Screening for Down syndrome

Anuradha Shajpal

Farah Siddiqui

Abstract

Down screening has been available within clinical practice for over 50 years during which time significant innovation and exciting new advances have improved the accuracy and safety of screening, and improved choice for women who are considering antenatal screening for Down syndrome. The UK National Screening Committee is responsible for setting the national standards regarding screening and it has steadily and consistently directed and facilitated an increase in the detection rate whilst minimising the screen positive rate of Down syndrome screening. This has reduced the number of false positive results and consequently the number of invasive diagnostic procedures and their related miscarriages. Non-invasive pre-natal testing (NIPT) using cell free DNA is a rapidly evolving field and it will soon be incorporated into the existing NHS antenatal screening programme for aneuploidy. It will be offered to women who receive a 'high risk' result following current screening methods (combined test or quadruple test), and will further reduce the number of invasive tests performed, whilst maintaining current detection rates.

Keywords aneuploidy; Down syndrome; non-invasive prenatal testing; prenatal diagnosis; screening

Introduction

Down syndrome was first described by John Langdon Down in 1862. He documented distinctive facial features and a single palmar crease in association with varying degrees of learning disability. In the 1930s it was speculated that Down syndrome may be due to chromosomal abnormalities. However the underlying cause, trisomy 21, was not determined until 1959.

The incidence of Down syndrome in the UK is approximately one per 1000 live births. It is currently the most common genetic cause of learning disability in the UK. The risk of a woman having a child with Down syndrome increases with her age. For someone who has had a previously affected pregnancy this risk is increased further by approximately 1% above their background age-related risk (Table 1).

The concept of prenatal screening for Down syndrome (trisomy 21) has been around for over 50 years. During this time, the screening tools have moved from the simplistic use of maternal age through to the sequencing and counting of millions of cell free DNA fragments in maternal plasma. The prevalence of Down syndrome pregnancies has increased over time, though the live birth rate has remained relatively static.

The association between increasing maternal age and the risk of having a pregnancy affected with Down syndrome

Age	Risk of Down syndrome
20 years	0.07%
30 years	0.1%
40 years	1%

Table 1

Terminology

In 1998 Sir Kenneth Calman, the first chairman of the UK National Screening Committee, said with regards to screening programmes: "Quality is dependent on a range of influences and needs to be addressed in a number of ways. We need to be sure that the new technologies for screening are effective; that they will not cause more harm than good; that the health needs of people determine the necessity to screen; that false hope is not raised by screening for conditions where an effective cure or treatment is unavailable, and that people's experience informs the continued improvement of screening services."

The effectiveness of a screening programme can be measured in a number of ways. The 'detection rate', or sensitivity, describes the number of affected cases identified by the screening programme. In the case of Down syndrome screening that would mean how many of the affected pregnancies are picked up as 'high risk' results.

A good screening test also needs to have a low 'false positive rate', which means very few of the non-affected cases should be highlighted as 'high risk'. With Down syndrome screening, the literature often refers to a 'screen positive rate' rather than 'false positive rate'. A 'screen positive rate' describes the proportion of all cases screened which would have a 'high risk' result.

Having a low screen positive rate is important because this is the group of patients that would go on to be offered invasive testing for a definitive diagnosis. Amniocentesis and chorionic villus sampling carry a 0.5–1% risk of procedure-related miscarriage, so it is important to minimise the number of invasive tests performed on unaffected pregnancies.

Background of Down syndrome screening

Antenatal screening for Down syndrome has been seen in clinical practice since the late 1960s. At that time the screening test was based on 'advanced' maternal age, with age 35 years or older being considered high risk. Thus, women who were 35 years or older were offered an invasive test (amniocentesis or chorionic villus sample). These invasive tests were also a recent advance in prenatal diagnosis at that time. The detection rates for trisomy 21 based on screening using a maternal age higher than 35 years were poor. Although it was recognised that increasing maternal

Anuradha Shajpal *MBChB MRCOG is an SpR in Obstetrics and Gynaecology, Leicester Royal Infirmary, University Hospitals of Leicester NHS trust, Leicester, UK. Conflicts of interest: none declared.*

Farah Siddiqui *MBChB DM FRCOG is a Consultant in Fetal and Maternal Medicine, Leicester Royal Infirmary, University Hospitals of Leicester NHS trust, Leicester, UK. Conflicts of interest: none declared.*

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age is linked to the incidence of trisomy 21, the majority of trisomy 21 fetuses were seen in younger mothers (as the pregnancy rates are higher). At best only up to 30% of fetuses with Down syndrome could be diagnosed antenatally with maternal age being used as the screening tool.

In the 1980s maternal serum markers were identified as being useful in clinical practice. Alpha fetoprotein (AFP) is a fetal-specific protein which is produced by the yolk sac and fetal liver. It was the first pregnancy specific biochemical marker to be discovered, and it was noted that Down syndrome was associated with reduced levels of AFP during the second trimester. Importantly, this was independent of maternal age. By 1987 it had been shown that raised levels of human chorionic gonadotrophin (HCG) were associated with Down syndrome and by combining the results of AFP and HCG levels with the maternal age related risk, the double test was born.

In the early 1990s a strong association between increased nuchal translucency (NT) and chromosomal abnormalities was reported. A study published in 1994 showed that when the NT was measured between 10 and 14 weeks it measured $\geq$2.5 mm in 84% of fetuses with trisomy 21 and in only 4.5% of chromosomally normal fetuses. Using the NT to identify fetuses with trisomy 21 resulted in a significant improvement in the detection rate, above that of the double test, whilst maintaining a low false positive rate.

With time other biochemical markers were discovered, many of which could be used for first trimester screening, which further helped to improve the quality of the screening test.

The National Down Syndrome Cytogenetic register for England and Wales have been collecting data since 1989 and is the only national source for the number of pre- and postnatal diagnosis of Down syndrome. Their latest report in 2013 highlighted that the prevalence of Down syndrome pregnancies has steadily increased, from around 1.5 per 1000 in 1989 when the register started, to 2.5 per 1000 births in 2013. This is thought to be due to increasing maternal age, a significant risk factor, but also due to the increase in prenatal diagnosis which will also have identified some pregnancies which would have spontaneously miscarried and otherwise remain undiagnosed and undetected without prenatal screening. During this time the live birth rate of Down syndrome pregnancies has remained stable at around one per 1000 live births. The proportion of women opting to terminate the pregnancy after a prenatal diagnosis of Down's syndrome has been approximately 92% since the start of this register in 1989, although this dropped to 90% between the years 2011–2013. The table below, from the National Down Syndrome Cytogenetic Register, shows that the increase in prenatal diagnosis has been greatest amongst the group of women under the age of 35 (Figure 1).

UK National Screening Committee

Despite the advances seen in prenatal screening, there was no consistent approach to who was offered Down syndrome screening, or how. Then, in 1996, the UK National Screening Committee (UK NSC) was founded. From the outset they were clear that screening must do more good than harm and that quality must be ensured. They developed a framework for screening, which included the definition and classification of population screening programmes. They also published a 'Handbook of population screening' which set the ground rules for the committee and the expectations on future screening programmes.

In 2001 the UK NSC advised that all pregnant women should be offered one of the available screening tests and by 2007 they had set the standard that 75% of Down syndrome should be

Graph showing the most significant increase in prenatal diagnosis is amongst women under 35 years of age

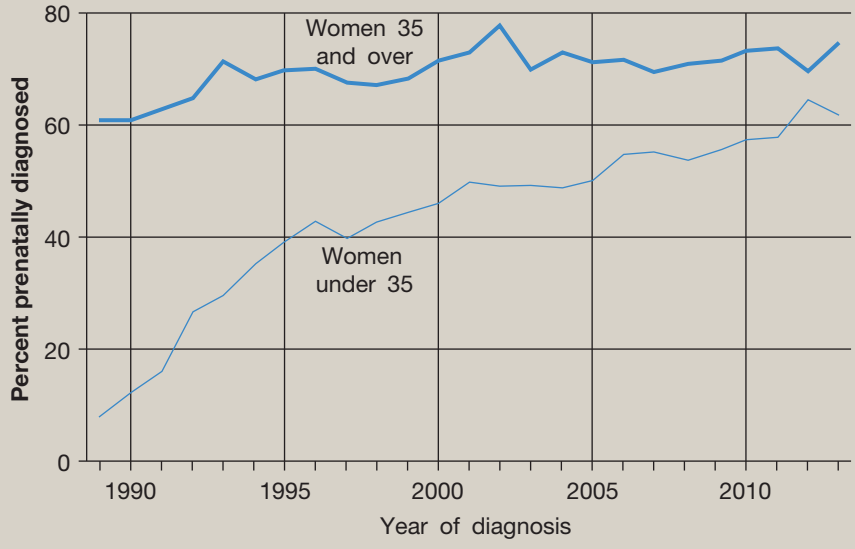

Figure 1

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