PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Trisomy 18.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Trisomy 18

Developed by Graeme Rinholm and Dr. Melanie Lewis for PedsCases.com.
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Introduction

My name is Graeme Rinholm. I am a 4th year medical student from the University of Alberta. This is a podcast about Trisomy 18 developed in conjunction with Dr Melanie Lewis a Professor of Pediatrics at the University of Alberta.

Objectives

1. Review the physical characteristics and potential medical concerns associated with a baby or child with Trisomy 18
2. Discuss prenatal and postnatal diagnosis
3. Develop a family-centered management plan for a newborn diagnosed with Trisomy 18
4. Review the prognosis of babies and children with Trisomy 18

What does Trisomy 18 mean?

Trisomy 18 is also known as Edwards syndrome named after Dr. John Edwards, who first described the syndrome in 1960. It is a genetic diagnosis based on the presence of three copies of a chromosome (the trisomy part) and the number 18 (referring to which chromosome has 3 copies). It has many associated signs and symptoms, which we will get into a bit later in the podcast. Within this diagnosis, there may be three copies of the entire chromosome 18 or two full copies plus an extra part of chromosome 18, specifically the long arm, or in genetics terms, the q arm. To make the picture even more complicated, this triple copy of chromosome 18 can be present in all cells, which is called a somatic change, or only some cells, which is referred to as genetic mosacism. Most of the time (around 85% to be specific), trisomy 18 is a result of an error in chromosome separation during the formation of eggs in a mother's ovaries, as in during oogenesis. In genetics terms, this is called a de novo (within the body) meiotic (cell division resulting in the formation of gamete/haploid cell) non-disjunction (incorrect separation). An egg ends up with two copies of chromosome 18 and one copy of every other chromosome. Once the egg is fertilized, there are three copies of chromosome

18, one from the sperm and two from the egg. When there is a paternal cause of trisomy 18, it typically occurs after the formation of sperm, during egg fertilization and two cell (zygote) formation. Both the sperm and the egg have the correct number of chromosomes, but during early cell division, one of the cells ends up with three copies of chromosome 18, and another with only one. The cell with one chromosome will no longer divide, and the result is a mixture of cells, some with two copies and some with three copies of chromosome 18. This is called genetic mosaicism.

How often does Trisomy 18 happen?

The incidence of this genetic transformation in utero is 1 in 2500 and it has the same in utero incidence between males and females. There is a high rate of intrauterine demise from the second trimester onwards however, estimated to be around 35%, that affects more males than females. As a result, the live birth incidence of Trisomy 18 is closer to 1 in 6000 with more affected female live births than male.

Any factors that might increase the likeliness of this happening?

Literature is limited on the potential risk factors for Trisomy 18. The recognized risk factors at this point include maternal age greater than 35 years and a previous affected pregnancy.

How does this first present?

After risk factors, the first suggestion that there may be a diagnosis of Trisomy 18 will be based on testing results during pregnancy. Since Trisomy 18 is a genetic diagnosis, test results during pregnancy may be suggestive of the diagnosis, but more accurately represent a change in the probability that a parent will have an affected pregnancy rather than a definitive diagnosis of Trisomy 18. Even genetic testing done on tissue samples collected during pregnancy require confirmation after birth for definitive diagnosis.

First Trimester Screening, with maternal serum markers including AFP (alpha feto-protein), PAPP-A (Pregnancy associated plasma protein A), hCG (beta-human chorionic gonadotropin), and E3 (Estriol), along with ultrasound, is the standard of care in many Canadian provinces. The primary change that would suggest a higher than average chance of an affected pregnancy is a decreased level of any of AFP, PAPP-A, and E3. Ultrasound has the potential to detect a broad range of abnormalities, though few of the changes are exclusively associated with Trisomy 18, making the Ultrasound findings or maternal serum marker changes useful at suggesting abnormal development in utero, but poor for determining a specific diagnosis. Some of the more common features associated with trisomy 18 that may be detected by US include: intrauterine growth restriction (typically seen at greater than 32 weeks gestation), in the brain: choroid plexus cyst or ventriculomegaly, a heart ventricular septal defect, or cleft lip, overlapping fingers, rocker bottom feet, and omphalocele. Polyhydramnios is found in

30-60% of trisomy 18 pregnancies. Affected pregnancies have also been associated with antepartum hemorrhage and preeclampsia.

We have discussed a fetus with Trisomy 18, but what are some of the issues that should be considered after birth?

There are a number of dysmorphic features that may be observed in infants with Trisomy 18, though they are non-specific. Low birth weight is common. In the head, changes may include microcephaly, prominent occiput, inverted triangular face, prominent nasal bridge, high-arched palate, micrognathia, narrow bifrontal diameter, low-set or malformed ears, hypertelorism, short palpebral fissures, epicanthal folds, corneal opacity, microphthalmia, and facial palsy. There may also be a webbed neck, short sternum, wide-spaced or small nipples, umbilical hernia, and small pelvis. In the extremities, clenched hand, crossed fingers, single palmar (simian) crease, absence of distal crease on fifth finger, limited hip abduction, syndactyly, polydactyly, hypoplastic to absent thumb, hyperextension of lower limbs, foot valgus, wide first and second toe space. Genital abnormalities have been noted including hypoplasia of labia majora with prominent clitoris, or hydrocele. Additionally, there may be the previously described omphalocele, cleft lip and palate, and rocker bottom feet. It is also important to look for an imperforate anus, cryptorchidism, hypospadias, as these may be correctable issues that could lead to improved quality of life.

What is the prognosis?

As previously mentioned, there is a 30-35% chance of intrauterine demise from the second trimester to delivery, and an additional 20-39% risk of demise during delivery. Delivery is frequently complicated by breech presentation (likely caused by polyhydramnios and intrauterine growth restriction) and fetal distress, often leading to delivery by C-section.

Historically, Trisomy 18 has been considered a non-survivable diagnosis. Average life expectancy of affected live births varies between studies but has been reported as between 3-70 days. Previous data has shown a one year survival rate of between 5-10%. Cardiorespiratory distress secondary to dysmorphisms (short sternum, rib abnormalities, cardiac anomalies) is the most common cause of mortality. For many years, it has been common practice to not offer life sustaining measures based on perceived futility of life sustaining therapy. This perspective was supported by the literature showing very low survival rates, making any attempt of life prolongation appear to be not only a potential misuse of limited healthcare resources, but also an unnecessary prolongation of patient suffering.

Recent case reports and studies have shown improved outcomes with full intervention management. Survival rates of 10-25% at one year and 10-15% survival rate at 5 and 10 years of age are noticeably higher than previous statistics. These improved survival rates are especially exciting considering that many centres included in these studies were still not offering life prolonging measures to infants diagnosed with Trisomy 18.

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With that in mind, there is significant potential for continued improvement in the long term outcomes of infants and children with Trisomy 18.

How to approach a diagnosis of Trisomy 18?

The first step is to ensure regular prenatal care including first trimester screening, which can identify pregnancies with a higher than average risk of being affected with a genetic anomaly. Follow up genetic testing should be offered along with an associated referral to genetic counselling. The current standard of care for prenatal diagnosis of Trisomy 18 is genetic testing by karyotype or microarray performed on a sample collected by choriocentesis or amniocentesis of fetal DNA. Both of these procedures come with a risk of causing fetal demise (choriocentesis around 1/100, amniocentesis 1/200), which should be discussed with the family while obtaining consent. There is no obligation to proceed with either testing option. Non-invasive prenatal testing is an additional option for identifying affected pregnancies. This requires a blood sample from the mother, and high sensitivity and specificity have been reported for detecting Trisomy 18. The advantage of NIPT is that it only requires a blood sample from the mother, meaning it has a significantly better risk profile, with a negligible chance of causing fetal demise.

An important question to ask a pregnant mother prior to genetic testing during pregnancy is how the test result is likely to affect ongoing treatment decisions. If an affected pregnancy is likely to be terminated, then the risk of obtaining a genetic diagnosis may be viewed differently than if the parent is likely to proceed with the pregnancy regardless of the genetic result. Additionally, it is important to mention that any prenatal diagnosis of Trisomy 18 requires confirmation after birth by repeat genetic testing.

Ongoing support through pregnancy is critical, with regular discussions, education, and counselling to help the patient in their treatment decision. Important considerations when counselling families about their potential care decisions include outcome statistics and an overview of the likely health complications to be encountered, namely global developmental delay along with the various previously discussed congenital anomalies.

Though comfort care focused on symptomatic treatment has been the previous treatment standard, attempts to provide more comprehension medical and surgical intervention have shown improved survival rates. As a result, the current literature supports management from palliative treatment to full intervention based on the wishes of each individual family. When counselling families, these options should be presented with positive evidence, so that parents can feel enabled to make the treatment decision that works best for their family. The decision for how to proceed with care rests with the parent or guardian as the centre of the healthcare team. This is likely one of the most difficult decisions a family will face and is often surrounded with guilt and grief. Appropriate counselling, services and support should be offered to assist families in there time of need. In Alberta, this interaction represents a goals of care discussion, offering treatment from full intervention to palliative care. Palliative care options may be

available within a hospital, in hospice care, or in a home setting with available community health supports, depending on the patient's location.

If the decision is made to pursue full interventions including resuscitation, what does that look like?

Affected pregnancies carried to term should be referred to obstetricians working at high risk centres in anticipation of complicated delivery with suspected complex post-natal care requirements. Post-natal testing should include repeat genetic testing to confirm the diagnosis of Trisomy 18. Echocardiogram is recommended to assess for congenital heart abnormalities as well as abdominal US to assess the kidneys.

Respiratory distress is common and should be anticipated prior to delivery with expected need for resuscitation and NICU admission. During the first months of life, apneic episodes may occur frequently and require investigation to differentiate central versus obstructive cause, as both are common.

Congenital cardiac malformations are common and may require surgical management. Heart failure and pulmonary hypertension may result from untreated cardiac malformation. Optimization of surgical candidates appears critical to potential improvement of survival rates, specifically aiming for patients to be between 3 to 6 months and heavier than 3kg body weight.

Feeding difficulties are common and may require NG or gastrostomy tube placement to prevent aspiration events and support growth and development. Cleft lip and palate (often caused by Pierre Reuben malformation) may require surgical intervention in early life. Gastroesophageal reflux disease is also common. As previously mentioned, omphalocele has been reported and may require surgical correction. Similarly, imperforate anus may be present requiring surgical correction.

Trisomy 18 is associated with universal profound neurocognitive deficits. Some developmental milestones have been reported as obtainable, though delayed. Neurologic complications also include hypotonia in infancy, which can complicate feeding and respiratory difficulties. This will likely develop into hypertonia in later childhood and adolescence. Seizures are common. Vision and hearing may both be affected and neonatal assessment is recommended.

In total, this represents a complex care team involving NICU, Cardiac Surgery, General Surgery, Ophthalmology, Audiology, and Neurology as well as a general pediatrician coordinating care in the first months of life. Ongoing care through an early intervention program is recommended. Aspects of the program may also include Physical Therapy, Occupational Therapy, and Speech Language Pathology. Abdominal US is recommended every 6 months until adolescence to screen for Wilm's Tumour as well as hepatoblastoma, which are both associated with Trisomy 18. Some sources recommend treatment with palivizumab to prevent infection with respiratory syncytial

virus in the first 1-2 years of life, as it can pose a serious risk of mortality given the fragility of the cardiorespiratory system.

Frequent follow up is recommended in the first months of life with regular follow up to be determined on an individual basis. Growth and development should be documented at every visit, along with diet, and a neurologic exam. Assessment for scoliosis is important for children after the age of 2. A regular immunization schedule should be pursued.

What is expected to change with regards to Trisomy 18?

With full intervention management being increasingly pursued, it is suspected that survival rates may continue to improve. It will be important for follow up studies to focus on classifying and treating the long term health complications associated with Trisomy 18 to further improve longevity, survivability, and quality of life associated with this diagnosis. There is potential to identify further risk factors with future study as well. It is likely that there will be increasing use of non-invasive prenatal testing for the genetic diagnosis of Trisomy 18 during pregnancy, though post-natal confirmation is still likely to be required.

This is the end of this PedsCases podcast on Trisomy 18. Thanks for listening!

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Resources

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