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Down Syndrome Screening in Singapore – The Effectiveness of a Second Trimester Serum Screening Policy Modelled on 29,360 Pregnancies in KK Women's and Children's Hospital

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ABSTRACT

Aim of Study: To assess the effectiveness of a proposed second trimester Down syndrome serum screening policy in Singapore.

Method: Auditing the effectiveness of an age-only policy and comparing it against a serum screening policy modelled on the same maternal population of KK Women's and Children's Hospital in 1994 and 1995.

Results: KK Women's and Children's Hospital's (KKH) maternal age distribution is similar to the national age distribution of mothers. Sixteen percent (16.7%) of mothers in KKH, in 1994 and 1995, were 35 years or older at delivery. Based on our hospital birth defect registry, 66% (35/53) of Down Syndrome pregnancies occurred in mothers who were 35 years or older at delivery and 43% (23/53) in the oldest 6.5% of mothers (38 years or older at delivery). Using various models on KKH's population structure to estimate the expected number of Down Syndrome livebirths expected, 52% – 55% and 34% – 36% of Down Syndrome livebirths were expected to occur in the oldest 16.7% and 6.5% of mothers respectively. These simulated figures are much lower than the figures from the data and needs further study, assuming that the Western Down Syndrome risk model to be applicable to our population. The overall uptake of amniocentesis irrespective of gestational age at booking was 28%. In mothers who were 35 years or older at delivery and booked before 22 weeks gestation, the uptake rate of amniocentesis was 49%. There was a substantial difference in the uptake rate when the counselling was done by trained counsellers compared to those who were not.

Conclusion: We would expect that for a fixed amniocentesis rate of 6.5% and 16.7%, serum screening would be able to detect 71% and 85% respectively of the Down syndrome pregnancies. This is more efficient than figures published from Western populations as our patients are older.

Keywords: Down syndrome, Singapore, serum screening, modelling

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INTRODUCTION

Significant congenital anomalies are present in about 2% of infants at birth. They are the most common cause for prolonged hospital admission in childhood. For survivors and their families, the human and economic costs are heavy since many of the affected individuals will need life-long support.

Trisomy 21 or Down syndrome (DS) is estimated to occur in about 1: 660 – 840 deliveries, making it the most common pattern of congenital malformation in man[1,2]. This translates to around 60 – 75 Down Syndrome births every year in Singapore (50,000 livebirths a year). The actual numbers delivered would depend on the national maternal age population structure, the extent of uptake of Down Syndrome screening antenatally and subsequent intervention of affected pregnancies.

The basis of screening for Down Syndrome pregnancies based on maternal age

The well-known association that a pregnant woman's risk increases steadily as her age advances comes from many epidemiological studies[3]. This formed the basis of screening test based on age for which amniocentesis and karyotyping were offered in the early 1970's when cytogenetic techniques became generally available.

When amniocentesis for fetal karyotyping was introduced (without ultrasound guidance then), the risk of the procedure was uncertain and it was therefore offered only to women with a minimum age of 40 years. Gradually as amniocentesis became more widespread and because it appeared quite safe, the 'high-risk' group was redefined to include women with a minimum age of 35 years; this 'high-risk' group constituted approximately 5% of the pregnant population in United Kingdom and the United States of America.

From epidemiological studies, the maternal age-related risk for Down Syndrome live births for a 35-year-old was about one in 385[3] and for a Down Syndrome pregnancy, it was about one in 250 at the time of amniocentesis[4]. Conveniently, this was apparently similar to the estimated procedure-related risk of miscarriage from amniocentesis. Thus was

created the concept that amniocentesis is offered to 5% of pregnant women and/or when the risk of an affected pregnancy is equal to or more than the risk of miscarriage from the test.

Second trimester serum screening for Down Syndrome pregnancies

Multiple-marker serum screening for fetal Down Syndrome using maternal alpha-fetoprotein (MSAFP) in combination with one or two other fetoplacental markers have been rapidly introduced into clinical obstetric practice since the late 1980's. All published studies so far confirm that this combination (using 2 or 3 markers) can increase the sensitivity of screening 2 – 3 fold, with a corresponding reduction in false-positive rate[5,6].

Although the method of gestational age estimation[7-9], laboratory quality control considerations[10], the type of algorithm used in the calculations[11] and serum distribution parameters adopted[12,13] are sources of error in estimating the risk, the accuracy is not critical from an epidemiological (or a national health-resource provider) point-of-view. Indeed, the cut-off risk chosen by most health care providers is determined from the economist's point-of-view, which is from a predefined screen positive rate. The latter is sometimes determined by the capacity of the cytogenetic laboratories. In the UK, to keep the screen-positive rate constant at 6%, Wald et al recommended using a term risk of 1: 250[6]. This is actually equivalent to an age-related risk of a 37-year-old mother. However, from the clinician's perspective and also from the mother's perspective, amniocentesis is offered when the risk of an affected pregnancy is equal to or more than the risk of miscarriage resulting from amniocentesis. The skill which incurs a low miscarriage risk is a necessary prerequisite.

Comparison of KK Hospital and national maternal distribution population

KK Women's and Children's Hospital's (KKH's) maternal age distribution population at delivery for 1994 and 1995 and the national age distribution of mothers at delivery in 1995 are essentially identical. The population distribution structure (frequency histogram) of KKH over 2 years (1994 and 1995) when superimposed over that from the national data shows similar profiles.

The mean and median maternal age for KKH were 29.3 years and 29.1 years respectively. The 95th centile was 38.1 years. Maternal age of 35.0 years at delivery corresponded to the 84th centile, ie. 16.7% (or 4,409) of mothers delivering in KKH in 1994 and 1995 were 35 years or older at delivery. The corresponding figures calculated from the Registry of Births and Deaths, National Registration Department Birth Statistics Registry are almost identical. The mean and median maternal age at delivery were 29.7 and 29.1 years respectively. The 95th centile was 37.0 years and 15.3% of mothers were 35 years or older at delivery.

The Singapore context

The majority of Down Syndrome pregnancies are born to mothers 35 years or older in Singapore[2]. However, it would be erroneous to compare this figure to those from UK or USA where the majority of Down Syndrome pregnancies are born to mothers younger that 35 years and to conclude that serum screening has little role in Singapore.

The majority of obstetricians in Singapore offer karyotyping to mothers at or older than 35 years at delivery. Serum screening has been offered by several laboratories in Singapore in the last few years and the risk cut-off used is apparently 1:250 at term. While there is now little doubt that serum screening when properly done is more efficient than an age-only policy to screen for Down Syndrome fetuses, no attempt has so far been made to analyse the impact of widespread implementation such a policy in Singapore.

A "positive" screen will not impact on the incidence of Down Syndrome livebirths if there is poor uptake of the screening test, poor uptake of the diagnostic test (amniocentesis) and poor rates of intervention (termination of pregnancy). This paper also examines these rates using the present screening policy in our hospital and in the context of our own maternal population distribution. It also compares the effectiveness of our present age-related screening policy to that of a simulated second trimester serum screening policy using a theoretical 100% uptake rate. The uptake of amniocentesis in KKH in 1994 and 1995 will be derived and the data extrapolated to serum screening to give an idea of the variation in cytogenetic workload resulting from the above-mentioned influences.

Effectiveness of an age-related Down Syndrome screening policy using data from the Birth Defect Registry

Our hospital delivers about a third of Singapore's livebirths and at present has not embarked on serum screening for Down Syndrome pregnancies. In 1994/1995, using the current policy of offering amniocentesis for mothers 35 years or older at estimated date of delivery (EDD), out of the 35 Down Syndrome pregnancies identified in the older mothers, 14 were aborted while 2 ended in stillbirths and 19 were born alive.

The proportion of older mothers who had a Down Syndrome pregnancy was 66% (35/53). This contrasts to the often quoted 33% of Down Syndrome pregnancies born to older mothers in England and in the United States.

As up to 30% of Down Syndrome pregnancies in mid-trimester end in demise[5], the predicted number of Down Syndromc livebirths in the absence of intervention is 45.

From our hospital birth defect registry, out of the 53 Down Syndrome pregnancies, 35 (66%) of the mothers were 35 years or older at delivery. This means that for a theoretical 16.7 % amniocentesis rate in KKH (2,202 anmiocentesis annually), we

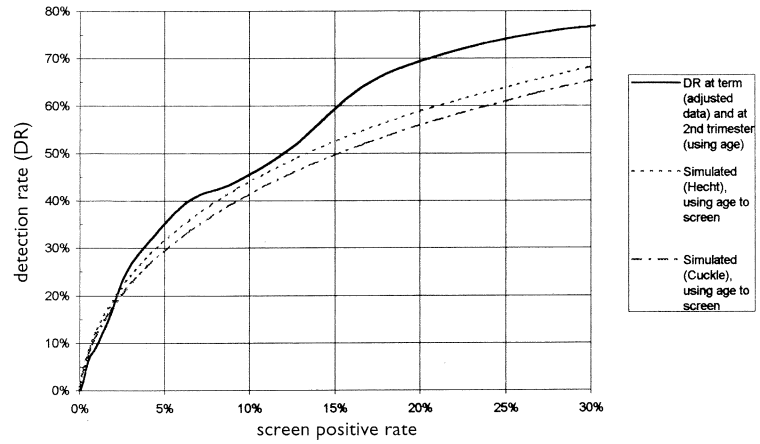

Fig 1 – Comparison of receiver operator curves (ROC) at term using actual and simulated data

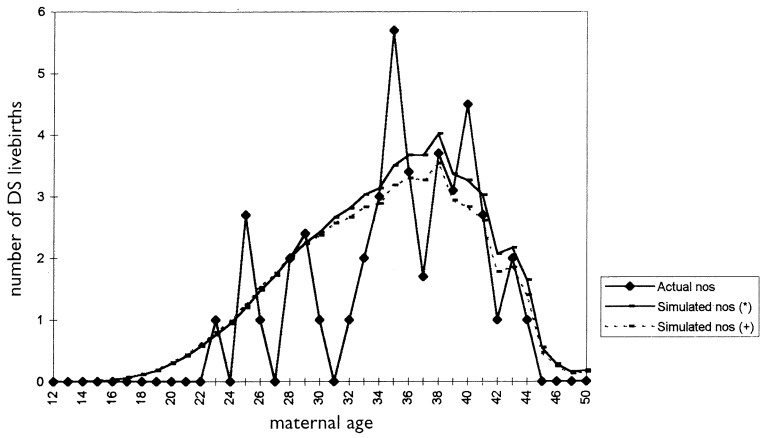

Fig 2 – Comparison of "actual" numbers of Down Syndrome livebirths with 2 simulated models
* Hecht & Hook most likely complete set[11]
\+ Cuckle et al[3]

would have been able to detect 66% of the Down Syndrome pregnancies (35 out of 53 Down Syndrome pregnancies).

Fig 1 shows the receiver operator curve (ROC) derived by varying age cut-offs and their corresponding detection rates for the given screen positive rates. In calculating the detection rate, the appropriate numerator and denominator either at term or in the second trimester should be used. At age 35 years as the cut-off risk, the screen-positive rate and detection rate are 16.7% and 64% respectively. At a 6.5% screen-positive rate (age 38 years and older), the corresponding detection rate is 40%.

Modelling the ROC using the local population distribution as a check on completeness of the Down Syndrome registry

One major weakness of deriving the ROC from raw data is that it is very dependent on completeness of the registry. The detection rate will be overestimated if the denominator data is underestimated. Because of the relative rarity of Down Syndrome pregnancies, an error of a few cases can result in a rather large difference in the detection rate. For example, if screening detected 60 Down Syndrome pregnancies out of a total of 90 known cases of Down Syndrome pregnancies (of which 10 were not identified), then the calculated detection rate would be 60/90 = 67% when than the 'true' rate is 60% (60/100).

To check this, the total number of Down Syndrome livebirths was simulated by using known Down Syndrome live birth risk algorithms derived from epidemiological data[3] integrated over the maternal population distribution.

Using the maternal age population structure to model the number of Down Syndrome livebirths, the number of Down Syndrome livebirths expected from this algorithm is 53. The total number of stillbirths (two stillbirths) expected is very small relative to the number of livebirths expected, even when using a much higher stillbirth rate of 15/1,000 livebirths (compared to national stillbirth rate of 3/1,000 livebirths & stillbirths in 1995 and 4/1,000 livebirths & stillbirths in 1994). Hence, Down Syndrome livebirths alone will be used for the rest of this paper[14].

In Fig 1, the ROC of the simulated population alongside another one derived from a more recent Down Syndrome age-risk algorithm by Hecht & Hook[11] and are compared to the ROC derived above. It can be seen that the simulated ROCs are somewhat less efficient than what we would expect compared to actual data. Keeping the screen-positive rate constant, on comparing the various detection rates, it appears that the modelling techniques underestimated the detection rate when compared to the actual data from the registry. A possible explanation could be due to under-detection of Down Syndrome infants in younger mothers. Another possibility is a selectively higher early pregnancy loss of Down Syndrome fetuses in the younger mothers, which is equally unlikely. It could be that the age-specific Down Syndrome risk of our maternal population is different from epidemiological data obtained from mainly Caucasian mothers. It is most likely that the differences are due to sampling errors as the numbers are small as seen from the frequency histogram in Fig 2.

Actual uptake of amniocentesis and the possible reasons for this low uptake rate

Out of a total of 53 mothers with Down Syndrome pregnancies in KKH in 1994/1995, 35 (66.0%) were aged 35 years or older at delivery. Of these 35, nine mothers (25.7%) had booked too late (after 22 weeks gestation) to be offered amniocentesis. This lower percentage as compared to 52.3% (2,569/4,909) of older mothers (aged 35 years or older at delivery) and who booked after 22 weeks gestation was probably fortuitous.

The proportion of older women presenting before 22 weeks gestation is 48% (2,340/4,909). The uptake of amniocentesis in these older mothers was 49.6% (1,161/2,340). The possible explanation behind this somewhat low uptake rate was investigated.

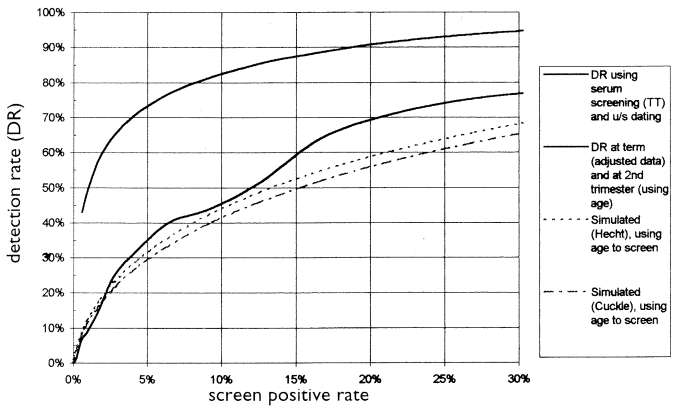

Fig 3 – Comparison of receiver operator curves (ROC) using Down Syndrome risks at term: age-related policy versus serum screening using triple test

In KKH, doctors can choose to counsel the mothers/couples themselves or/and refer her/the couple to be counselled by a team of trained counsellors. The counsellors spend on average 20 minutes for each mother/couple referred for pre-natal counselling going over the implications of Down Syndrome birth, their assigned risk based on maternal age and the procedural associated loss rates. The counselling is non-directive and the patient's/couple's wishes are respected. They then decide whether or not to have an invasive procedure either on the day of counselling or after a period of deliberation. The procedures are usually scheduled more than 48 hours after counselling and not later than 21 weeks gestation by ultrasound dating.

In the absence of selection bias, if the mother's decision for an invasive procedure was not influenced by the person counselling, we would expect that the uptake rate of amniocentesis in the group counselled by the counsellors and the group counselled by doctors to be about the same as the overall rate of 49.6%. However, data from counselling records show that in 1994/1995, the uptake rate of procedures was 88.8% for 854 elderly mothers counselled by the team; much higher than the rate of 10.4% counselled by doctors. A selection bias in that patients who were keen for antenatal karyotyping were more likely to be referred for counselling than those who were not, is one possible explanation. The patient's decision is more likely influenced by the person who gives (or perhaps did not give) the necessary and/or appropriate information[15-17]. Another reason could be that non-verbal cues are just as important as the message being imparted.

Using a serum-screening policy modelled onto local population distribution

As a prelude to the serum screening programme, we did an epidemiological simulation of the impact of implementing serum screening modelled according to KK Women's and Children's Hospital's maternal age at delivery distribution structure derived from the period 1/1/94 to 31/12/95 (29,360 deliveries).

The detection rates and screen-positive rates were obtained by using Monte Carlo simulation[18]. This statistical simulation approach involves repeated random sampling from an assumed population of normal and Down Syndrome outcomes, using Wald's serum distribution parameters[12] and the maternal age distribution of KKH population in 1994/1995. The assumed population of normal and Down Syndrome outcomes are described by multivariate Gaussian class conditional distributions and a representative maternal population distribution. Many simulations are then performed, simulating multiple samplings and the paired detection rates and screen-positive rates obtained.

The receiver operator curve (ROC) of this simulation (Fig 3) is compared to the ROC derived earlier in this paper. It shows that for any given screen-positive rate, the detection rate of Down Syndrome is far more efficient using serum screening than using age alone.

Comparison of different screening policies

a) Comparison between triple serum screening in UK and in Singapore

In the United Kingdom, only 6% – 8% of the mothers are 35 years or older at delivery. Using age at 35 years as a screening method, they would detect about 30% of Down Syndrome pregnancies. Using serum biochemistry, they projected that they can improve the detection rate to as much as 60% while keeping an amniocentesis rate of 6% – 8%[6].

Extrapolating these detection rates and screen-positive rates to our local population would be erroneous as there are significant differences in the two populations. Compared to the United Kingdom, the age distribution of Singapore mothers is normally distributed with equal numbers of mothers above and below the mean/median age of 29.3 years, with 16% of mothers 35 years or older at delivery. In contrast, the population in UK is skewed towards the left with more mothers in the younger age group and a younger median age of 26.9 years and only 6% – 8% of the mothers are 35 years or older at delivery.

As serum screening also takes the maternal age into account, it would be expected that the detection rate of Down Syndrome fetuses would be higher for a given amniocentesis rate in a population of relatively older mothers. The ROC in Fig 3 shows the detection rates expected in Singapore, at various fixed screen-positive (amniocentesis) rates. Table I summarises this data and compares: (1) the detection rate in UK at a fixed screen-positive rate of 7% – 8% under an age alone policy and a serum screening policy, and (2) the detection rate in Singapore at a fixed screen-positive rate of 6.5% under a serum screening policy and an age alone policy.

b) Comparison between age-related screening policy, triple serum screening policy and a combination of both for the KKH 1994/1995 maternal population

Table II shows the predicted number of amniocentesis to be performed in order to detect

Table I – Comparison of various screen positive rates (SPR) and detection rates (DR) under 3 different policies keeping: 1) the SPR constant, and 2) the cut-off risk constant

	UK		Singapore	
Using age alone, cut-off risk of 1:350 at term (equivalent to 35 years or older)	SPR 7% – 8%	DR 30%	SPR 15.3%	DR 51% – 61%
Using serum screening, cut-off risk of 1:250 at term (equivalent to 37 years)	SPR 7% – 8%	DR 60%	SPR 6.5%	DR 71%
Using age alone, cut-off risk of 1:250 at term (equivalent to 37 years)	SPR 5.2%	DR 23%	SPR 6.5%	DR 35%

Table II – Predicted efficiency of different Down Syndrome screening policies in detecting one Down Syndrome livebirth in KKH in 1994/95

Policies	Description	Screen-positive rate	Detection rate	No. of amniocentesis for 1 Down Syndrome detected	No. of DS detected for every fetal loss
Policy A: present policy	Age alone: cut-off age 35 yrs or older = 1:350-380 @ term	16.7%	52%	163	1.8
Policy B	Age alone: cut-off age 38 yrs or older = 1:165-185 @ term	6.5%	34%	97	3.1
Policy C	Serum alone: cut-off risk of 1:230 @ term	6.5%	71%	46	6.5
Policy D	Serum alone: cut-off risk of 1:680 @ term	16.5%	85%	98	3.1
Policy E	Serum alone: cut-off risk of 1:350 @ term	9.5%	77%	62	4.8
Policy F	Serum alone: cut-off risk of 1:185 @ term	5.0%	68%	37	8.1

Table III – Predicted efficiency of different Down Syndrome screening policies in detecting one Down Syndrome livebirth in KKH in 1994/95

Policies	Description	Screen-positive rate	Detection rate	No. of amniocentesis for 1 Down Syndrome detected	No. of DS detected for every fetal loss
Policy G	Policy A for older mothers	100%	100%	156	1.9
Policy H	Serum: cut-off risk of 1:230 @ term	4%	56%	65	4.6
Policy I	Serum: cut-off risk of 1:350 @ term	6%	63%	90	3.4
Policy G +H	Combination of Policy A for older mothers + Policy C for younger mothers	20.0%	79.5%	127	2.4
	Equivalent serum screening policy at the same SPR applied to all ages	20.0%	84.0%	121	2.5
Policy G + I	Combination of Policy A for older mothers + Policy E for younger mothers	21.7%	82.6%	133	2.3
	Equivalent serum screening policy at the same SPR applied to all ages	21.7%	88.6%	124	2.4

one Down Syndrome livebirth in KKH and the fetal losses expected at a procedural-associated loss rate of 1 in 300 using different screening policies.

Looking at the current policy; Policy A, the number of amniocentesis in 1994/95 was 48 (1,160/24) a month. The efficiency of different policies can be compared using the number of amniocentesis needed to detect one Down Syndrome livebirth. This is equivalent to the positive predictive value (PPV) or the odds of being affected given a positive result (OAPR). This gives the "average" risk of a mother who is "screen-positive". The more efficient the policy, the lower the PPV or OAPR and the higher the number of Down Syndrome pregnancies detected for every fetal loss, through amniocentesis. Comparing the policies A to F, it can be seen that serum is more efficient than age alone (smaller positive predictive value) and its efficiency increases with a higher cut-off risk used.

When serum-screening was initially introduced, most of the evidence of its effectiveness came from retrospective studies. It was therefore recommended at that time, that mothers who were older could continue to opt for amniocentesis, based on age-related risk alone[19]. As the evidence from prospective studies continues to accumulate, the above policy has been criticised[19-21]. This is because the advantage of increasing the number of Down Syndrome pregnancies detected for the same number of amniocentesis is lost. It is usually not immediately obvious that the number of Down Syndrome missed in the older mothers by serum screening is more than compensated for by the Down Syndrome pregnancies detected in the younger mothers, who would otherwise not be screened using age alone.

Using a combination of current policies which are offering amniocentesis to all mothers at or older than 35 years at term and serum screening for mothers < 35 years, would result in the numbers shown in Table III. Policy G is where all the older mothers undergo amniocentesis and where all (100%) of the Down Syndrome pregnancies in the older mothers would be picked up. Policies H and I are serum screening detection rates and screen-positive rates obtained by applying serum screening to younger mothers only (using the Monte Carlo simulation). Two cut-off risks of 1:250 at term and 1:350 at term are chosen and their corresponding detection rates and screen-positive rates are shown. Combining the age-policy for older mothers and serum-policy for younger mothers would result in policies G + H and G + I. It can be seen that their PPVs are less efficient when compared to serum-screening alone policies for an equivalent screen-positive (amniocentesis) rate.

DISCUSSION

1. The use of a cut-off risk to interpret the serum screening results

At present, all the Down Syndrome serum screening

software programs interpret the mother's individual risk as either "screen-positive" or "screen-negative", according to the prior cut-off risk chosen. Mothers and clinicians would then act based on this risk assessment grouping.

In counselling mothers who have been classified as "screen-positive" or "screen-negative", the positive predictive value (PPV) or the OAPR (odds of being affected given a positive result) should be used for counselling rather than the individualised risk calculated. As an example, when using Policy C, a mother who is "screen-positive" has a PPV of 1 in 47 or 2.15% chance (41:1,908) of delivering a Down Syndrome livebirth versus a "screen-negative" mother who has a 99.938% chance (27,435/27,452) that she will not have a Down Syndrome livebirth. Using various other cut-off risks, their respective PPVs can be similarly derived. As the maternal population for each laboratory is likely to differ (for example, more affluent and perhaps younger educated mothers deciding for private care), even if the laboratories used identical assays with identical quality controls and identical Down Syndrome risk algorithm software with identical cut-off risks, the screen-positive rates would still be different. From a national health-resource provider point of view in a tax-funded health economy model, the ideal situation would be a single laboratory where there would be only one ROC derived from the nation's screened population and the screen-positive rate chosen according to available resources.

2. Using individualised risk

Singapore's health system is a mixed system of health financing encompassing: 1) Tax funding in the form of government subsidies; 2) Compulsory savings; 3) Financing by health insurance, and 4) Fee for service[22]. As such, it is unlikely that a uniform policy of screening based on a uniform cut-off risk as described above, can be implemented easily. Another problem with classifying the individual risk result into "screen-positive" and "screen-negative" is that mothers and clinicians may not know the difference between a screening test and a diagnostic test.

By assigning individual risk, thereby avoiding the concept of classifying the spectrum of results dichotomously, mothers will have a choice of deciding on their own level of cut-off which they are comfortable with. As the interpretation of risk by mothers and clinicians are probably coloured by personal experiences, knowledge, culture and socio-economic circumstances, this area deserves more study in Singapore as they are not easily extrapolated from experiences of other countries[15-17,23].

The main disadvantage of allowing a mother to weigh her risk is that, at present, risks generated by different laboratories may not be comparable. Indeed, national external quality control audits in the UK show that even with the same sample, differing multiple of the medians are generated by different laboratories even before the risks are calculated.

Giving the mother an accurate risk assessment is only part of the issue as the procedural-associated fetal loss rates need to be accurate as well in order for the mother to weigh the balance. While the auditing of fetal loss rates is more easily done in institutions, a national audit may be needed to provide more accurate risks assessments.

3. Combining an age policy for older mothers and a serum screening policy for younger mothers

As shown in Table III, combining an age-related policy for older mothers with a serum-screening policy for younger mothers would actually be less efficient than using a serum screening policy alone.

The clinician needs to realise that the serum-screening risk algorithm takes the mother's age into account and that the risk calculated is the best estimate based on her age and other independent serum markers. At present, most if not all of Down Syndrome serum screening software generate a pair of results that give the mother's risk based on her age alone (either at term or adjusted for second trimester) and her risk based on serum screening (also either at term or adjusted for second trimester). This may confuse mothers more as they may think that there are 2 ways of calculating the Down Syndrome risk and may choose to believe either the better or the worse risk of the two. The problem may be compounded if she decides to repeat the serum test and gets a further set of results. Repeat testing is not recommended as the result tends to regress towards normality and the second test should take the first test's results into account[24].

4. Standard of care

While no official recommendations exist in Europe, USA or Australia concerning serum screening for Down Syndrome pregnancy, the Canadian Task Force on the Periodic Health Examination recently[25] made a grade B recommendation that "there is fair evidence to offer triple-marker screening through a comprehensive program to pregnant women under 35 years of age." If serum screening becomes widespread and becomes an accepted standard of care, the manner and standards in which pre-test counselling is provided will become an important issue as well.

CONCLUSION

More studies need to be done on the factors that affect mother's decision on the uptake of serum screening and amniocentesis locally. Pre-test counselling is an area identified that appears to have a large influence on the mother's decision to undertake amniocentesis. This is consistent with findings from other studies[16,17]. However, it is important to realise that the success of counselling is not defined by the detection and termination of a fetus with Down Syndrome but rather by the extent to which individual personal choice has been facilitated.

Education of clinicians who are the primary providers of care of mothers would be important in determining the success of counselling. Lack of knowledge can be overcome but misinformation provided to the patient will be doubly difficult to overcome. Serum screening for Down Syndrome should ideally be offered to those mothers who have had adequate counselling and ultrasound estimation of gestational age prior to the test.

Whether a cut-off risk is used to classify results needs careful consideration of its implications. The advantage of using a single cut-off risk value associated with a known screen-positive rate to determine selection for amniocentesis is appealing in that the accuracy of the risk obtained is not crucial in determining policy. However, given the present health system in Singapore, the accurate risk derivation becomes crucial if some form of consistent policy on serum screening were to be formulated. This being the case, the greatest error introduced in calculating the risk is in the accuracy of gestational dating of the pregnancy[7-9].

If serum screening becomes widespread, the shift from age-related screening policy to serum-screening policy of all mothers needs to be accomplished without dwelling too long on a combined policy of karyotyping all older mothers and younger mothers who are "screen-positive" on serum screening. Some sort of audit of Down Syndrome pregnancies to gather accurate denominator data would be important to determine the performance of any screening policy implemented.

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