



Screening for genetic conditions during pregnancy

Bulletin for Doctors | July 2019

This information is provided to assist doctors in discussing with their patients the pros and cons of screening for different genetic conditions during pregnancy. This document does not review the clinical features of these conditions, the technical performance of the screening tests available, nor the appropriate care pathway for women and couples having such testing.

Please note: We have excluded two sex chromosome abnormalities, Triple X (XXX) and Jacobs syndrome (XYY), from this summary as the associated clinical features are so mild as to frequently be undetectable.

Screening for genetic conditions during pregnancy

Screening for fetal trisomy is routinely offered to pregnant women in Australia. The common trisomies of chromosomes 21 (Down syndrome), 18 (Edwards syndrome) and 13 (Patau syndrome) are usually *de novo* abnormalities, and they are more likely to occur with increasing maternal age. Non-invasive prenatal testing has recently revolutionised prenatal screening for these conditions. The range of additional screening tests for genetic conditions that can affect a developing baby has rapidly expanded in recent years:

- > Non-invasive prenatal testing can also screen for abnormalities of fetal sex chromosome number, such as Klinefelter syndrome (XXY) and Turner syndrome (X0). These, too, are usually *de novo*. Klinefelter syndrome is more likely to occur with increasing maternal age, while Turner syndrome does not demonstrate an association with maternal age.
- > The Harmony® non-invasive prenatal test (NIPT) can also include a test for the most common microdeletion, that is, a deletion at chromosome 22q. These deletions are usually *de novo*, but can be familial. The risk of a 22q deletion does not change with maternal age.
- > A fourth area of screening is testing a couple for heritable variants in their genes to determine if they are at increased risk of having a child with a serious childhood-onset recessive disorder. Screening for

carriers can be limited to common conditions, such as Fragile X syndrome, cystic fibrosis and spinal muscular atrophy. Carrier screening can also be expanded to include hundreds of different recessive conditions. The risk of having a child with a recessive disorder does not change with maternal age. This bulletin provides graphs that summarise the chance of a woman carrying a baby with one or more of these genetic conditions at term and at different maternal ages. We present the chances as:

- the absolute risk of a given condition at term
- the combined risk of a number of conditions at term
- the relative risks of a number of conditions at term, that is, if a baby were to have a genetic condition, what is the probability of it being each type of condition.

The risks for some of these conditions will be higher at 10–14 weeks' gestation, that is, the time when screening tests are typically done. We have focused on the risks at term, as managing this risk is the principal goal of prenatal screening.

The risks for some of these conditions will be higher at 10–14 weeks' gestation, that is, the time when screening tests are typically done. We have focused on the risks at term, as managing this risk is the principal goal of prenatal screening.

Screening for genetic conditions during pregnancy

Bulletin for Doctors | July 2019

Absolute risk of different chromosome conditions at term

Figure 1 shows the absolute risk of a woman having an at-term baby with a chromosome disorder that can be detected by the Harmony non-invasive prenatal test. These are the risks in the absence of any prenatal screening or specific risk factors.

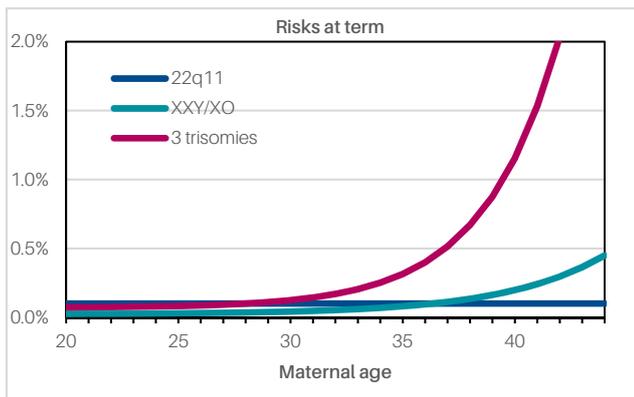


Figure 1. Absolute risk for at-term baby having a chromosome disorder

The risks of the three common trisomies (trisomy 21, 18 and 13) are combined, as are the risks of Klinefelter syndrome (XXY) and Turner syndrome (XO).

The risks are presented for mothers of different ages. Note that the risk of fetal trisomy rises rapidly for mothers over the age of 35 years. The risk of fetal Klinefelter syndrome (XXY) also rises with maternal age, masking the fact that the risk of Turner syndrome does not change with maternal age.

The risk of a chromosome 22q11 deletion (0.1%) does not change with maternal age. For a woman under the age of 28 years, the risk of a fetal microdeletion of 22q is greater than the risk of fetal trisomy, Klinefelter syndrome or Turner syndrome.

Combined risks of different chromosome conditions at term

Figure 2 shows the combined risk of a woman having a baby with one of the chromosome conditions that can be tested by the Harmony non-invasive prenatal test, that is, one of the common trisomies, Klinefelter syndrome (XXY), Turner syndrome (XO) or 22q11 deletion. The risks are presented at different maternal ages.

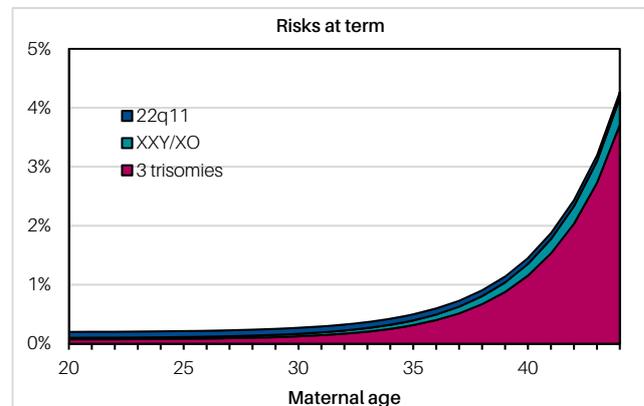


Figure 2. Combined risk for at-term baby having a chromosome disorder

Relative risks of different chromosome conditions at term

Figure 3 shows the relative risks of these chromosome conditions at different maternal ages. In other words, if a woman has a child with one of the conditions tested by the Harmony test (trisomies, Klinefelter syndrome (XXY), Turner syndrome (XO), 22q deletion), the figure shows the proportion of affected babies with each condition.

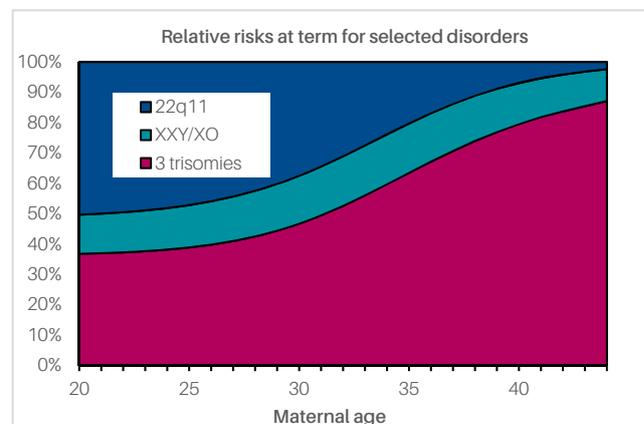


Figure 3. Relative risk for at-term baby having a chromosome disorder

For example, if a woman aged 30 years were to have a baby with one of these conditions, there is a 46% chance that the condition would be one of the common trisomies, 16% chance that the condition would be Klinefelter syndrome or Turner syndrome, and 38% chance that the condition would be 22q11 deletion.

You will note that the proportion of affected babies with Klinefelter syndrome or Turner syndrome changes little with maternal age (Figure 3), even though the absolute risk of these conditions does increase with maternal age (see previous figures).

Screening for genetic conditions during pregnancy

Bulletin for Doctors | July 2019

The risk of other chromosome conditions at term

The chromosome conditions tested by the Harmony non-invasive prenatal test represent the majority of chromosome disorders identified after birth. There is a diverse group of microdeletions that is not tested by Harmony. Each of these microdeletions is very uncommon, having a frequency at birth of less than one in 1,000. Nonetheless, as a group they constitute a small but significant risk at term.

Figure 4 below shows the absolute risks of the conditions tested by Harmony and the combined risk of these other microdeletions. These are the risks in the absence of prenatal screening or specific risk factors. The risks are presented at different maternal ages.

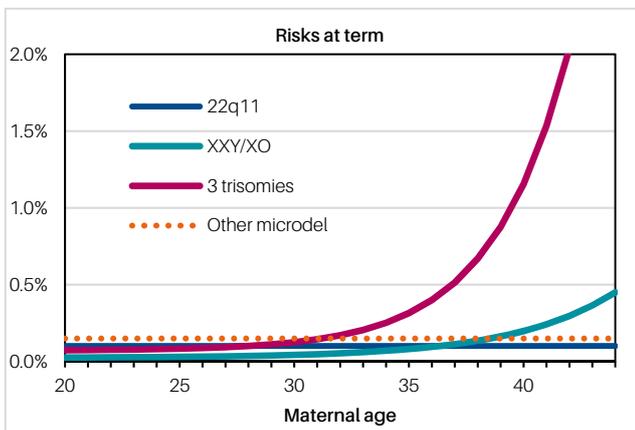


Figure 4. The risk for at-term baby having other chromosome conditions

Figure 5 shows the relative risks of these chromosome conditions and the rare microdeletions at different maternal ages. In other words, if a woman has a child with one of these conditions, the figure shows the proportion of affected babies with each condition. At all maternal ages, the Harmony test can detect the majority of these conditions.

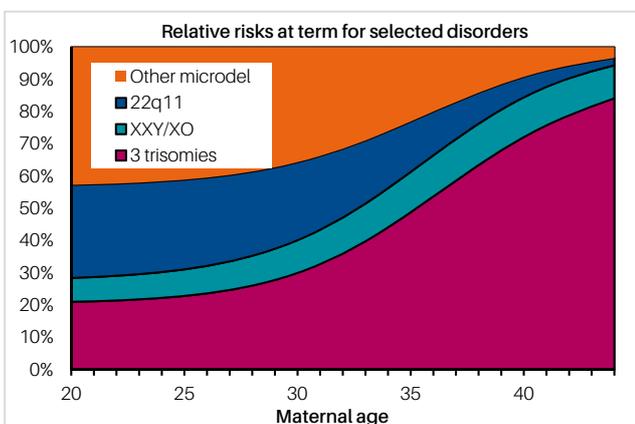


Figure 5. The relative risk of chromosome conditions and rare microdeletions

As yet, none of these rare microdeletions can be reliably detected by any non-invasive prenatal test. The only means of reliably detecting these microdeletions is by invasive testing (chorionic villus sample or amniocentesis) and microarray analysis.

Absolute risk of recessive conditions at term

Sonic Genetics provides carrier screening for couples for autosomal and X-linked recessive conditions. We provide two such tests. The first ('3-gene carrier screen') covers three common conditions: cystic fibrosis (CF), spinal muscular atrophy (SMA) and Fragile X syndrome (FXS). Note that **this screen does not include thalassaemia**, which may be a significant risk in some ethnic groups.

The second test ('Beacon expanded carrier screen') covers these three conditions and a further 400 rarer conditions. In examining more genes, the probability that a couple will be identified as being at risk of having of an affected baby is increased. The genes included in this screen are restricted to genes responsible for recessive serious childhood-onset disorders for which there are limited treatment options.

Figure 6 shows the absolute risk at term of various chromosome disorders (presented above, included here for comparison), the risk of having a child with one of the three common recessive conditions, and the risk of having a child with one of the 400 rare recessive conditions.

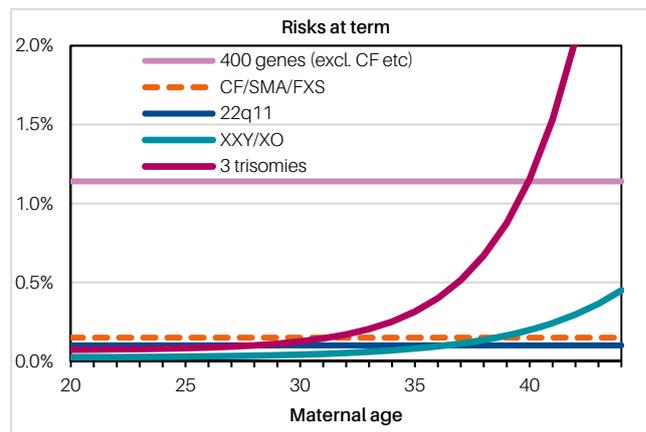


Figure 6. The absolute risk of recessive conditions at term

The risks are shown at different maternal ages. These are the risks in the absence of any prenatal screening or specific risk factors. The risks of recessive disorders do not vary with maternal age.

Screening for genetic conditions during pregnancy

Bulletin for Doctors | July 2019

Combined risks of different chromosome and recessive conditions at term

Figure 7 shows the combined risk of a woman having a baby with one of the chromosome conditions that can be tested by Harmony, the three common recessive disorders (CF, SMA and FXS), and the 400 rare recessive disorders.

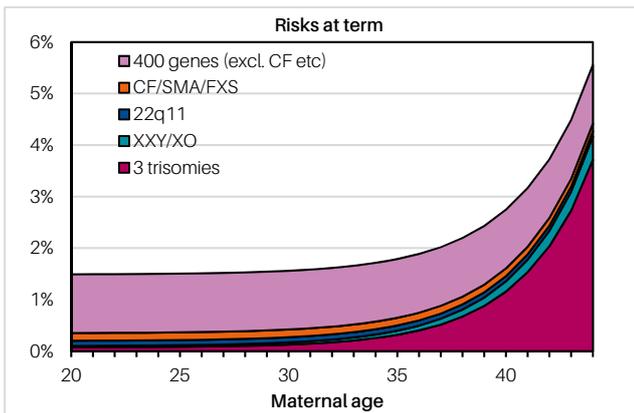


Figure 7. Combined risks of different chromosomes and recessive conditions at term

These are the risks in the absence of prenatal screening or specific risk factors. The risks are presented at different maternal ages.

Relative risks of different chromosome and recessive conditions at term

Figure 8 shows the relative risks of the chromosome conditions detected by Harmony and **just the three common recessive disorders** (CF, SMA and FXS) at different maternal ages. In other words, if a woman has a child with one of these conditions, the Figure shows the proportion of affected babies with each condition.

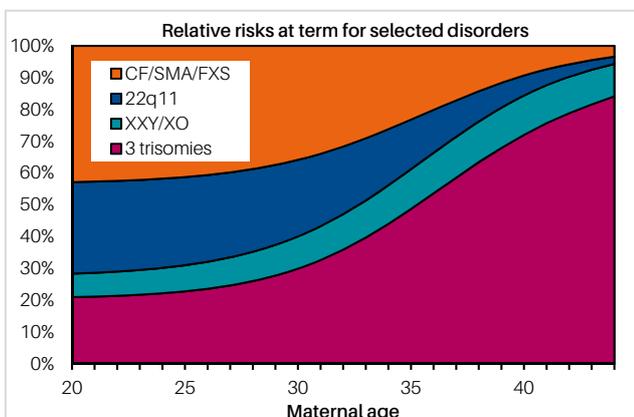


Figure 8. The relative risk of Harmony-detected chromosome conditions

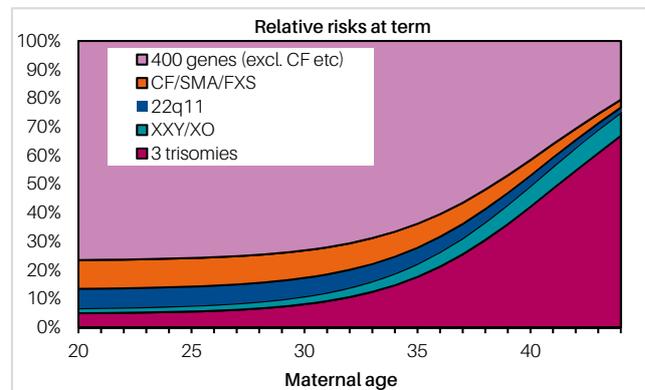


Figure 9. Relative risks of chromosome conditions detected by Harmony

Figure 9 shows the relative risks of the chromosome conditions detected by Harmony, the three common recessive disorders (CF, SMA and FXS), and the **400 rare recessive disorders** at different maternal ages. In other words, if a woman has a child with one of these conditions, the Figure shows the proportion of affected babies with each condition.

Disclaimers and sources of information

These Figures are derived from the sources detailed below. There are differences in the methods used to generate the data described in these sources, and so the summary statistics presented in this document should be regarded as indicative rather than definitive measures of the risk of a genetic condition. The Figures incorporate the differences in risk associated with maternal age (as appropriate), but do not incorporate other differences, such as the carrier frequencies for different disorders in specific ethnic groups. Where possible, the carrier frequencies are representative of general Western populations. In particular, please note that these Figures do not make any allowance for personal or family history of either a chromosome or recessive condition.

For further information, please visit our website www.sonicgenetics.com.au or contact us via email at info@sonicgenetics.com.au. Should you have any enquiries or wish to speak with one of our genetic pathologists, please call 1800 010 447.

1. Hilder L, et al. Australia's mothers and babies 2012. Perinatal statistics series. 2014; No. 30. Cat. no. PER 69. Canberra: AIHW
2. Nybo A, et al. Maternal age and fetal loss: population based register linkage study. *BMJ*. 2000; 320(7251):1708-1712
3. Snijders R, et al. Maternal age-specific risks for trisomies at 9-14 weeks' gestation. *Prenatal Diagn*. 1994; 14(7): 543-552
4. Snijders R, et al. Maternal age and gestational age-specific risk for chromosomal defects. *Fetal Diagn Ther*. 1995; 10(6):356-367
5. Snijders R, et al. Maternal age- and gestation-specific risk for trisomy 21. *Ultrasound Obstet Gynecol*. 1999; 13(3): 167-170
6. Gardner R, et al. Chromosome Abnormalities and Genetic Counselling. 2018. New York: Oxford University Press
7. Grati F, et al. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenat Diagn*. 2015; 35(8):801-809
8. Fulgent Genetics. Recessive allele frequencies (2019)