Editorials

The risk figure of 1/270

One of the most commonly quoted risk figures in the field of prenatal diagnosis is 1 in 270. This represents the second trimester risk of Down's syndrome in a 35 year old pregnant woman.[1] From the beginning of medical training in obstetrics this risk figure is used to differentiate between mothers at "high risk" for cytogenetic disorders in their fetus and those at "low risk". It has also led to the inauspicious designation that women ≥ 35 years are of advanced maternal age. It is now widely accepted as dogma in the United States that a pregnant woman with a risk for a fetal abnormality of 1 in 270 or greater, whether due to maternal age ≥ 35, a positive biochemical screening test, a sonographically detected fetal abnormality, or a family history of a congenital anomaly, should be offered a prenatal diagnosis procedure (amniocentesis or chorionic villus sampling). The arbitrary cut off of 1/270 seems to have been chosen for two reasons. Firstly, the risk of miscarriage from amniocentesis is often cited as 1/200 (although a randomised trial estimated this as $1/100^2$), and this is roughly equivalent to the cut off risk used in screening for Down's syndrome. (In fact the average risk in women with positive screening results is about four times as high as this cut off.) Secondly, when originally implemented, about 5% of the pregnant population was aged 35 or above, and this was the amniocentesis workload that cytogenetic laboratories were able to process at the time.

Over the past few years at least 25 medical publications have evaluated the risk of trisomy 18 in fetuses which appear entirely normal when examined by prenatal ultrasound except for the presence of choroid plexus cysts (isolated choroid plexus cysts). A compilation of data from these articles, which considers over 1500 fetuses with isolated choroid plexus cysts, shows an approximately 1% risk of chromosome abnormalities in these pregnancies, 75% of the aneuploidies being trisomy 18 (reviewed in refs 3–6). Some investigators also believe there may be an increased risk of Down's syndrome (trisomy 21) in fetuses with isolated choroid plexus cysts as well. Based on this 1% risk of chromosome abnormalities (predominantly trisomy 18), statements such as the following have been made, "Since a detection rate of 0·5% is considered high enough to warrant invasive procedures (i.e. age 35 risk), we conclude the finding of an isolated choroid plexus cyst places the fetus at significant risk for a chromosome abnormality such that invasive prenatal cytogenetic testing should be offered".[7] At first glance this reasoning seems logical and conforms to the dogma of prenatal diagnosis: offer amniocentesis if the risk of fetal abnormality is >1/270. There is a serious flaw in this approach, however. Trisomy 18 is not trisomy 21. Although the cost effectiveness and risk/benefit ratio of screening for Down's syndrome using a risk cut off of 1/270 has been established,[8] the cost effectiveness and risk/benefit analysis of screening for trisomy 18 using an even greater cut off (1%) results in the loss of 25 normal pregnancies due to the amniocentesis procedure for every one fetus with trisomy 18 that survives past five months. In addition, the cost for the detection of one infant with trisomy 18 destined to survive past five months has been calculated as $5 000 000.[9] Sonographic screening for trisomy 18 results in much more harm than good. It is evident that a cost effectiveness and risk/benefit analysis must be developed and evaluated critically for each disorder considered in a screening protocol.

An important distinction between screening for Down's syndrome and screening for trisomy 18 is not to equate risk with burden. What is the burden of delivering a child with Down's syndrome compared with the burden of having an infant with trisomy 18? For most parents, these are both devastating occurrences. However, about 10% of infants with Down's syndrome die during their first year compared with about 95% of infants with trisomy 18. In addition, the life expectancy of children with Down's syndrome exceeds 50 years.[10] As a result, trisomy 18 is not a major public health problem whereas trisomy 21 is.

It is not my intention to diminish the lifelong emotional and psychological consequences which develop in parents after delivering a child with trisomy 18, even one who dies shortly after birth. I am well aware of these effects. I am also aware of the joy these children bring to their families, even if they live for only a short time. Similarly, I cannot discount the guilt, despair, and sense of loss which comes from the miscarriage of a chromosomally normal pregnancy after an amniocentesis. I believe that the burden of a pregnancy loss after amniocentesis, especially one which is chromosomally normal, is comparable with the burden of delivering a child with trisomy 18 who dies shortly after birth. I was staggered to realise that when a screening protocol that advocates offering amniocentesis to women with a risk of trisomy 18 >1/270 is used, there will be 25 pregnancy losses due to amniocentesis for detection of one child with trisomy 18 that survives past five months.[9] Analysis of such a screening programme shows clearly that the risk far outweighs the benefit.

I must admit that in the past I have counselled patients with prenatally diagnosed isolated choroid plexus cysts to consider amniocentesis because their risk for a chromosome abnormality exceeds 1/270. It was not until I reviewed critically the risk, cost, and benefit data of this approach that I realised how inappropriate this policy is. The process of carrying out this review and examination of the evidence that emerged have influenced my personal clinical practice. In addition, my colleagues, who have also judged the data, found there was a compelling argument against offering amniocentesis in the presence of isolated choroid plexus cysts, a complete reversal of most of their previous positions.

I have learnt a valuable lesson from this exercise. Often, doctors develop clinical practice patterns that reflect what they have been taught, told, or read. We rely on conventional wisdom that has been imparted from our mentors and colleagues, which we believe to be irrefutable, and we perpetuate these policies. It is important constantly to

challenge these dogmas, especially as they are applied to situations for which they were not originally intended.

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Screening clips

We are pleased that Tony Smith, associate editor of the *British Medical Journal*, has agreed to produce a column, "Screening clips", based on papers published in other journals on screening related topics. This issue contains the first contribution (p 60).