UK NATIONAL SCREENING COMMITTEE

Second trimester quadruple testing for T21 in twins

21 November 2013

Purpose

This paper provides background on the agenda item addressing second trimester quadruple testing for T21 in twins.

Background

In singleton pregnancies the accepted standard of care is to offer all women first trimester combined screening (ultrasound measurement of CRL, NT and maternal serum PAPP-A + free-β hCG) for T21. Women who present after 14 weeks and 1 day, are offered the quadruple test (maternal serum AFP, intact or free βhCG, inhibin A + oestriol).

While recommendations for first trimester screening for T21 in twins have been made by FASP, the recommendation for second trimester screening in this population remains unresolved.

An earlier version of the attached paper was discussed by the FMCH in July 2012.

In terms of content, the Subgroup considered that the paper should be developed to highlight the likely size of the population to be screened, the likely number of invasive tests, cases detected and false positive rate which may arise from implementation of the quadruple test in twins.

In terms of process, the FMCH also considered that a limited consultation would help with the discussion on this issue. This approach, rather than a full consultation, was taken as the issue related to a small subgroup of the screened population, the questions were limited in scope, published data was limited and the assessment relied on modelling. As such it was agreed that very few experts would be able to contribute to the debate so a direct approach to these people would allow for a sufficient level of transparency. The FMCH would discuss the resulting document and consider whether any further work was necessary.

Current document and consultation

The attached paper was developed by Professor Dave Wright following a meeting of experts held earlier this year. The document emphasises that quadruple test performance in twins (particularly dizygotic twins) is less reliable than in singleton pregnancies but that the population offered the test would be extremely small.

The paper was circulated to Professors Nick Wald, Howard Cuckle, Mark Kilby and Kypros Nicolaides. These individuals were chosen because of their expertise in the field.

Comments were received from Nick Wald and Howard Cuckle and these are attached for consideration. The responses highlight the limited evidence base and the ongoing debate about the prevalence of T21 in twins and the uncertainties relating to use of the quadruple test in twins.

FMCH meeting

The document and responses were considered at the October 29th meeting of the FMCH. The Subgroup noted the problems relating to the test in this population, for example the estimated performance was below the minimum threshold recommended for singleton pregnancies, but also the lack of evidence based alternatives. The particular group of women (with twins who present late in pregnancy) would be managed within specialist care and it is within this expert environment that the test would be offered and its pros and cons discussed.

It was also noted that NICE currently recommend the quadruple test in this population.

Given this context the FMCH recommended that the test should be integrated into the FASP Programme Standards

Action

The UK NSC is asked to approve this recommendation.

Quadruple Testing in Twin Pregnancies

Summary

- Second trimester screening for twins has been available for over 20 years.
- Quadruple testing for twins is available within the software used within NHS screening laboratories in England.
- Screening performance is poor in twins compared to singletons with detection rates of over 60% for a false positive rate of 10%.
- There are likely to be between 500[a] and 1,200[b]women with twin pregnancies in the screened population each year that fall outside of the combined testing programme who may be offered second trimester quadruple testing. Amongst these, fewer than four affected pregnancies would be expected.
- If the test were offered and a 50% uptake is assumed, then between 25 and 60 screen positives would be expected each year to detect just over 60% of affected twin pregnancies.

Prevalence

Evidence on the prevalence of Down's syndrome in twin pregnancies can be considered from the theoretical and empirical perspectives. The prevalence depends on zygosity which can be inferred during pregnancy from information on chorionicity, method of conception, fetal gender and maternal age; in some cases with certainty and in others probabilistically. In monozygotic twin pregnancies either both twins are unaffected or they are both affected. In dizygotic twins either one of the twins or, in rare cases, both can be affected.

Ignoring any differences in survival rates between singletons and twins, the theory would suggest that in monozygotic pregnancies, Down's syndrome will affect the pregnancy, with both fetuses being affected, with the same maternal age specific risk as that for a singleton pregnancy. In dizygotic pregnancies, the theory would suggest that Down's syndrome affects each fetus with the same maternal age specific risk as a singleton pregnancy. At a given maternal age, the risk of either or both of the twins being affected in dizygotic pregnancy would be expected be close to double the the risk for a singleton pregnancy. The empirical evidence on live birth prevalence, described by Cuckle (1998), is somewhat contradictory in that it suggests a lower live birth specific prevalence for twins than singletons. As Cuckle (1998) points out, this discrepancy could be accounted for by a higher rate of intrauterine deaths amongst affected fetuses in twins than singletons.

Two widely used approaches to the specification of prior risk used in risk assessment in twin pregnancies are

(i) using the same prior risk model for twins as for singletons (see for example Wald and Rish, 2005)

(ii) using a prior risk model that distinguishes between monozygotic and dizygotic pregnancies (see for example, Cuckle, 2006a).

These are available in different screening software used within NHS in England. The two different methods of risk calculation are described below.

Quadruple testing using pseudo risks

Second trimester screening of twin pregnancies using the pseudo-risk approach has been available for over 20 years (Wald *et al*., 1991) with quadruple testing for twins first described in 1996 (Watt *et. al*., 1996). Pseudo-risks are computed by assuming that, after adjustment, the effect of Down's syndrome on marker levels is the same as that in singletons. It is recognised that pseudo-risks should not be interpreted as risks in the conventional sense. However, for a given cut-off and maternal age, they will give the same false positive rate as in singletons. The overall false positive rate would be expected to be somewhat higher because the older maternal age distribution associated with twin pregnancies.

Quadruple testing using risks

The approach to modelling the distribution of risks in affected twin pregnancies (Cuckle and Wilson, 2006b) assumes that, for dichorionic pregnancies with one fetus affected and one unaffected, the adjusted median MoM is half way between the median for the unaffected pregnancy and an affected singleton pregnancy. As illustrated for the case of AFP in Figure 1. This reflects the contribution of one the affected fetus (median = 1) and the unaffected fetus (median 0.73 for AFP). This distribution would therefore be centred on a median of (1+0.73)/2 = 0.85. In monozygotic twins, where both twins are affected, the distributions are assumed to be the same as singletons.

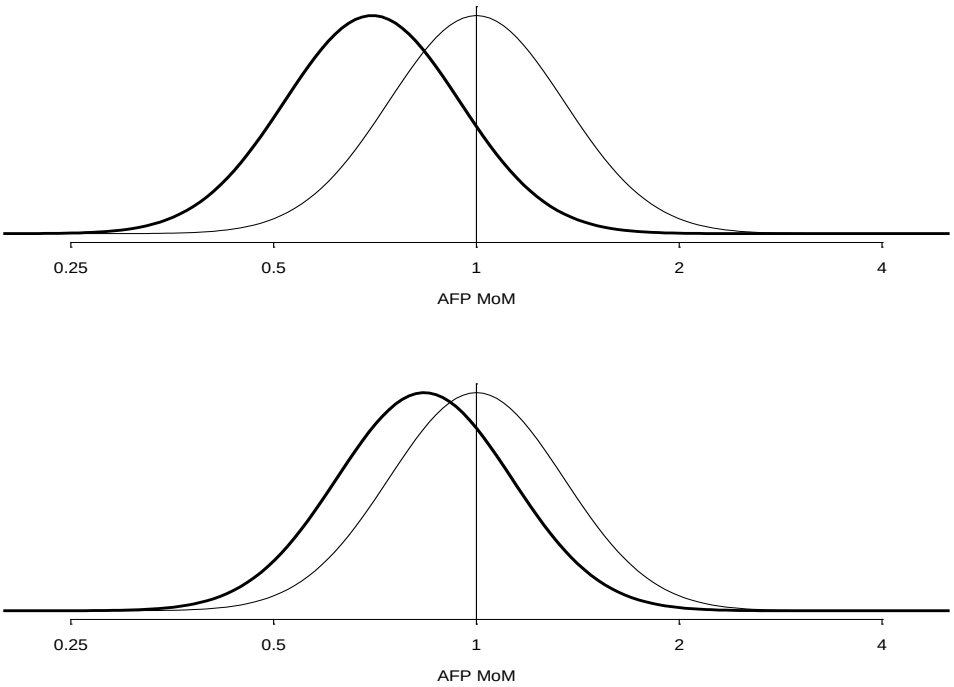

Figure 1: *Distributions of MoM values for AFP (log scale) in unaffected and affected pregnancies (bold). The top panel shows the distributions in singleton pregnancies. The bottom panel shows the distributions in twin pregnancies when, in the case of affected pregnancies, the median MoM value lies half way between the unaffected and affected median for a singleton pregnancy.*

Screening Performance

It has long been established that the performance of screening for twin pregnancies depends on zygosity Neveux *et. al* (1996). In monozygotic twin pregnancies, the screening performance is similar to that of singletons. In dizygotic twins, accounting for 70-80% of all twin pregnancies, the screening performance is worse than in singletons. This arises because of the assumed dilution of the marker concentration from the affected twin with that from the unaffected twin; as illustrated for AFP in Figure 1.

The evidence from prospective studies on screening performance of quadruple testing in twin pregnancies is very limited because of the paucity of data. For the double test with maternal age, AFP and free β hCG, the paper of Garchet-Beaudron et.al. (2008) reports detection rates of 71% in pregnancies where both twins are affected and 60% when just one twin is affected for false positive rates of just over 10%. These results are based on prospective screening of 11,040 twin pregnancies in which 27 pregnancies were affected. The results are consistent with modelling using fitted Gaussian distributions.

For the quadruple test including AFP, free β hCG, uE3 and Inhibin with maternal age the modelled ROC curves for twin pregnancies are shown in Figure 2.

(1) In monozygotic twin pregnancies, the quadruple test will detect close to 80% of pregnancies with Trisomy 21 with an overall screen positive rate of around 3%.

(2) In dizygotic twin pregnancies, with one affected fetus and one unaffected fetus, the quadruple test will detect close to 40% of pregnancies for a screen positive rate of around 3%, around 50% for a false positive rate of 5% and just over 60% for a false positive rate of 10%.

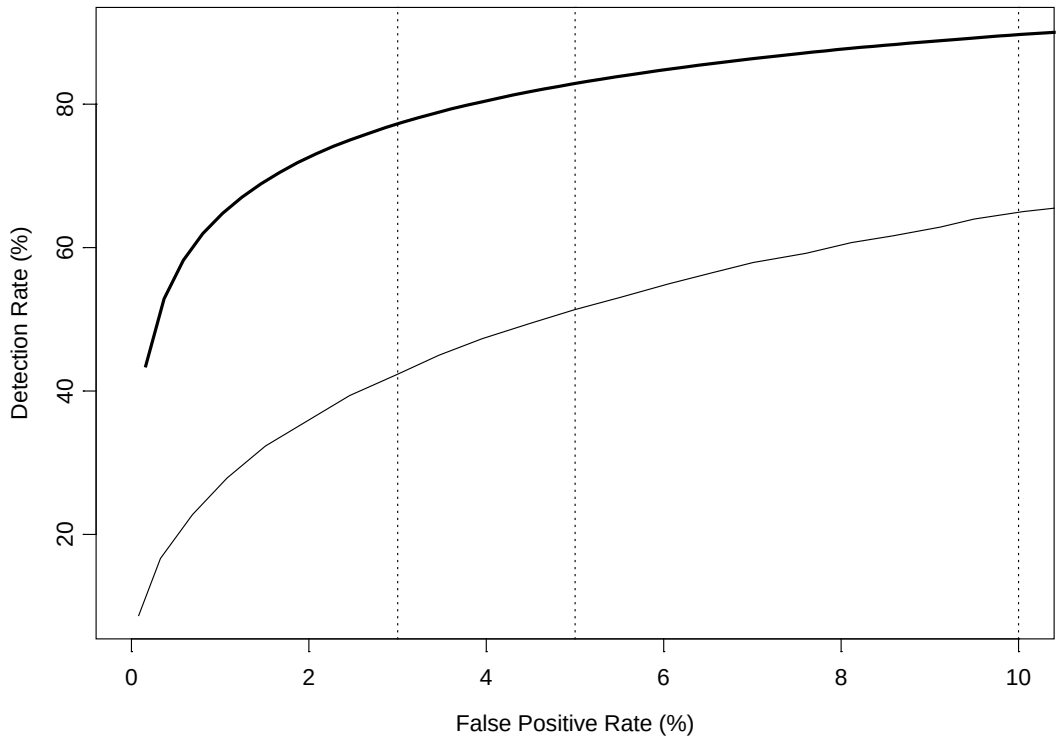

Figure 2: *Receiver Operating Characteristic (ROC) curves for screening using quadruple testing in twin pregnancies for monozygotic pregnancies (bold) and dizygotic pregnancies.*

Quadruple testing for twins in the NHS in England

In England women with twin pregnancies are currently offered the first trimester combined test. There is evidence from prospective data that this is superior to quadruple testing Masden *et. al.* (2011). In the light of this, special attention is being given to maximising the offer of combined testing in twins.

For the relatively small number of women for which the combined test cannot be offered, there is the option of offering the quadruple test. There are likely to be between 500[a] and 1,200[b]women with twin pregnancies in the screened population each year that fall outside of the combined testing programme who may be offered second trimester quadruple testing. These figures are based on (a) a screened population of 5,000 twin pregnancies with 10% offered quadruple testing and (b) a screened population of 8,000 with 20% offered quadruple testing. Amongst the population of women who would be offered quadruple testing, dependent on the maternal age distribution, fewer than four affected pregnancies would be expected. If 50% of these were to accept the offer of a quadruple test with a false positive rate of 10% this would lead to between 25 and 60 screen positives each year to detect just over 60% of the Down's syndrome pregnancies in the screened population. With a false positive rate of 5% the number of false positives would be reduced to between 12 and 30 at the cost of a reduction in detection rate to around 50%.

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