CME ARTICLE

Patients' perception of risk: informed choice in prenatal testing for foetal aneuploidy

Mahesh Choolani[1], FRCOG, PhD, *Arijit Biswas*[1], FRCOG, MD

ABSTRACT Each of us perceives risk differently, and so do our patients. This perception of risk gets even more complex when multiple individuals and interactions are involved: the doctor, the patient-pregnant mother, the spouse-father and the foetus-unborn child. In this review, we address the relationship between different levels of information gathering, from clinical data to experiential knowledge – data, information, knowledge, perception, attitude, wisdom – and how these would impact the perception of risk and informed consent. We discuss how patients might interpret the risks of the same event differently based upon past experiences, and suggest how risk data could be presented more meaningfully for patients and family to assimilate for informed decision making. Finally, we demonstrate how patients' expectations and risk management can impact scientific research and clinical progress by way of the most topical subject of risk screening in pregnancy – non-invasive prenatal testing using cell-free DNA in maternal plasma.

Keywords: cell-free foetal DNA, heuristics in medicine, informed consent, non-invasive prenatal testing, perception of risk
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"*One of the major biases in risky decision making is optimism. Optimism is a source of high-risk thinking.*" – Daniel Kahneman, Nobel Prize in Economics, 2002.

INTRODUCTION

Knowledge delivered is not necessarily the same as knowledge received. In fact, large chasms divide the six hills of data, information, knowledge, perception, attitude and wisdom. Data is what researchers generate through their various laboratories, and social and clinical experiments. Information is the meaning that can be extracted and gleaned from that data, after statistical manipulation. Knowledge is contextualising this information to the person and the clinical scenario. Perception is an inward cognition that is coloured by personal life experiences, whereas attitude projects these internalised ideas and feelings toward the subject/issue being discussed. Wisdom calibrates all of these by including the variation observed in similar yet different real-life situations, and provides the ballast and the balance to clinical decision making. This is why, to this day in an age of scientific medicine and evidence-based medicine, we continue to revere the experience and wisdom of senior clinicians who may have "*seen it all, and done it all*".

INFORMED CONSENT

When patients give verbal or signed informed consent, we generally assume that they understand the information that has been provided to them, and that they have made their decision after considered thought. In fact, evidence points to the contrary, especially when discussing likelihood events, such as likelihood of a therapeutic success or likelihood of an adverse event. Less than one in five patients appear to understand these numbers well;[1] many quickly forget the information,[2] while about a third may not recall any risk associated with a surgical procedure that had been previously explained to them,[3] and more than one in three patients may not even recall the diagnosis told to them.[4] This is important, since in cases of negligence where notes may have been inadequately kept and the patient and doctor's memory is relied upon, it is often assumed that the patients' recollection of the event is more likely to be accurate because the particular consultation in question was unique to the patient but routine to the doctor.[5]

Colliding with these complexities of data assimilation, and the understanding and perception of risk is the ready access to vast amounts of unfiltered information on the Internet. These have now come to bear heavily on obstetrics, from natural birthing options such as HypnoBirthing and WaterBirths to Trial of Labour after Caesarean to prenatal screening and diagnosis. We are witnessing a shrinking family size and family-formation efforts shifting within our society from more serious pregnancy-related mortality and morbidity concerns to boutique reproductive options. These are juxtaposed with a higher expectation of a successful reproductive outcome and a lower tolerance for failure of the healthcare service with an ever rapidly changing medical technology front and an evolving medical-legal milieu. The doctor now faces the triad of faddist obstetrics, medical litigation and explanation of advances in medicine to patients in a way that they can best understand it. One such moving front is prenatal screening for foetal aneuploidy.

INTERPRETATION OF RISK

There is no single correct way to deliver information on risk,[6] and risk appears very different when expressed in a different

[1]Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Correspondence: A/Prof Mahesh Choolani, Senior Consultant and Director of Research, Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University Health System, NUHS Tower Block, Level 12, 1E Kent Ridge Road, Singapore 119228. mahesh_a_choolani@nuhs.edu.sg

TABLE I. Risk assessment matrix.

Likelihood		Consequence			
Probability	Definition	Severity			
		Catastrophic	Critical	Moderate	Negligible
Rare	Almost impossible	S	S	M	L
Unlikely	Not likely to occur	S	S	M	L
Possible	Could occur	H	S	M	L
Likely	Known to occur	H	H	S	M
Almost certain	Common occurrence	H	H	S	M

Risk rating
H: High – High risk of mortality or serious morbidity.
S: Significant – Possible risk of mortality, high risk of serious morbidity.
M: Moderate – Risk of moderate to severe morbidity.
L: Low – Low risk of mortality or severe morbidity.

TABLE II. Performance characteristics of prenatal screening tests used in Singapore and newer non-invasive prenatal tests.

Test	Gestational age (wks)	DR (%)	DR (X-in-Y)	FPR (%)	FPR (X-in-Y)
Triple test	14–20	71	7-in-10	6	1-in-16
Nuchal translucency	9–14	77	8-in-10	5	1-in-20
Combined test	9–14	85-89	9-in-10	5	1-in-20
NIPT[42]	9 wks onwards	99	Almost all; will miss 1-in-100*	1	1-in-100

*Must be considered a screening test, and not diagnostic.
DR: detection rate; FPR: false positive rate; NIPT: non-invasive prenatal testing

way.[7,8] For instance, patients generally consider a 1-in-20 risk greater than a 5% risk of an event. Furthermore, the perception of the same risk in different scenarios is often very different.[9] In two real-life cases, the first trimester screen risk for trisomy 21 was 1 in 50. One mother, who had delivered a child with trisomy 21 in a previous pregnancy, felt this risk was too high, and requested and underwent an amniocentesis. Another mother, who had had multiple miscarriages before, felt that this still meant that there was at least a 98% chance that her foetus would not be affected by trisomy 21 and declined invasive foetal testing. To help patients better understand the meaning of a particular risk or probability, it is useful to compare it with either a daily event such as the risk of a road traffic accident or other similar events/tests whose risks have been known for a long time and have recently changed.[10] Interestingly, ratios larger than 50:1 tend to get underestimated,[11] especially if the subject matter is generally unfamiliar to the patient, e.g. foetal abnormality.[12] In contrast, risk of common events and risks to oneself are often underestimated.[13] Ways are now being developed to summarise the quality of evidence of risk available (Cochrane Collaboration) and the 'Italian flag' approach to visually depict incomplete knowledge in any domain.[14] Another important and useful tool in describing risk that is particularly underutilised in medicine is the risk assessment matrix (Table I). Patients and couples generally appreciate a '1-in-X' description of risk better, but should also be provided the 'Z%' risk of an event for comparison, where appropriate.

When it comes to risk and benefit, what doctors/healthcare professionals feel is important, what patients feel is key and what doctors think patients feel is critical are often three completely separate things. A good example is the choices people make for Down syndrome testing. Hill et al[15] showed that there is a significant disparity between what women and healthcare professionals value in prenatal testing; the latter place high value on the accuracy of the test, but women place strong emphasis on and preference for tests with no risk of miscarriage. Such information is useful in directing research funding using taxpayer dollars, nationwide healthcare policy and doctor-patient interactions. It behoves the clinician to be aware of newer tests for increasing accuracy with no risk of miscarriage, and to at least discuss these with the patient/couple.

FOETAL ANEUPLOIDY SCREENING

There is a large body of literature on screening for Down syndrome that investigate the numerous approaches and combinations of ultrasonography, biochemistry and multimodal screening performed in the first and/or second trimester.[16-25] The detection rates and false positive rates reported vary significantly between studies due to variations in study design, gestational age at screening, biochemical assays, cut-off levels, ultrasonography operator skill and chance variation. In Table II, we summarise the performance characteristics of prenatal screening tests currently used in Singapore and the newer non-invasive prenatal tests that have recently come into the market globally.

Since 2007, the United Kingdom National Screening Committee (Screening for Down syndrome, 2011)[26] has recommended that all pregnant women be offered screening for Down syndrome using any test that has at least a 75% detection rate (for a 3% false positive rate). Similar recommendations have been made in the United States,[27] Australia and New Zealand.[28] Clinicians could be legally liable if prenatal screening is not

offered, and it is likely that wrongful birth litigation will increase over time.[29] Women at a 'high risk' for foetal trisomy are then offered invasive prenatal diagnostic testing by chorionic villus sampling (CVS) or amniocentesis. These invasive tests carry a risk of miscarriage. The excess risk of miscarriage following an amniocentesis is 1% (Evidence level 1b).[30,31] Some papers have suggested a lower risk for amniocentesis, but some more recent evidence still suggests that the risk of CVS is 30%–100% greater than amniocentesis.[32-35]

A number of serum biomarkers have been found to be associated with Down syndrome, and this first made screening for all pregnant women possible. This is important since even though the risk for Down syndrome increases with age, the majority of children with Down syndrome are born to women below 35 years of age. In the first trimester, we now measure human chorionic gonadotropin (hCG – total and free beta) and pregnancy-associated plasma protein A, while in the second trimester, we measure hCG, alpha-foetoprotein, unconjugated oestriol and dimeric inhibin A. The 'double test' is rarely performed in Singapore these days due to a low detection rate of about 66%. The performance of the 'triple test' is reported in Table II. The 'quadruple test', which has a detection rate of 75% for a 5% false positive rate, is not routinely available here in Singapore. Also, the serum integrated screening test, which requires two serum samples obtained at two different appointment times in pregnancy, is not practical here.

During the last decade, the nuchal translucency measurement for Down syndrome at 11–14 weeks of pregnancy has gained importance as part of the routine screening for trisomy here in Singapore. It is routinely combined with the first trimester serum biomarkers as part of the First Trimester Screen or Combined Test, which has an almost 90% detection rate for a 5% false positive rate (Table II).

NON-INVASIVE PRENATAL TESTING

Therefore, with either the 'triple test' or the Combined Test, approximately 5% of all women screened here in Singapore would be offered an invasive prenatal diagnostic test. The discovery of cell-free foetal DNA in maternal circulation[36] has created the possibility of an alternative, non-invasive approach to diagnostic testing. Since the improvement of molecular genetic technologies and the harnessing of the powers of massively parallel sequencing, several large-scale validity studies have been conducted to demonstrate the utility of such an assay.[37-41] The test is still considered as a screening test with a very high sensitivity and specificity of 99%, and a low false positive rate of approximately 1%. This suggests that an invasive test would still be required to confirm a positive result ('high risk'), but the number of invasive tests is expected to decrease dramatically by 95% with a more widespread introduction of this assay.[39]

CONCLUSION

The doctor-patient decision-making process needs to be studied in more detail and with greater scientific rigour, if we are to deliver to the patients–our clients–what they truly desire, rather than what we think they need/want. Matching doctor-patient expectations of health outcomes would reduce patients' recourse to litigation as a means of having their voices heard and desires met. Much more effort needs to be empirically placed now, and more appropriately, in the future by developing a body of knowledge on patients' perception of risks, how these have been constructed and how they are influenced. A more informed choice would enhance the patient's experience of the doctor's care and lead to improved health outcomes.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201210A)

	True	False
Question 1. About risk and perception of risk:		
(a) Data, information, knowledge, perception, attitude, wisdom, each and all, contain identical amounts of information upon which patients could make informed decisions about their medical care.	☐	☐
(b) All patient care decisions must be made upon the basis of good randomised control trials.	☐	☐
(c) Patients' perception of risk is independent of the doctor's perception of risk.	☐	☐
(d) Patients readily understand the concepts of risk and likelihood ratios.	☐	☐
Question 2. Regarding how people interpret risk:		
(a) Risk is absolute; the same risk presented in different ways means the same.	☐	☐
(b) Risk is absolute; the same risk presented in different ways is perceived in the same way.	☐	☐
(c) The risk assessment matrix could help patients understand the relationship between the probability of an event and its possible consequences to the patient and family.	☐	☐
(d) People often underestimate the quantum and implication of risk to oneself.	☐	☐
Question 3. Regarding Down syndrome screening in pregnancy:		
(a) Down syndrome screening during pregnancy is rarely performed here in Singapore.	☐	☐
(b) The Triple test has a suitably high detection rate for Down syndrome when compared with other tests such as nuchal translucency, the Combined Test and non-invasive prenatal testing using cell-free foetal DNA in maternal blood.	☐	☐
(c) All pregnant women should be offered screening for Down syndrome.	☐	☐
(d) All screening options for Down syndrome, and their respective detection rates and false-positive rates, should be discussed with the couple.	☐	☐
Question 4. Regarding invasive prenatal diagnosis:		
(a) Amniocentesis is generally regarded as a safer procedure than chorionic villus sampling (CVS).	☐	☐
(b) There is good evidence from randomised control trials specifically designed to compare the risks of amniocentesis and CVS that the latter does not carry any higher risk of foetal miscarriage.	☐	☐
(c) Overall, the risk of miscarriage associated with invasive prenatal diagnostic testing is negligible.	☐	☐
(d) A large drop in the number of invasive prenatal diagnostic procedures is expected in the next few years.	☐	☐
Question 5. Regarding non-invasive prenatal testing:		
(a) Non-invasive prenatal testing carries a very small risk of foetal miscarriage.	☐	☐
(b) Patients who opt for non-invasive prenatal testing cannot miscarry.	☐	☐
(c) The false-positive rate with non-invasive prenatal diagnosis using cell-free DNA in maternal plasma is 1%.	☐	☐
(d) 19 out of 20 patients who undergo amniocentesis after being screened as 'high risk' after a first trimester Combined test will have a normal foetal karyotype and be unnecessarily exposed to the risk of foetal miscarriage.	☐	☐

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