MATERNAL SCREENING FOR DOWN'S SYNDROME

Down's syndrome is the most common chromosomal disorder, with an incidence of about 1.2 per 1,000 births in Australia. It is characterised by mental retardation, hypotonia, prominent tongue, oblique palpebral fissures and epicanthic folds and is associated with congenital heart disease and strabismus. Down's syndrome can be diagnosed in pregnancy by chorionic villus sampling or amniocentesis. However, it is not feasible to apply these invasive procedures to all pregnant women. This article compares the impact in NSW of current screening practice and a proposed new test to identify women who are at increased risk of a Down's syndrome pregnancy.

The risk of a Down's syndrome pregnancy rises with increasing maternal age. This is the basis of current prenatal screening practice for Down's syndrome in NSW, whereby amniocentesis or chorionic villus sampling is offered to all women 37 years of age or over. But age alone is an unsatisfactory screen because the great majority of Down's syndrome pregnancies occur in younger women. A screening test which identifies high-risk pregnancies at all ages is needed. Four case-control studies[1-4] and one prospective trial[5] have shown that a combined screening test, which uses maternal age and three maternal serum markers (alpha-fetoprotein, unconjugated oestriol and human chorionic gonadotrophin) to calculate a woman's individual risk of having a Down's syndrome pregnancy, is better than maternal age alone.

SCREENING BY MATERNAL AGE ALONE

If the maternal age-specific incidence rates for Down's syndrome are applied to the distribution of maternal ages at birth in NSW during 1990 then 125 Down's syndrome babies would be expected to be born in that year. Of these, 35 (28 per cent) would occur in women aged 37 years and over, and 90 (72 per cent) in those aged less than 37 years. While the risk of Down's syndrome births is higher in the 37-plus age group, the majority of births are to women aged less than 37 years, and the majority of Down's syndrome births are also to women aged less than 37 years. The sensitivity of screening by maternal age alone is therefore 28 per cent (this assumes all eligible women agree to amniocentesis).

Of the 87,587 births in NSW during 1990 an estimated 4,586 (5 per cent) were to women aged 37 years or over. Only 35 of the infants born would be expected to have Down's syndrome. Thus, while the risk of Down's syndrome is higher in women aged 37-plus, most Down's syndrome-affected pregnancies occur in younger women, because the great majority of pregnancies occur in younger women. Screening by maternal age alone gives a false positive rate of 5 per cent, which may be expressed as a specificity of 95 per cent.

The amniocentesis rate in NSW for women aged 37 years and over is, in fact, about 50 per cent. Under the current screening program using maternal age alone, it is therefore expected that 17 (14 per cent) Down's syndrome pregnancies would be detected per year as a result of 2,293 amniocenteses and 108 (86 per cent) Down's syndrome pregnancies would be missed. Assuming a fetal loss rate of 0.5 per cent after amniocentesis, it is expected that about 11 normal fetuses will be lost.

SCREENING USING THE TRIPLE TEST

The likely impact of the triple test in NSW can be calculated from known sensitivity and specificity measurements, and estimates of amniocentesis uptake rates.

TABLE 4

SENSITIVITY AND SPECIFICITY OF THE TRIPLE TEST AT DIFFERENT MATERNAL AGES

Maternal age (years)	Sensitivity	Specificity
20	40.4	97.4
25	43.9	97.0
30	51.9	95.2
35	70.5	87.1
40	89.8	63.7

Source: Canick JA, George JK. Multiple marker screening for fetal Down syndrome. Contemporary Ob/Gyn, 1992, April, pp. 3-12.

TABLE 5

EXPECTED NUMBER OF TRUE POSITIVES, FALSE POSITIVES AND TOTAL POSITIVES FOR MATERNAL SERUM SCREENING USING THE TRIPLE TEST, ASSUMING 100 PER CENT AMNIOCENTESIS UPTAKE RATE, BY RISK CUT-OFF LEVEL, NSW, 1990 (a)

Risk cut-off level	True positive	False positive	Total positive
1:100	55	1,489	1,544
1:150	65	2,452	2,518
1:200	71	3,416	3,487
1:250	77	4,379	4,456
1:300	80	5,343	5,423
1:350	84	6,306	6,390

(a) Sensitivities and specificities are taken from Wald et al[2].

The triple test has a sensitivity of 61 per cent and a specificity of 95 per cent at a risk cut-off of about 1:250 (equivalent to the risk for a woman aged 37 years if age alone were the screening criterion)[2]. This means that, if all women with a calculated risk of a Down's syndrome pregnancy of 1:250 or higher are referred for amniocentesis, then 61 per cent of Down's syndrome pregnancies would be detected and 5 per cent of the pregnant population would have a positive test result, assuming all eligible women agree to amniocentesis.

However, the sensitivity of the triple test increases and the specificity decreases with increasing maternal age (Table 4). The test is therefore better for detecting Down's syndrome pregnancy at older maternal ages, at the cost of a higher false positive rate.

The proportion of Down's syndrome pregnancies which is detected can be increased by reducing the risk cut-off level. But this will also increase the number of false positive results and the total number of amniocenteses. Table 5 shows the effect of raising or lowering the risk cut-off level for referral for amniocentesis for the NSW population.

It is unlikely that amniocentesis uptake rates will reach 100 per cent. Figure 1 shows the effect of varying amniocentesis uptake rates on the number of Down's syndrome pregnancies detected and missed, and the number of fetuses lost (assuming a fetal loss rate due to amniocentesis of 0.5 per cent), at a risk cut-off level of 1:250. The number of Down's syndrome cases detected exceeds those missed at an amniocentesis uptake rate of about 90

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per cent or more. At the more likely amniocentesis uptake rate of 50 per cent more than twice the number of Down's syndrome pregnancies is missed than detected.

Figure 2 shows the same information as Figure 1 but for a lower risk cut-off level of 1:350. This will increase the yield of Down's syndrome pregnancies to 84 (67 per cent) — an increase of seven affected cases — for an increase in the number of amniocenteses by 1,934 to 6,390. The number of Down's syndrome cases affected will be greater than the number missed at amniocentesis uptake rates of 70 per cent or more. At the more likely uptake rate of 50 per cent, about twice as many Down's syndrome pregnancies will be missed as will be detected. However, at a fetal loss rate of 0.5 per cent due to amniocentesis, it is expected that 16 fetuses will be lost. It is therefore likely that a reduction in the risk cut-off to 1:350 will result in more additional fetuses lost than additional Down's syndrome pregnancies detected.

DISCUSSION

Maternal serum screening with the triple test yields about twice the number of Down's syndrome pregnancies as screening by maternal age alone, for a similar number of amniocenteses and a similar number of fetuses lost. A range of screening strategies is possible using maternal age or the triple test or a combination of both. Table 6 shows the expected results of five screening strategies, assuming an amniocentesis uptake rate of 50 per cent. The highest yield of Down's syndrome pregnancies is produced by a strategy which combines amniocentesis for all pregnant women aged 35-plus and 'triple test screening' for the remainder. This will identify 35 per cent of Down's syndrome pregnancies at a 'cost' of 6,405 amniocenteses, which is equivalent to 7.3 per cent of the pregnant population. However, triple test screening alone is expected to detect 30 per cent of Down's syndrome pregnancies for 2,228 amniocenteses. The combined strategy of amniocentesis for all women aged 35-plus and triple test screening for the rest will therefore

TABLE 6

EXPECTED NUMBER OF DOWN'S SYNDROME CASES DETECTED AND MISSED, AND EXPECTED TOTAL NUMBER OF AMNIOCENTESES AND FETUSES LOST FOR VARIOUS POPULATION-BASED MATERNAL SCREENING PROGRAMS, FOR AN AMNIOCENTESIS UPTAKE RATE OF 50 PER CENT (a)

Screening program (b)	Number of Down's pregnancies detected		Number of Down's pregnancies missed		Number of amniocenteses	Number of fetuses lost (c)
	No.	%	No.	%		
1	18	**14**	107	**86**	2,293	11
2	24	**19**	101	**81**	4,642	23
3	38	**30**	87	**70**	2,228	11
4	42	**34**	83	**66**	4,363	32
5	44	**35**	81	**65**	6,405	41

(a) These figures are based on the maternal age distribution for NSW births, January-June 1990
(b) Screening programs as follows:
1 Maternal age ≥ 37 years
2 Maternal age ≥ 35 years
3 Triple test screening (incorporating age) only
4 Maternal age ≥ 37 years plus triple test screening of remainder with triple test cut-off of 1:250
5 Maternal age ≥ 35 years plus triple test screening of remainder with triple test cut-off of 1:250
(c) Expected number of fetuses lost is estimated at 0.5 per cent of total amniocenteses

FIGURE 1

Expected number of Down's syndrome pregnancies detected and missed and number of normal fetuses lost as a result of maternal serum screening using the 'triple test' at a risk cut off level of 1:250, by amniocentesis uptake rate, NSW, 1990.

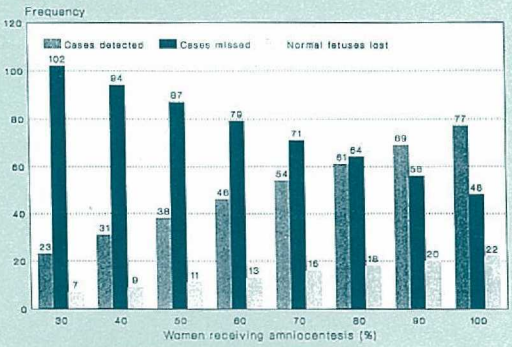
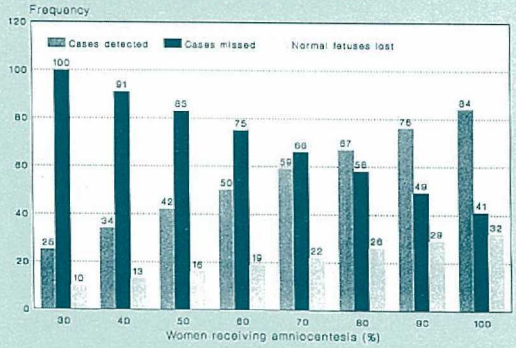


FIGURE 2

Expected number of Down's syndrome pregnancies detected and missed and number of normal fetuses lost as a result of maternal serum screening using the 'triple test' at a risk cut off level of 1:350, by amniocentesis uptake rate, NSW, 1990.



detect an additional six Down's syndrome pregnancies as a result of an additional 4,177 amniocenteses. The combined strategy is not substantially better than triple test screening alone because the triple test already has maternal age incorporated into the algorithm.

The yield of Down's syndrome pregnancies detected may be increased in two ways. First, the risk cut-off level for the triple test could be reduced. This will probably result in the number of additional fetuses lost due to amniocentesis exceeding the number of additional Down's syndrome pregnancies detected. Second, the proportion of women who agree to amniocentesis could be increased. For example, in order to detect 50 per cent of Down's syndrome pregnancies using triple test screening alone, an amniocentesis uptake rate of 82 per cent would be required, entailing 3,653 amniocenteses, equivalent to 4 per cent of the pregnant population. In order to detect 50 per cent of Down's syndrome pregnancies using a strategy which includes the offer of amniocentesis to all women aged 37-plus and triple test screening for the remainder, an amniocentesis uptake rate of 74 per cent would be required, entailing 6,457 amniocenteses, and equivalent to 7 per cent of the pregnant population.

Population-based maternal serum screening for Down's syndrome using the triple test is the most efficient screening test available. A risk cut-off of 1:250 gives the best yield in terms of maximum Down's syndrome pregnancies detected for the fewest number of

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amniocenteses. However, even if all women who screen positive accept amniocentesis, only 61 per cent of Down's syndrome pregnancies will be detected. Triple test screening will also result in large numbers of false positive test results and some false negative results. Each mother screened will need to be carefully advised on the meaning of the test result, be it positive or negative. The result of an amniocentesis is known after about three weeks, and should be available by the 20th week of pregnancy so the family may decide whether to proceed with the pregnancy. Counselling services will need to be available almost immediately the test results are available, so a decision about amniocentesis can be reached and acted on promptly. For families living in rural regions, an amniocentesis will entail travel to a major centre at short notice.

The rate of some other chromosomal defects increases with increasing maternal age. These include trisomy 18, trisomy 13 and XXY abnormalities. Some trisomy 18 pregnancies have been detected after screening with the triple test, but the reliability of the test in regard to trisomy 18 is not known. If amniocentesis is offered only to women whose risk is high according to the triple test, regardless of maternal age, some affected pregnancies which would have been detected under screening based on maternal age will be missed.

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Meningitis surveillance 1991

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of detection was lowered in part by some PHUs actively seeking only cases of meningococcal meningitis.

Table 3 shows that while most PHUs did not identify as many cases from their Area/Region as the ISC, two PHUs identified more. There are several explanations for the discrepancies. Active surveillance, in some instances, was based on hospital admissions while the ISC reports separations so patients may have been admitted in the surveillance period but discharged after June 30, 1991 when the ISC closed. Also, patients may cross borders. In some cases more detail was provided on active surveillance. For example, a case identified to South Western Sydney PHU as meningococcal meningitis, on clinical grounds, was discharged as 'meningitis due to unspecified bacterium (ICD9-320.9)' because no organism was isolated. Finally, the ISC was not a full enumeration of all hospital separations for the study period. Full enumeration of all public hospital separations began on July 1, 1991 and will begin for all private hospital separations on July 1, 1993, which will alleviate this problem in the future.

Innovative changes to public health in NSW should assist passive surveillance of meningitis. The Public Health Act 1991 has made Hib meningitis a notifiable condition. It is to be notified by both hospitals and laboratories, which should not only increase detection rates but allow swift public health action to prevent secondary cases. This is also the case for meningococcal meningitis.

Another positive public health development has been the licensing of a first vaccine against Hib infections. Although immunisation for Hib infections will not be added to the childhood immunisation schedule until a vaccine that is suitable for children less than six months of age becomes available[10], a PRP-D vaccine is available on a retail basis for children aged 18 months.

RECOMMENDATION

That the NSW Health Department Inpatient Statistics Collection provides the most cost-effective method for annually reviewing trends in bacterial meningitis in NSW.

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