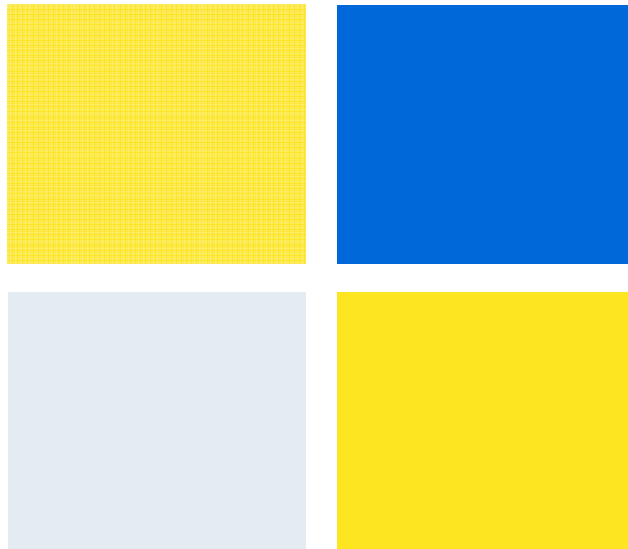


Unique

Mosaic Trisomy 16



What is Mosaic Trisomy 16?

There are usually 46 chromosomes in the cells of the body. Chromosomes come in different sizes and are numbered from largest to smallest according to their size, from number 1 to number 22, in addition to the sex chromosomes, X and Y. We have two copies of each of the chromosomes (23 pairs), one inherited from the father and one inherited from the mother but someone with mosaic trisomy 16 (MT16) has some cells with a third chromosome 16, making 47 chromosomes in those cells. Cells with 46 and 47 chromosomes exist alongside each other in different body tissues and organs, exerting different effects. The picture changes, with the number of cells with the extra chromosome usually falling in time, especially in blood.

How common is MT16?

Full trisomy 16 with an extra chromosome 16 in every cell is believed to be the most common of all chromosome abnormalities at conception (when a baby is made), and is found in 1 to 2 per cent of all confirmed pregnancies. However, babies with full trisomy 16 are almost always lost in very early pregnancy and virtually none have been born. Even babies with MT16 are very rare. Researchers who recently surveyed every MT16 pregnancy published in the medical literature gathered 162 pregnancies worldwide. Among these pregnancies they confirmed that mosaic trisomy 16 appears to be slightly more common in girls than in boys (Yong 2003; Benn 1998).

Chromosome 16



A note

This leaflet describes what is known from published medical research and from the experience of *Unique* and of the Disorders of Chromosome 16 Foundation support group. Although recent research into MT16 is of a very high quality, children who come to doctors' attention and feature in research reports are likely to be the ones who have experienced effects on their health or development from their unusual chromosomes. Those who experience few or no health problems will not be described. This means that the picture we paint may appear more negative than it really is. *Unique* has published a companion booklet of *Mosaic Trisomy 16 Stories*, describing families' experiences. References to medical research are shown in brackets and a full reference list is available from *Unique*.

How is mosaic trisomy 16 diagnosed in pregnancy?

Mosaic trisomy 16 is usually first suspected and diagnosed during pregnancy. The first tests are non-specific. Usually either ultrasound scans or blood tests for certain chemicals (maternal serum screening) suggest there may be a problem and a general test for the most common chromosome abnormalities is performed either on the developing placenta (with chorionic villus sampling, CVS) or on amniotic fluid (from an amniocentesis). If this shows trisomy 16 in some cells, the pregnancy has mosaic trisomy 16.

There are three possible outcomes for the baby:

- **Either** the only effects are on the baby's growth rate
- **Or** the baby will be apparently unaffected
- **Or** the baby will be affected.

You will be offered tests to try to clarify which is the case for you.

The tests that show that mosaic trisomy 16 is present cannot unfortunately show directly how slightly or severely affected your baby will be. However, when the tests are put together with information from ultrasound scans, a clearer picture will emerge.

CVS (chorionic villus sampling)

Two types of early pregnancy CVS test can be done on the cells from the developing placenta.

- A rapid test (called direct sampling) gives a result within a day or two.
- The placenta cells are cultured (grown), with the results in a week or two.

You should wait for both results. Most often, they show that all the cells in the developing placenta have the extra chromosome 16. Less often, they show a mixture of trisomy 16 cells and ordinary cells. This means that the placenta does contain trisomy 16 cells but usually none are found in amniotic fluid and your baby does not have any. This is called confined placental mosaicism. Even when the cultured CVS shows trisomy 16, the fetus does not usually turn out to have mosaic trisomy 16.

The chromosomes in the placenta and in the baby can differ because the placenta and the baby develop from separate clusters of cells. But early in the pregnancy it is only safe to take cells from the developing placenta.

Confined placental mosaicism

In confined placental mosaicism, the developing placenta and the tissues outside the baby have the extra chromosome, but the baby has entirely or mostly normal cells. Your baby is likely to grow slowly in the womb and be born tiny or very tiny. Babies with mosaic trisomy 16 are almost always born after a pregnancy with confined placental mosaicism. A blood or skin sample from the baby usually reveals no trisomy 16 cells.

Amniocentesis

Cells from the baby's skin, urine, intestinal tract and lungs are shed into the amniotic fluid and give a more direct picture of the presence of trisomy 16 cells in the baby than CVS. Generally speaking, the outlook is less good if trisomy 16 cells are found in amniotic fluid. However, even finding trisomic cells in amniotic fluid does not mean that your baby will necessarily have trisomy 16 mosaicism. If they are found in the baby at all, they are usually confined to just one body tissue such as the skin or the lungs. The trisomy 16 cells may diminish over time and they may vanish altogether. In some pregnancies, no trisomy 16 cells are found in amniotic fluid but they are found later in the baby.

If mosaic trisomy 16 has been diagnosed during pregnancy, a blood sample will be taken at birth from the umbilical cord. This often shows no trisomy 16 cells. There is a specialist research centre at the University of British Columbia that uses a particularly sensitive molecular test to identify trisomy 16 cells but even if this is negative, it is not possible to entirely rule out low levels of trisomy 16 cells in other parts of the body. You can find them at this website: www.medgen.ubc.ca/wrobinson/mosaic/index.htm.

Ultrasound

Ultrasound scans, ideally undertaken at a fetal wellbeing centre, will give important information about the baby's health. In skilled hands at least 50 per cent of birth defects can be identified and the baby's growth rate can be carefully monitored, especially in the third trimester when it is most likely to slow down. However, even an apparently clear scan is no guarantee.

“In the end a couple has to brace themselves for the possible worst case scenario where the baby would have undetected birth defects, developmental delay or learning difficulties - Clinical geneticist

“Hope for the best, prepare for the worst - Parent

Does the percentage of trisomic cells matter?

The proportion of T16 cells and their distribution in the tissues of the body depends partly on the time in the pregnancy when mosaicism was established and partly on a tendency for the ordinary cells without the extra chromosome to grow more effectively.

Your geneticist or genetic counsellor will very likely tell you the percentage of cells with trisomy 16 but what this means is not always clear. It is helpful to know the percentage for a CVS result because when the CVS (either rapid-result or cultured) shows 100% trisomy 16 cells rather than mosaic trisomy 16, the baby's growth delay is likely to be more severe.

It is much less helpful to know this for an amniocentesis result. There does not appear to be any obvious link between either the degree or the distribution of trisomy cells at amniocentesis and the severity of the effects on your baby, either in terms of growth delay or birth defects.

The authors of the most recent and authoritative survey of mosaic trisomy 16 say that an amniocentesis should not be considered to be anything more than a snapshot (Yong 2003; Hsu 1998; Benn 1998).

This seems to be true after birth as well. Common sense suggests that tissues and organs with more T16 cells will be more obviously affected than tissues with lower levels or none. That is not necessarily the case. Different levels of T16 cells are found in different parts of the body and it is especially common for no T16 cells to be found in the baby's blood. In one case, doctors who performed surgery on a baby girl to correct narrowing of the aorta, the main artery from the heart, took samples from her aorta, her lungs, skin, lymph and blood. They found no link between her defects (in the heart) and the levels of trisomy 16 cells (Greally 1996).

Making a decision

It is very hard to make a decision when there is little certainty. Many couples have praised the support available from the Disorders of Chromosome 16 Foundation (DOC16 at www.trisomy16.org), founded by the mother of a girl with mosaic trisomy 16. At *Unique* we also aim to support parents with our information, helpline and contact with similarly affected families.

The UK support group Antenatal Results and Choices (www.arc-uk.org; +44 (0) 207 631 0285) has a series of handbooks for family members.

On the net, you can also turn to:

<http://bbs.babycenter.com/board/pregnancy/prenatalhealth/>

where there are a number of helpful message boards, including Continuing a Pregnancy with Poor Prenatal Diagnosis and Termination for Medical Reasons.

What is likely to happen during pregnancy

If you make the decision to continue with your pregnancy, you will have regular scans and tests of your baby's heart beat and movements. This is to monitor your baby's growth and to identify any signs that it is time to intervene. Your own blood pressure will also be monitored carefully as hypertension (high blood pressure) is more common in mosaic trisomy 16 pregnancies.

A large review of mosaic trisomy 16 pregnancies suggested strongly that many would end in a premature birth. It showed that babies' average age at birth was just under 36 weeks and out of 70 babies, 30 were born between 35 and 37 weeks and 22 were born between 27 and 34 weeks. It isn't known whether the premature birth was spontaneous or induced due to concern over the baby's growth or any complications (Yong 2003).

Will my baby survive?

Until very recently the outlook for mosaic trisomy 16 pregnancies was thought to be very bleak. A large recent survey of 162 pregnancies has shown a much more optimistic picture. Two out of three pregnancies ended in the birth of a baby and the great majority of these babies survived the newborn period. Seventeen per cent of babies died before birth or in the newborn period (Yong 2003). No long term studies of the outcomes have been published yet. However, the short term outcomes for babies look very reassuring. Of the babies born with MT16, 93 per cent survived the newborn period and so long as babies are in good health at birth they are believed to usually progress quite well. You may find it helpful to read the stories in *Unique's Mosaic Trisomy 16 Stories* leaflet and those on the website of the DOC16 Foundation.

Common effects on babies and children

Two recent surveys have shown that most babies with MT16 are born small for their gestational age but are otherwise healthy. Isolated medical conditions have been found in a minority of babies, but most of these were no more common than among babies without MT16. Just two conditions did occur more commonly – although they were still unusual: a hole in the heart (between the left and right chambers) and in boys, hypospadias, a condition where the hole normally at the end of the penis is on the underside instead (Yong 2003; Benn 1998).

When your baby is examined, the clinicians will be particularly alert to the following body tissues and systems. This is because they have been most often affected in the minority of babies with MT16 who have been found to have a clinical condition.

- Heart
- Lungs
- Hands
- Kidneys, urinary and genital systems
- Digestion and intestines
- Head and face
- Joints and bones
- Skin

Growth

The typical growth delay before birth is generally attributed to inadequate placental functioning. This means that growth after birth may be normal but we don't know yet whether children completely catch up in height.

Two copies of the mother's chromosome 16

Children without mosaic trisomy have two chromosome 16s, one from their father and one from their mother. In at least one third of mosaic trisomy 16 pregnancies, the cell line with two chromosome 16s instead of three contains two of the mother's chromosome 16s and none of the father's. This is called maternal uniparental disomy 16 (UPD 16 mat) and may intensify the growth delay before birth caused by the trisomy 16 cells. It is possible that maternal UPD 16 may have additional effects on the baby, but if so these are likely to be subtle (Yong 2003/2).

Trisomy rescue

After conception, there are almost always three chromosome 16s, usually two from the mother and one from the father. A natural attempt to correct the mistake is then partly successful, leaving two cell lines, one with the extra chromosome 16, the other without.

Skewed X-inactivation

The mechanism that results in trisomy rescue also leads to a situation known as 100% skewed X-chromosome inactivation. This means that a baby transcribes genes from either a maternal or the paternal X chromosome, but not both. Research suggests that this seems to be linked with poorer outcomes at birth but it should have no important effects afterwards (Penaherrera 2000). The only likely effect is that in a girl, the risk of rare X-linked recessive disorders (such as muscular dystrophy or haemophilia) might rise to that of a typical boy.

Why did it happen?

Almost all MT16 pregnancies start as a pregnancy with a complete extra chromosome 16. During the formation of the egg cells in the mother, an error occurs in the natural process by which chromosomes separate. This leaves an extra chromosome 16 in the egg cell. Much more rarely the same mistake occurs when the father's sperm cells are forming. After conception, there are three chromosome 16s, usually two from the mother and one from the father. A natural attempt to correct the mistake after conception is then partly successful, leaving two cell lines, one with the extra chromosome 16, the other without. This is the process called correction or trisomy rescue.

Can it happen again?

There is no evidence that couples are likely to have another baby affected by MT16. However, if the original trisomy (third chromosome) was caused by a failure of the mother's chromosomes to separate when her egg cells were forming and she is an older mother (over 35), she may have a raised chance of having another pregnancy affected by trisomy.



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Disorders of Chromosome 16 Foundation

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Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This leaflet is not a substitute for personal medical or genetic advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication and the medical content has been verified by Dr Wendy Robinson, Associate Professor of Medical Genetics, University of British Columbia and Monica Pearson BSc 2004.

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