations with different aims. Medical screening has been defined as "the identification, among apparently healthy individuals, of those who are sufficiently at risk of a specific disorder to justify a subsequent diagnostic test or procedure, or in certain circumstances, to direct

preventive action."[8] Screening tests are generally simple, inexpensive and safe whereas diagnostic tests are specific. However, diagnostic tests are more likely to carry some risks to the pregnancy.

ULTRASOUND EXAMINATIONS TO CONFIRM 'NORMALITY'

It is common practice to screen for foetal abnormalities by ultrasound at 18 to 20 weeks of gestation. The detection rate of structural malformations varies between 20 and 80% depending upon the ultrasonographer's training and experience, and the resolution of the ultrasound machine used.[9]

Cardiac defects are the most commonly missed congenital malformations.[9] However, experienced ultrasonographers using detailed foetal echocardiography can detect 86% of major cardiac defects in unselected populations including the four-chamber view, outflow-tracts and colour-flow.[10] Specificity and sensitivity of ultrasound examinations, as diagnostic tests, in high risk populations to detect foetal malformations are much higher when conducted by foetal medicine specialists.[9] With improved ultrasound machines and the wider use of vaginal sonography, screening[11] and diagnostic[12] ultrasound examinations can be carried out at 12 to 14 weeks with a similar level of efficacy.

Sonographic measurement of nuchal translucency at 10 to 14 weeks is the most effective screening test for Down syndrome and other aneuploidies.[13] (Figure 1) An enlarged first trimester nuchal translucency is associated with chromosomal disorders and structural anomalies eg. cardiac, diaphragmatic, skeletal defects and certain genetic syndromes.[14] Unfortunately, technical errors result from a common misconception that nuchal translucency can be determined by any investigator who is familiar with scanning. It needs to be stressed that special training and continuous audit are necessary to ensure good performance.

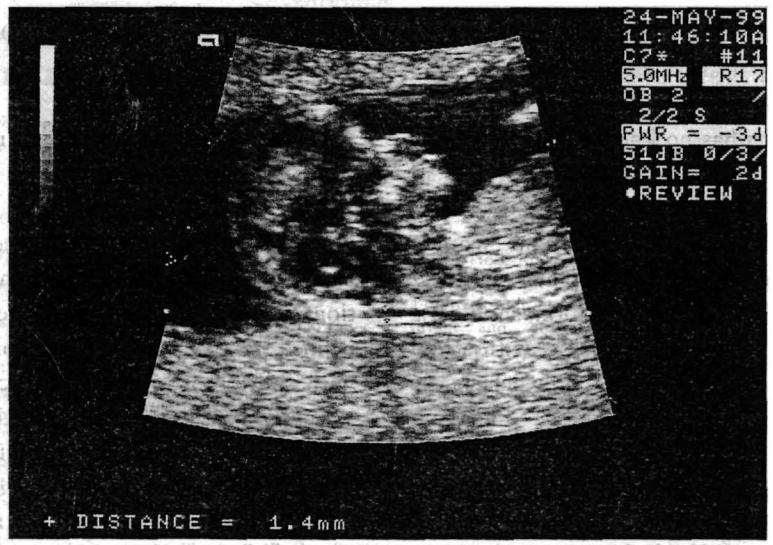

Figure 1. Ultrasound examination of a foetus at 12 weeks showing a sagittal section of the head, neck and chest for measurement of the nuchal translucency.

SCREENING AND DIAGNOSIS OF DOWN SYNDROME AND OTHER CHROMOSOMAL ABNORMALITIES

Screening

Maternal age is the most traditional and commonly used parameter in screening for Down syndrome. However, using this alone, only 30% of Down syndrome pregnancies are detected, with a 5% false positive rate. Combinations of maternal age with various second trimester serum markers eg. human chorionic gonadotrophin (hCG), free-α hCG, free-β hCG, unconjugated oestriol, alpha-fetoprotein and inhibin-A, can give detection rates of 60 to 80%, with the same 5% false positive rate.[15] Second

trimester serum screening has become an established practice in many countries.[16-18] Accumulating evidence suggests that serum screening using free-β hCG and pregnancy associated plasma protein-A (PAPP-A) can be carried out in the first trimester (instead of the usual second) of pregnancy without jeopardising sensitivity.[19,20] Combinations of PAPP-A, free-β hCG and nuchal translucency determination in the first trimester can detect 89% of Down syndrome pregnancies, with a 5% false positive rate.[21] Furthermore, integration of the first and second trimester markers may be feasible, giving a detection rate of 85% with a very low false positive rate of 0.9%.[22,23]

Diagnosis

Cytogenetic studies of foetal tissues obtained by various invasive procedures such as amniocentesis, chorionic villus sampling or cordocentesis remain the gold standard in the diagnosis of chromosomal disorders. Conventional karyotyping takes 7 to 14 days which is too long, especially if sonographic signs of abnormality have already been indicated. Fluorescence-based PCR assays with tandem-repeat markers[24] or fluorescence in situ hybridisation using commercially available chromosome-specific probes[25] can give an accurate report within 1 to 2 days. However, these techniques are not always successful and can only detect certain types of aneuploidies and translocations.

Foetal tissue sampling techniques are invasive and are associated with a small risk of miscarriage. Amniocentesis is normally carried out between 15 and 20 weeks, whereas chorionic villus sampling is between 10 and 12 weeks. Amniocentesis performed at 11 to 13 weeks is associated with a higher rate of talipes equinovarus and foetal loss than conventional amniocentesis and chorionic villus sampling.[26,27] This should be taken into consideration when invasive prenatal diagnosis is indicated.

Because of the risks of invasive sampling techniques, attempts have been made to isolate foetal cells from the maternal circulation. Most research has focused on the enrichment and isolation of foetal nucleated red blood cells or erythroblasts. Although great strides are being made in this field, such techniques are unlikely to replace invasive methods.[28] Currently, foetal cells isolated from the maternal circulation cannot be cultured efficiently. This compromises the sensitivity and specificity when diagnosing chromosomal disorders. In addition, because the technique is labour intensive and expensive, it will remain unsuitable for use as a screening test until automated isolation and scanning facilities are developed.

PRENATAL DIAGNOSIS OF GENETIC DISORDERS

Advances in molecular biology and gene mapping now allow accurate prenatal diagnosis of most genetic disorders. This highlights the need for a detailed family history in order to identify those at risk of an inherited condition so that they may be targeted for screening. When diseases are prevalent in particular populations (eg. thalassaemia in Southeast Asians), antenatal screening of asymptomatic carriers is justified.

These screening and diagnostic procedures allow an accurate prenatal diagnosis of foetal abnormalities in most instances. A woman carrying a foetus affected by major abnormalities may elect to have her pregnancy terminated. In certain instances, intrauterine treatment may be instituted with successful outcomes.[29-32] For couples wishing to avoid a selective termination of an affected pregnancy, preimplantation diagnosis may ensure the conception of an unaffected pregnancy in those at risk. Since the first reported birth using preimplantation diagnosis,[33] the technique has been performed in many centres for the diagnosis of aneuploidy and single gene disorders. However, before it can be employed in routine clinical practice, further research is needed to address problems such as allele dropout, contamination and amplification.[34]

CONCLUSION

Efforts to ensure a 'normal' foetus should start before conception. These include periconceptual folate supplementation and attempts to stop smoking and drinking alcohol. Various prenatal screening and diagnostic methods can identify foetuses with major congenital abnormalities. These are then either terminated or subjected to various prenatal or postnatal treatments. Pre-implantation diagnosis offers the hope of a 'normal' conception. However, existing prenatal screening and diagnostic methods cannot guarantee a 'normal' baby for every pregnancy at this time.

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