1.2 Summary

Screening for Down's syndrome has been in practice since it became possible to diagnose this chromosomal defect prenatally. Until 1984, screening was based purely on maternal age and previous history. Since 1984, the options available to screen for Down's syndrome have increased considerably and research has been aimed at optimising the screening process.

Optimising a screening process involves increasing the sensitivity and specificity so that as many as possible of the affected individuals are identified (in this case, pregnant women carrying fetuses affected by Down's syndrome) with as few as possible "normal" pregnancies being labelled as "increased risk". Screening always requires further tests to verify its results. Should a screening process identify all the affected individuals and none of the unaffected (*ie* 100% sensitivity and 100% specificity), then it would be considered a diagnostic test. By definition, screening will never achieve the same detection efficiency as a diagnostic test, and as such, a comparison between the two modalities is inappropriate.

Over the last 12 years, there has been a constant drive to optimise Down's syndrome screening . In this thesis, several ways of improving Down's syndrome screening have been investigated.

The group of women over 35 years of age are considered at high risk of having a fetus with Down's syndrome according to the original (pre-1984) screening criteria. In countries where antenatal testing for Down's syndrome was offered, all the women in this group were considered "screen-positive" and were offered an invasive diagnostic test. Although screening alternatives are now available, most countries still offer invasive tests to this group of older women. However, many of these women are hesitant about undergoing invasive antenatal diagnostic testing because of the risk of fetal loss caused by the test itself. Many of these women have often endured prolonged infertility, or consider this a "last chance" pregnancy. They are looking for ways to minimise their need for an invasive test, whilst not losing too much in detection efficiency.

The currently used second-trimester maternal serum-screening protocol (in this thesis, a combination of maternal age, alpha-fetoprotein (AFP) and total human chorionic gonadotropin (hCG) estimations) was able to do this. Only 28% of women aged 36 years or older were screen-positive and all the fetuses with Down's syndrome were in this screen-positive group. Larger studies elsewhere have also confirmed that, with a dramatic reduction in the number of women needing an invasive test, more than 88% of fetuses with Down's syndrome can be detected.

Women pregnant after *in vitro* fertilisation (IVF) also belong to a special group. They are often older, and becoming pregnant has been more difficult than for many other women. As such, these women are also quite reticent about undergoing a diagnostic

pregnant through IVF are screen positive than expected using the existing second trimester screening programme, biochemical screening is still superior to screening with age alone.

Why women, pregnant as a result of IVF, have different biochemical parameters than those spontaneously pregnant is not clear. This provides an interesting field for further research.

Many women and their pregnancy care-givers consider an earlier screening test an advantage as it would provide earlier reassurance (for the majority) and an earlier and medically safer termination of pregnancy if desired, should the fetus be shown to have Down's syndrome.

The move to bring serum screening into the first trimester of pregnancy has not been as rapid as was originally expected. In the multicentre trial of which we were part, biochemical screening (using free-βhCG and pregnancy associated plasma protein-A (PAPP-A)) has been shown to potentially be able to detect 63% of fetuses with Down's syndrome for a screen-positive rate of 5.5%. However, our own study into biochemical markers highlighted one of the continuing problems in first-trimester screening. What is considered to be one of the best biochemical markers (PAPP-A) has still not become a reliable, commercially-available assay. Until this happens, the introduction of first-trimester biochemical serum screening will need to be delayed unless a lesser efficiency in the programme is acceptable and only age and free-βhCG are used as parameters.

Other potential biochemical markers have been studied in this thesis, but have not shown the detection efficiency required to optimise first-trimester serum screening.

Schwangerschafts Protein-1 (SP1) levels discriminate between pregnancies carrying a Down syndrome fetus and those without. However, free-βhCG discriminates better, so adding SP1 to the screening protocol would not improve screening efficiency.

Urinary β-core hCG, which may well improve second-trimester serum screening, has been shown in this thesis not to be able to differentiate between Down's syndrome and chromosomally normal fetuses in the first trimester of pregnancy.

Ultrasound (US), using a nuchal translucency (NT) measurement, has been promoted as a superior method of screening for Down's syndrome in the first trimester, with detection rates of greater than 80 per cent for a less than 5 per cent screen-positive rate. Our study showed that US screening was not effective if performed on all women presenting for ultrasounds in the first trimester of pregnancy. Prior to 10 weeks' gestation, the NT could only be measured in 45 per cent of fetuses; this would have necessitated a second ultrasound for more than half of the women. Performing the measurements routinely in first-trimester scans would add more than three minutes to the US scan-time in many women. This would make it impractical in a busy practice. Furthermore, performing a screening test for Down's syndrome on a

group of women having an US for other reasons neglects the need for informed consent. Unless women are aware of what is being screened for, and the implications of a screen-positive result (i.e. the need to undergo an invasive diagnostic test) then this extra measurement should not be made. A thorough explanation and time to consider the options are required before this test is performed.

Finally, women's opinions of moving Down syndrome screening from the second to the first trimester were assessed, to see if the potential users of such a service considered it an advantage. Our study suggests that women already making use of the second-trimester programme would also use first trimester screening. Those who had consciously decided against second-trimester serum screening would also decline it in the first-trimester. Older women, who were being offered an invasive first trimester antenatal diagnostic test because of their age alone would, in many cases, welcome the availability of another form of screening on which to base their decision.

Any form of screening in the first trimester would always need to take into account that up to 50 per cent of Down syndrome fetuses will suffer spontaneous demise between the time of the test and term.

Serum screening for Down's syndrome in the second trimester is a fact of life in many countries and this thesis illustrates some of the efforts that have been made to optimise this form of screening.

Before first-trimester screening is implemented (be it biochemical- and/or ultrasound-based), large prospective studies on low-risk populations are needed to assess whether this is truly an optimisation of screening in both technical and human terms.