Antenatal Screening for Downs Syndrome

Determining screening performance (detection rates and false positive rates)

Start with:-

i) Sample of pregnant women with data on maternal age, gestational age, levels of the screening markers and outcome of pregnancy

ii) A study that reports the age-specific birth prevalence of Down’s syndrome

Convert marker levels into MoMs

Determine the means, SDs, correlation coefficients for the logarithm of marker MoMs for affected and unaffected pregnancies

The screening markers are shown to have acceptable Gaussian distributions, which can be used to determine likelihood ratios for the study sample or for a standard population

Study Specific Method

Determine likelihood ratios (LRs) using multivariate Gaussian modelling for each woman in the study

LRs are then applied to the age specific risks of Down’s Syndrome to obtain the risk of Down’s syndrome for each pregnancy. (The likelihood ratio is the ratio of the proportion of affected and unaffected pregnancies with a particular combination of marker levels)

For a given risk cut-off the detection rate (DR) and false positive rate (FPR) are determined, respectively, by the proportion of Down’s syndrome and unaffected pregnancies with risks equal to or above the risk cut-off. These proportions are obtained by counting the number of Down’s syndrome pregnancies and unaffected pregnancies that have a risk estimate equal to or greater than the risk cut-off, and dividing by the total number of Down’s syndrome and unaffected pregnancies, respectively.

Similarly, the DR for a given FPR can be determined by counting. For example, the DR for a 5% FPR is determined by counting the proportion of Downs Syndrome pregnancies that have a risk estimate equal to or greater than the risk estimate at the 95th centile of unaffected pregnancies. Alternatively, the same can be done by determining the risk cut-off for a given DR and then determining the FPR for that DR.

General Method

Apply the age specific risk of Down’s syndrome to a standard population of maternities (e.g. England & Wales 1996-98) to give the expected number of Down’s syndrome pregnancies and unaffected pregnancies at each year of age

From the multivariate Gaussian distribution of screening markers LRs are obtained from the ratio of the heights of these distributions for combinations of the screening markers in specified intervals, usually about 100 intervals per marker covering a wide range of values (say +/-4SD). These LRs are then applied to the affected and unaffected pregnancies at each year of age to give risks for the resulting marker combinations.

In addition, the proportion of Down’s syndrome and the proportion of unaffected pregnancies within each of the specified intervals of the screening markers is estimated from the corresponding area under the multivariate Gaussian distributions in Down’s syndrome and unaffected pregnancies respectively.

For a given risk cut-off the detection rate (DR) and false positive rate (FPR) are determined, respectively, by the proportion of Down’s syndrome and unaffected pregnancies with risks equal to or above the risk cut-off. These proportions are obtained by summing the proportions of Down’s syndrome and unaffected pregnancies, with risks equal to or higher than the risk cut-off, across all maternal ages and screening marker categories.

Similarly, the above step can be repeated by determining the risk cut-off corresponding to a given DR and then summing the proportions of the unaffected pregnancies with risks equal to or higher than the risk cut-off to estimate the FPR for that DR. Alternatively the same can be done by determining the risk cut-off for a given FPR and then determining the DR for that FPR.

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Advantages

Intuitive

Each woman in a particular study is assigned a risk and the proportions of affected and unaffected pregnancies exceeding different risk cut-offs are determined by counting the women in the study.

Disadvantages

The resulting proportions (DRs and FPRs) are dependent on the age distribution of women in the study sample so the results are not generalisable.

Estimates of DRs (and FPRs) are imprecise due to the small number of pregnancies in a given study.

Advantages

Overcomes the problems of differences in maternal age distribution between studies.

It minimises imprecision in estimating DRs and FPRs because estimates of the proportions in the tails of the risk distributions are less subject to random sampling error.

Disadvantages

Less intuitive.

Summary and conclusions

The two methods are similar, but the Study Specific Method calculates each woman’s likelihood ratio for her particular MoM combination while the General Method uses the distributions of likelihood ratios derived from the distributions of MoM values and then applies these likelihood ratios to each year of maternal age in a distribution of pregnancies (affected and unaffected) in any given population.

The general method is the standard and preferred method for estimating DRs and FPRs. The Study Specific method is only reliable in very large studies based on several hundred affected pregnancies and tens of thousands of unaffected pregnancies and even then is still applicable only to the particular age distribution of women in the study.

Abbreviations

MoM: Multiples of the median
SD: standard deviation
LR: likelihood ratio
DR: detection rate
FPR: false-positive rate
Alternative Method using Monte Carlo Simulation

Apply the age-specific birth prevalence of Down’s syndrome to a standard population of maternities (e.g. England & Wales 1996-98) to give the number of Down’s syndrome pregnancies and the number of unaffected pregnancies expected at each year of age.

Assign each pregnancy a MoM value for each marker (this simulates the marker values that would be found in a large population of affected and unaffected pregnancies) by drawing values at random from the corresponding Gaussian distribution of marker levels, according to whether the pregnancy is affected or unaffected.

Determine the Likelihood ratio (LR) for each woman using the same procedure as for the Study Specific Method and the General Method.

Apply the LR to the age specific risks to obtain the risk of Down’s syndrome for each pregnancy.

Determine the detection rate (DR) for a given false positive rate (FPR) by counting as for the Study Specific Method.

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January 2004