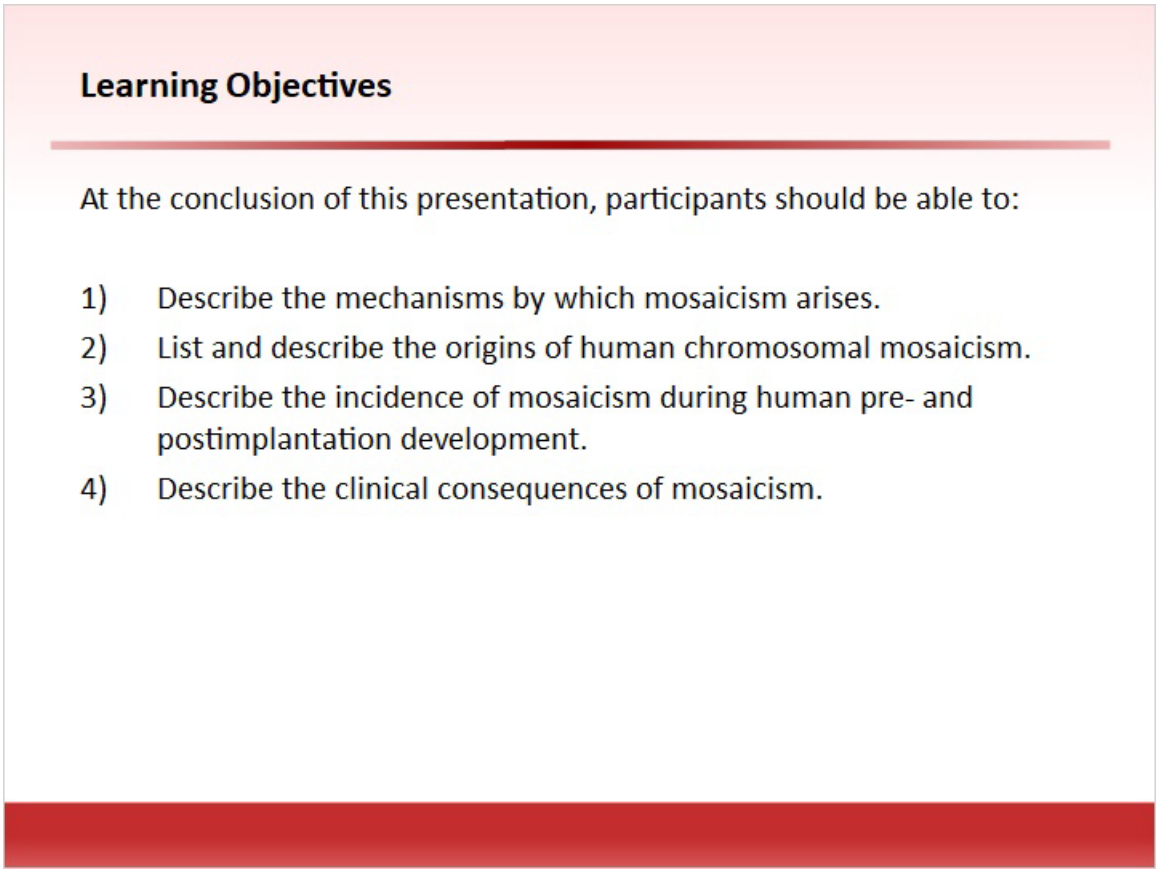
LABCC100 Lesson 9

1.1 Mosaicism in Humans

Notes:

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is Mosaicism in Humans.

1.2 Learning Objectives

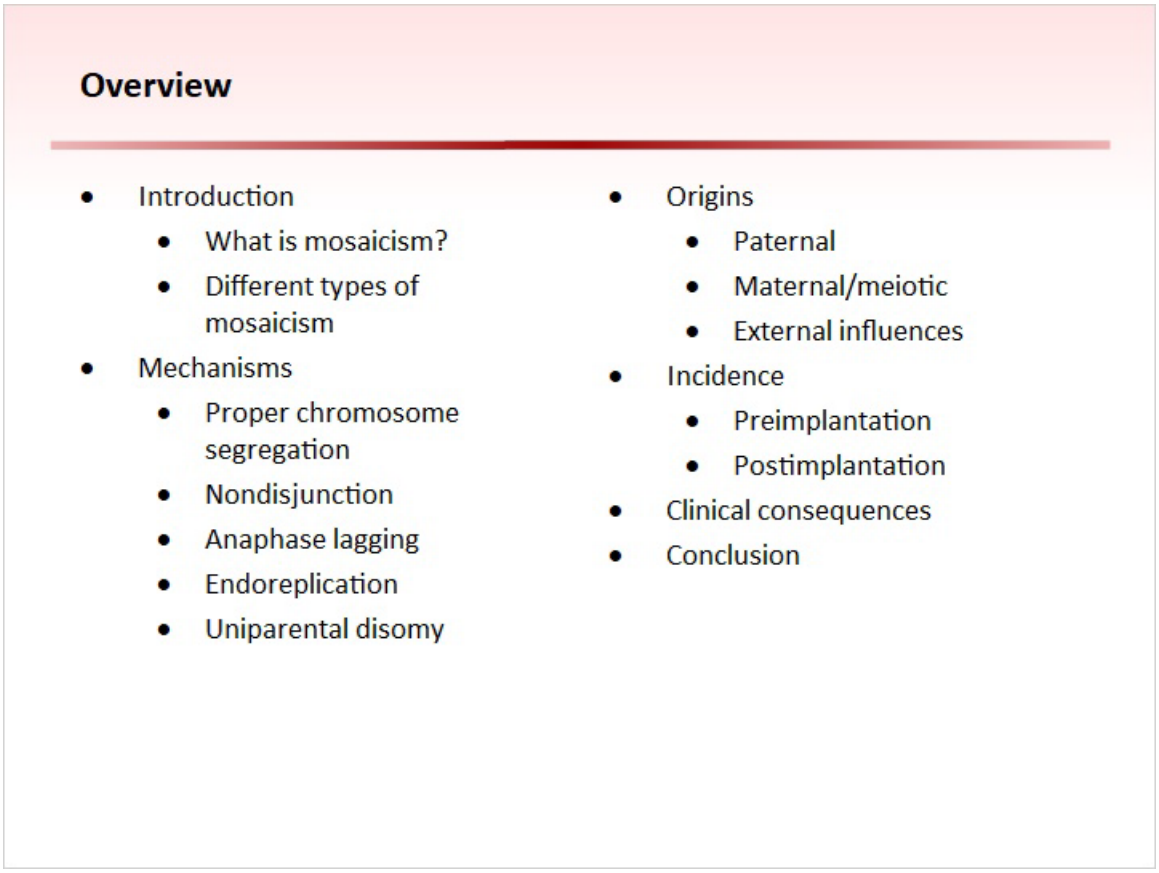


Notes:

At the conclusion of this presentation, participants should be able to:

1)Describe the mechanisms by which mosaicism arises.
2)List and describe the origins of human chromosomal mosaicism.
3)Describe the incidence of mosaicism during human pre- and postimplantation development.
4)Describe the clinical consequences of mosaicism.

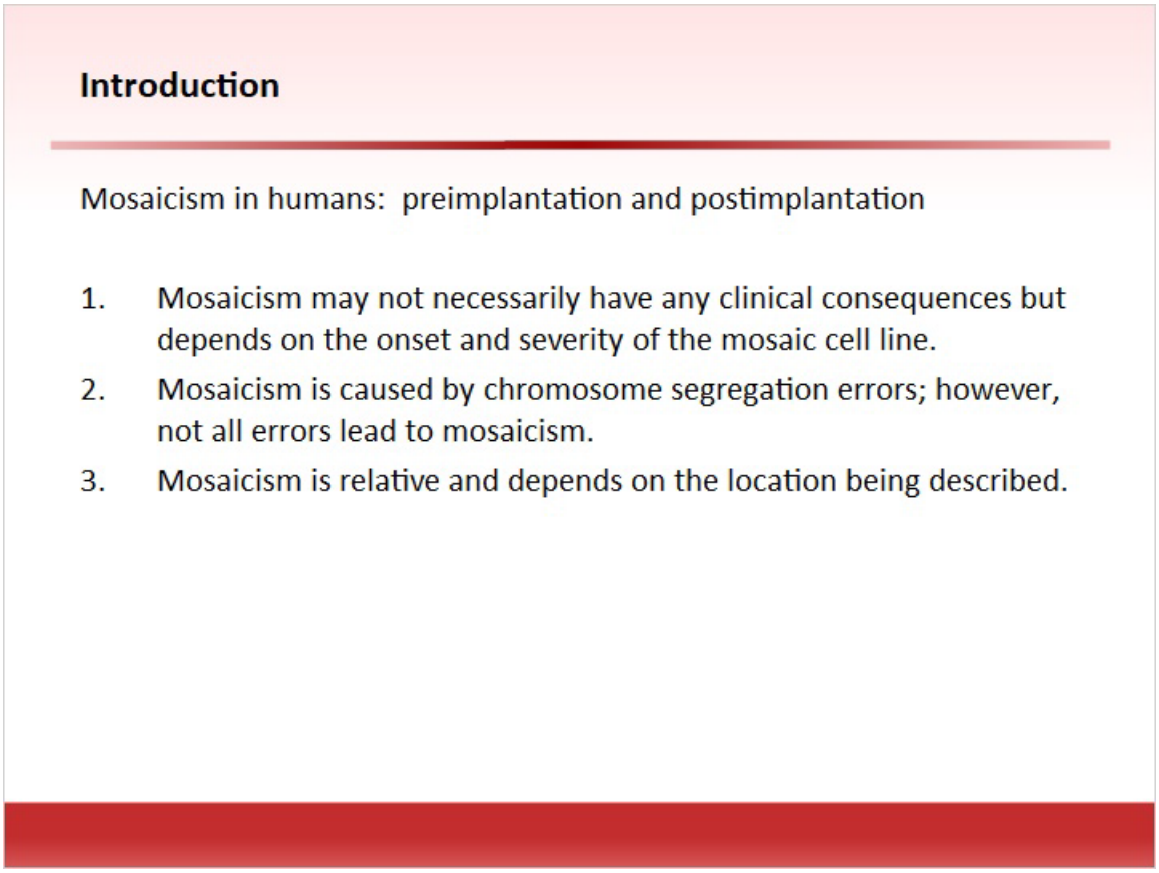
1.3 Overview



Notes:

This presentation will address genetic mosaicism. First, mosaicism will be introduced by defining it and describing the different types. This will be followed by a discussion of the mechanisms by which mosaicism arises, including proper chromosome segregation or mitosis. Then the origins of mosaicism, including paternal, maternal, and external influences, will be covered. Finally, the incidence of mosaicism during both pre- and postimplantation and clinical consequences of mosaicism will be discussed.

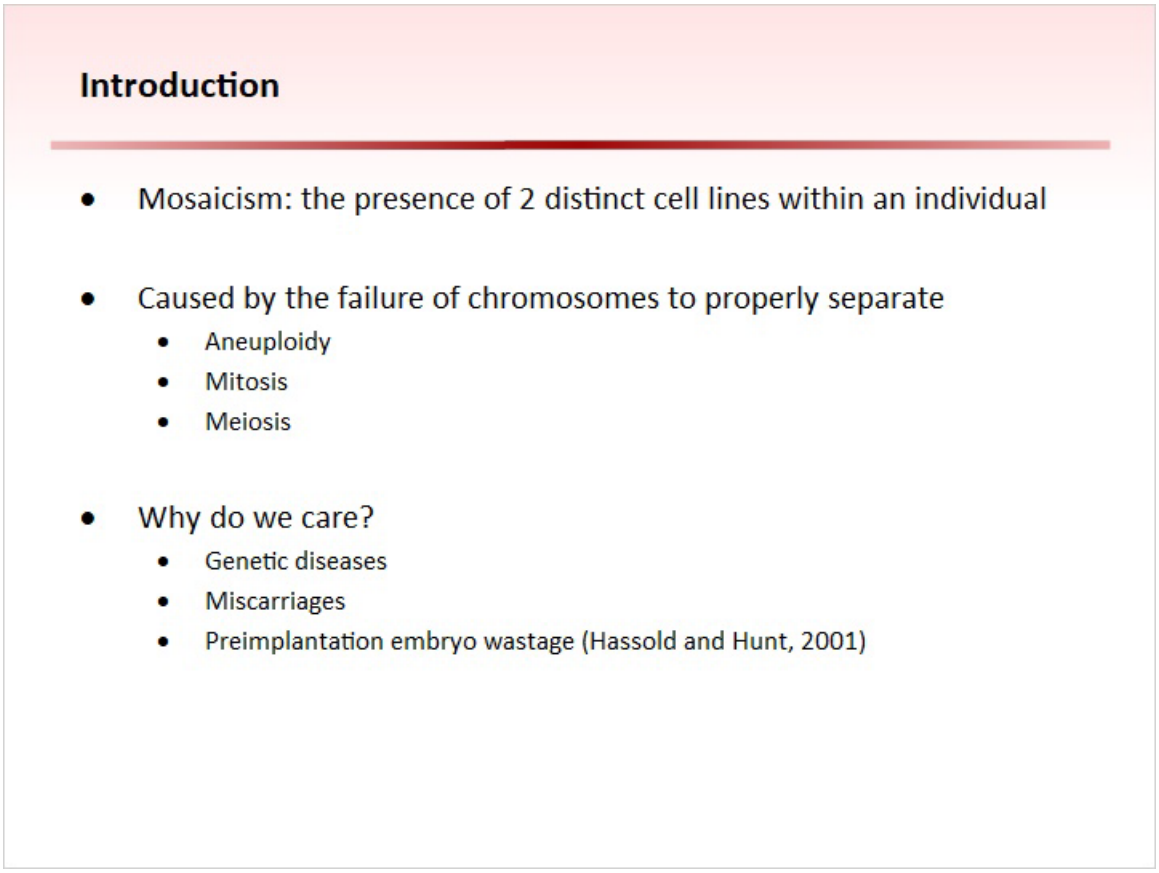
1.4 Introduction



Notes:

This presentation deals with mosaicism in humans-not just preimplantation, but postimplantation as well. Several concepts will be important to note. First, mosaicism may not necessarily have any clinical consequences but depends on the onset and severity of the mosaic cell line. Second, mosaicism is caused by chromosome segregation errors; however, not all errors lead to mosaicism. Third, mosaicism is relative and depends on the location within the embryo being described.

1.5 Introduction



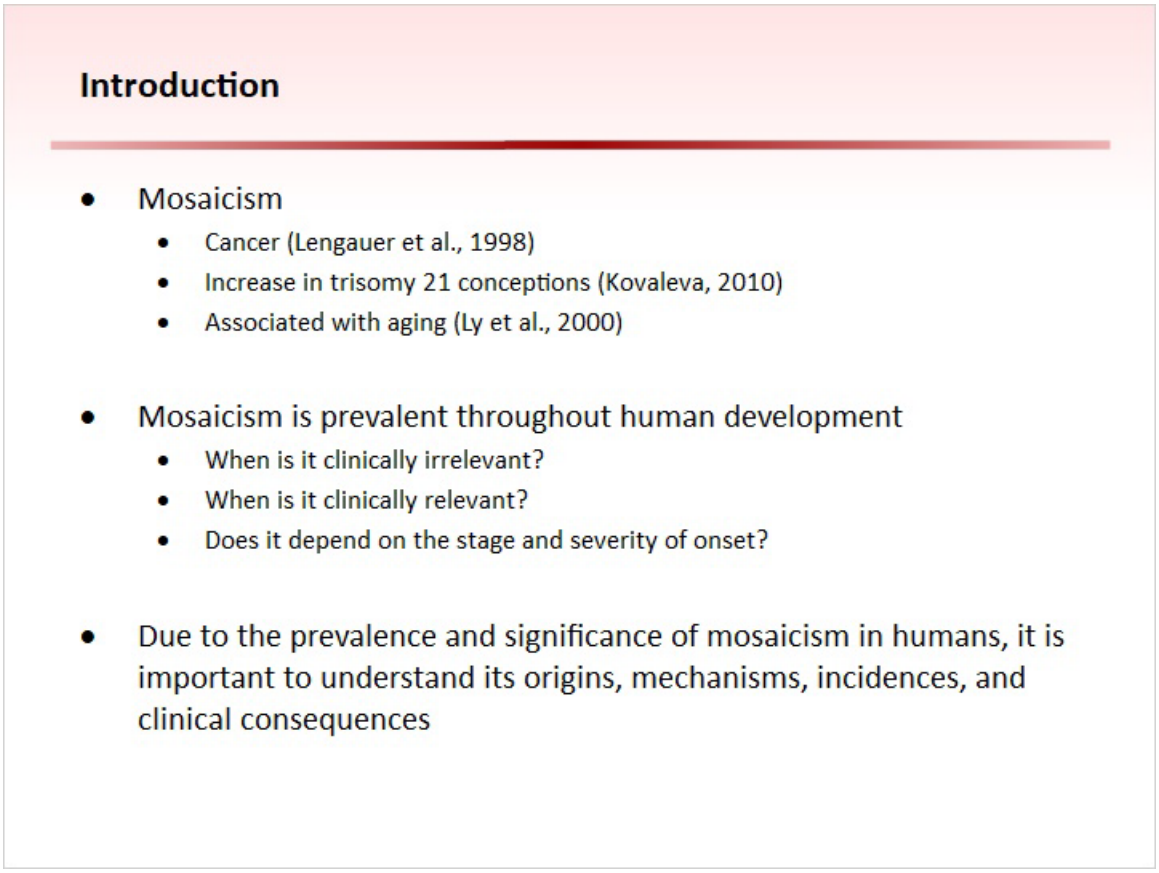
Notes:

By definition mosaicism is the presence of 2 distinct cell lines within an individual. For example, if a cleavage-stage embryo has 8 cells and 7 of them are euploid while 1 is trisomy 3, is that embryo a mosaic? Yes. If the cleavage-stage embryo has 8 cells and all 8 are euploid, is that embryo mosaic? No. Lastly, if the cleavage-stage embryo has 8 cells and all 8 cells have a different chromosomal constitution, is that embryo mosaic? Yes. One can begin to see that mosaicism encompasses a large spectrum.

So what causes mosaicism? As previously mentioned, all mosaicism is aneuploid, but not all aneuploidy leads to mosaicism. Mosaicism is a product of mitosis, but can have its roots in meiosis.

Finally, why is mosaicism important? Chromosomal abnormalities lead to genetic diseases, miscarriages, preimplantation embryo wastage, and attribute to the low success rates of in vitro fertilization (IVF).

1.6 Introduction



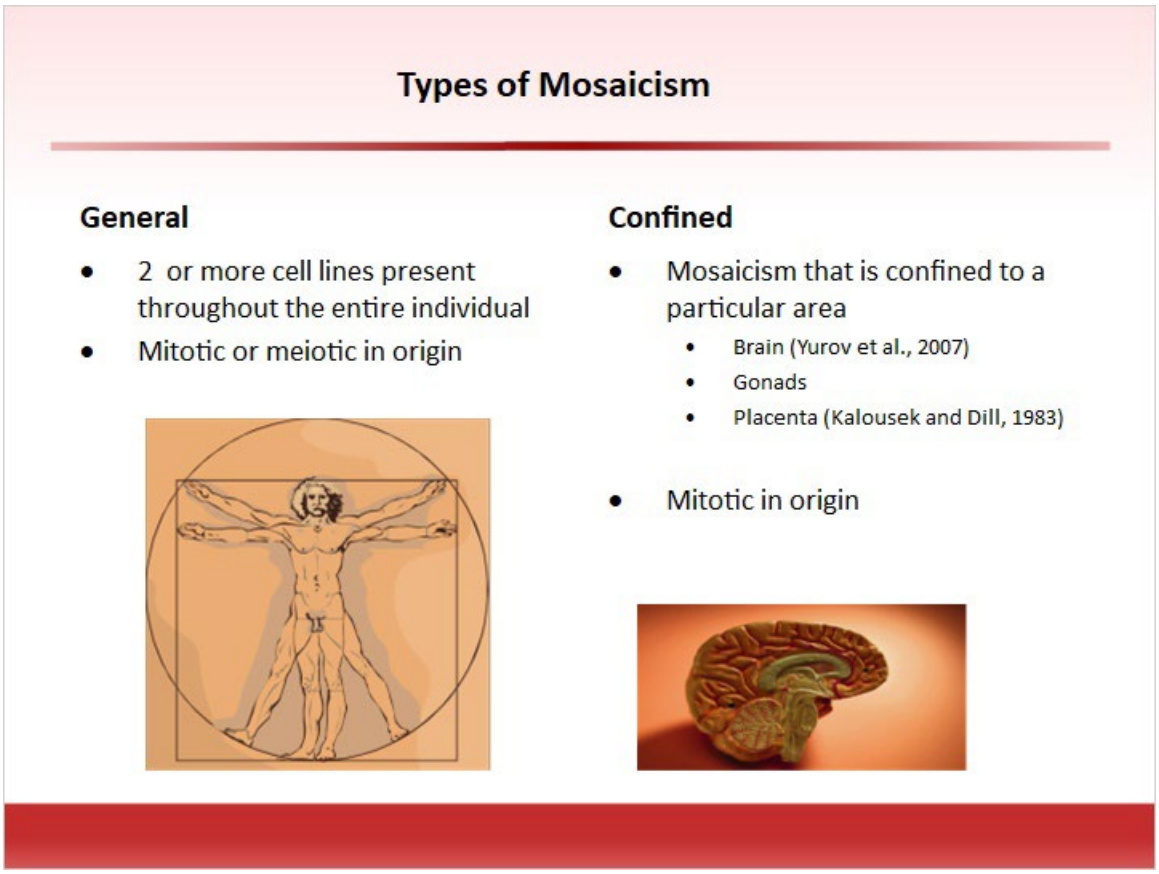
Notes:

There has been much research indicating that mosaicism occurs during preimplantation development. However, mosaicism is also prevalent in cancer, has been shown to lead to an increase in trisomy 21 conceptions, and has also been associated with aging.

Mosaicism during preimplantation development deserves its own review as it is extremely complex and depends on a multitude of factors. Although this presentation will touch on some of these factors, it will primarily focus on embryonic development as a whole, from the zygote, cleavage-stage embryo, blastocyst, to extraembryonic tissue. Due to its prevalence during embryonic development, it is important to understand when mosaicism becomes clinically relevant. When should there be concern? What are the limiting factors? With all the cells in the body, it is hard to imagine that cell division occurs properly all the time. If that's the case, are all humans mosaics? If so, why are there not signs of mosaicism? Clearly there is a threshold in which mosaicism become clinically relevant.

Due to the prevalence and significance of mosaicism in humans, it is important to understand its origins, mechanisms, incidences, and clinical consequences.

1.7 Types of Mosaicism

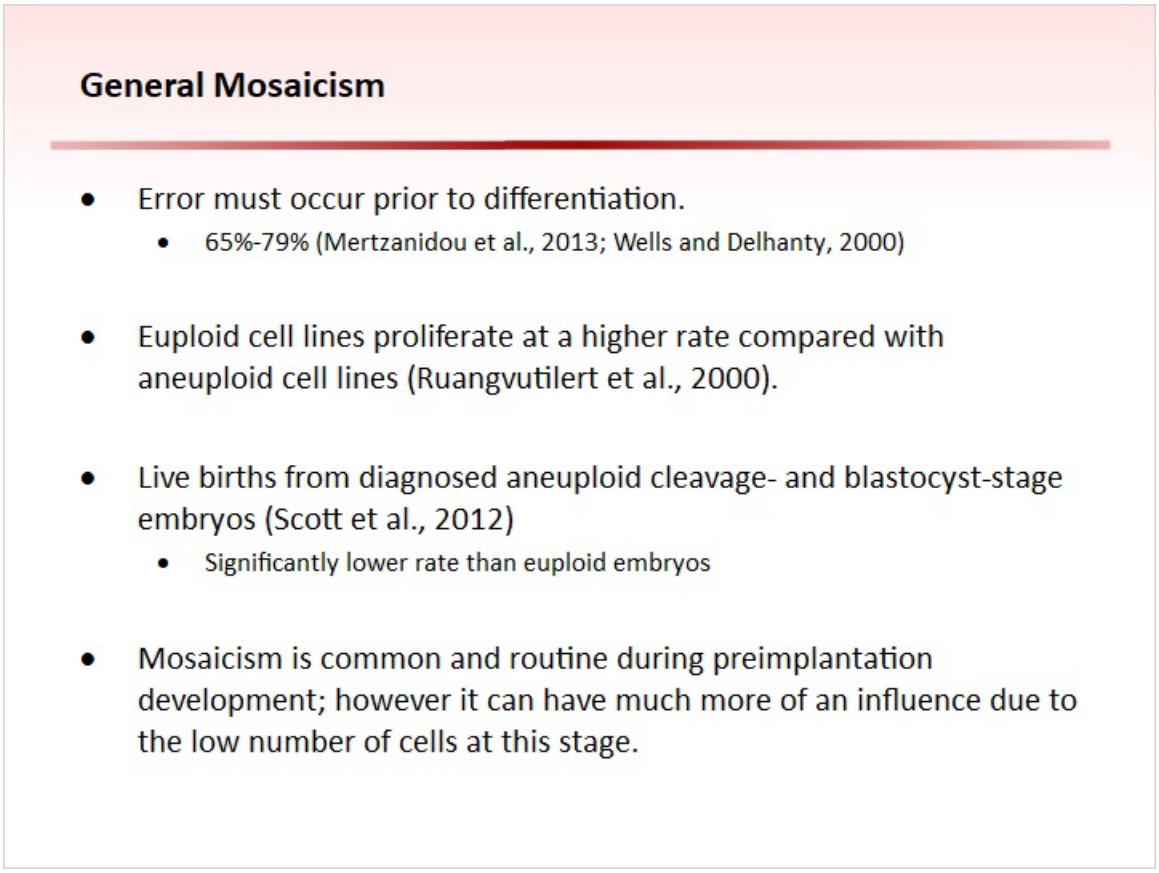


Notes:

There are 2 types of mosaicism: general and confined.
General mosaicism occurs when 2 or more cell lines that are mitotic or meiotic in origin are present throughout the entire individual. Meiotic in origin does not mean the mosaic cell line in question derives from meiosis. It simply means that the mechanisms may be faulty from the onset. This will be explained in more detail later.

Confined mosaicism is mosaicism that is present in only a particular area. For example, if the individual is euploid and the brain contains a cell line that is aneuploid. Other areas that could present with mosaicism are the gonads, placenta, and skin, among others.

1.8 General Mosaicism



Notes:

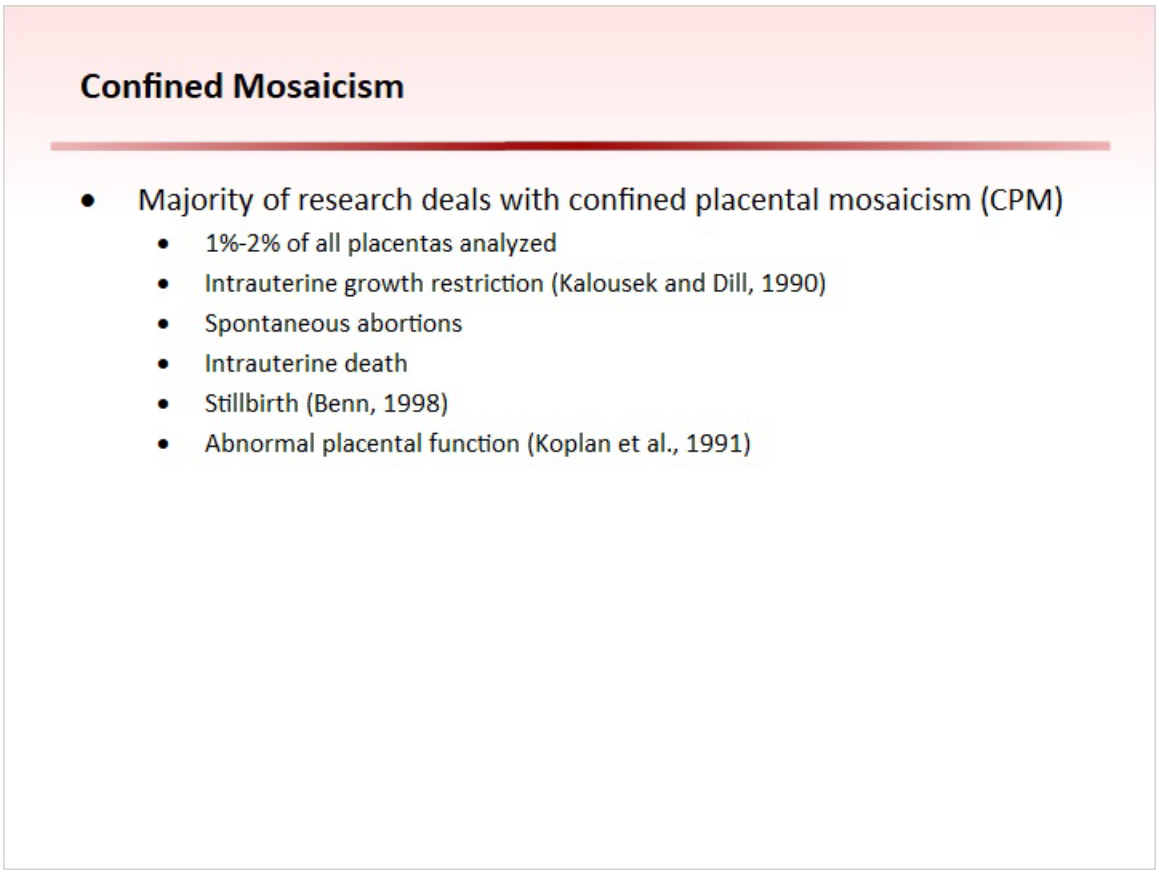
In order for a mosaic cell line to propagate through the entire individual and pregnancy, the error must occur before differentiation. Prior to differentiation in the preimplantation embryo, the mosaicism rate has been found to be approximately 65 to 79%. However, just because the mosaic cell line exists at this stage does not mean that the abnormalities will persist throughout development. Research has shown that euploid cell lines can proliferate at a higher rate compared with aneuploid cell lines. Scott and colleagues described live births from diagnosed aneuploid cleavage-stage and blastocyst-stage embryos. The live births occurred at a significantly lower rate with the diagnosed aneuploid embryos as opposed to those with euploid cells. There are a few possible reasons for this result:

1)No test is 100% accurate, and the test returned an inaccurate result.
2)The cell removed was aneuploid. However, it was the only cell that was aneuploid, hence the removal of the aneuploid cell "corrected" the embryo.
3)Lastly, the embryo was an actual mosaic, containing aneuploid and euploid cell lines.

Preimplantation mosaicism is common and routine during embryonic growth. However, mosaicism can have much more of an influence due to the low number of cells present

during this time. Furthermore, mosaicism can become isolated during embryonic development, leading to mosaicism confined to a particular area.

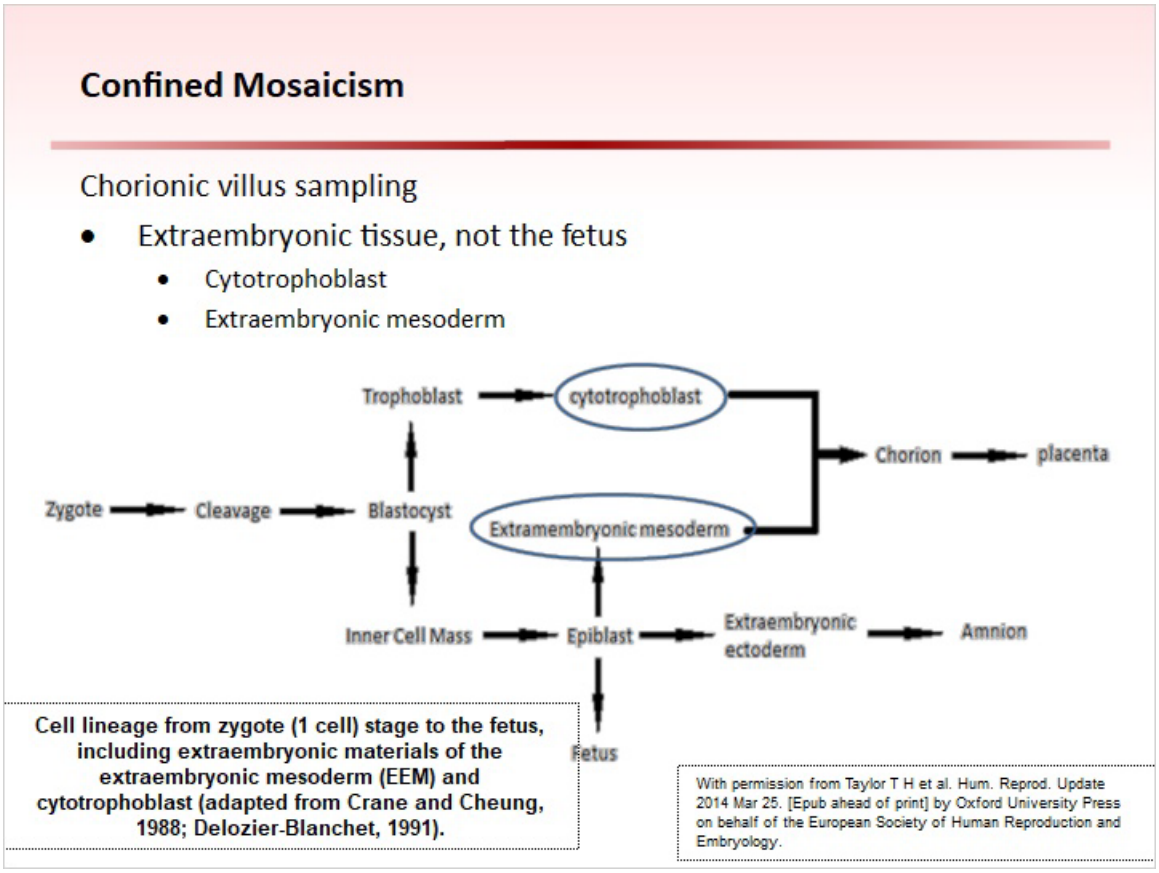
1.9 Confined Mosaicism



Notes:

As previously discussed, confined mosaicism refers to chromosomal mosaicism that is only present in a particular area. The majority of research in this area deals with the phenomenon known as confined placental mosaicism or CPM. Simply, CPM is chromosomal discordance between the fetus and placenta. CPM is believed to occur in approximately 1%-2% of all placental tissue analyzed and has been linked to intrauterine growth restriction, spontaneous abortions, intrauterine death, stillbirth, and abnormal placental function.

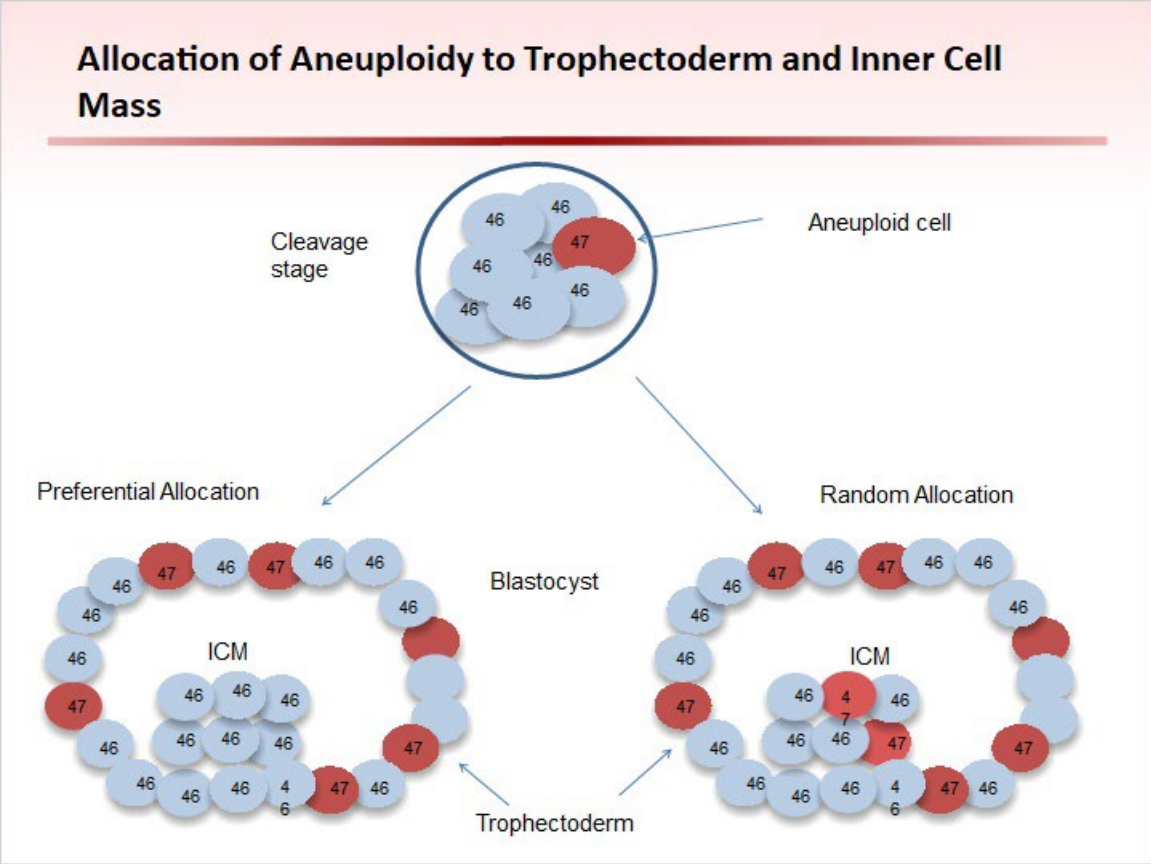
1.10 Confined Mosaicism



Notes:

There are 2 types of invasive procedures utilized in prenatal testing: chorionic villus sampling (CVS) and amniocentesis. Both procedures determine the chromosomal constitution of the fetus by sampling extraembryonic tissue rather than the fetus proper. CVS involves sampling from either the cytotrophoblast or the extraembryonic mesoderm. Alternatively, amniocentesis involves the sampling of amniotic fluid. What is important is that none of these tests directly analyzes the chromosomes of the fetus proper. Regardless of whether mosaicism is present in the entire individual or confined, the mechanisms by which mosaicism occurs are the same.

1.11 Allocation of Aneuploidy to Trophectoderm and Inner Cell Mass



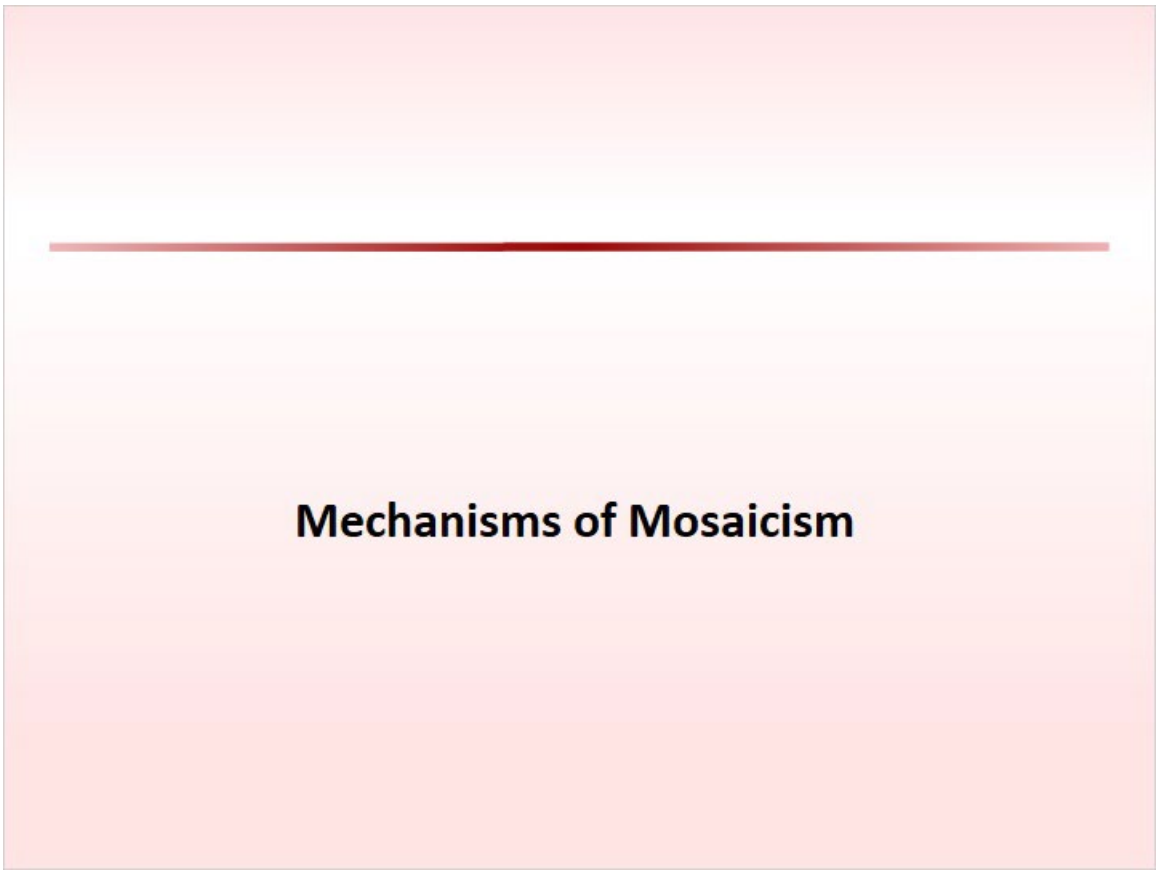
Notes:

With the increased use of blastocyst biopsy, the chromosomal relationship between the trophectoderm and inner cell mass (ICM) becomes increasingly important. Do aneuploidies that occur at the cleavage stage become incorporated into the ICM or trophectoderm? If the aneuploidies were forced to the trophectoderm, this would certainly explain confined placental mosaicism (CPM). Confined placental mosaicism occurs in roughly 1-2% of all pregnancies indicating that discrepancies between the ICM and trophectoderm exist (Ledbetter et al., 1992). However, upon closer examination, CPM has been shown to be meiotic in origin (Robinson et al., 1997) or induced after implantation with the invasion of the cytotrophoblast into the uterine wall (Weier et al., 2005).

When IVF utilizes blastocyst biopsy and an aneuploidy is diagnosed, it is assumed that this aneuploidy is present throughout the embryo as well. Research has shown a high concordance between the trophectoderm and ICM (Capalbo et al., 2013). However this research was conducted utilizing fluorescence in-situ hybridization which may not be accurate (Treff et al., 2013). Utilizing single nucleotide polymorphism (SNP) array, Johnson and colleagues (2010) examined all the chromosomes from the ICM and trophectoderm and found a 96% concordance rate between the two tissues. These data

suggest that the preferential allocation of aneuploidy to the trophectoderm is a random event.

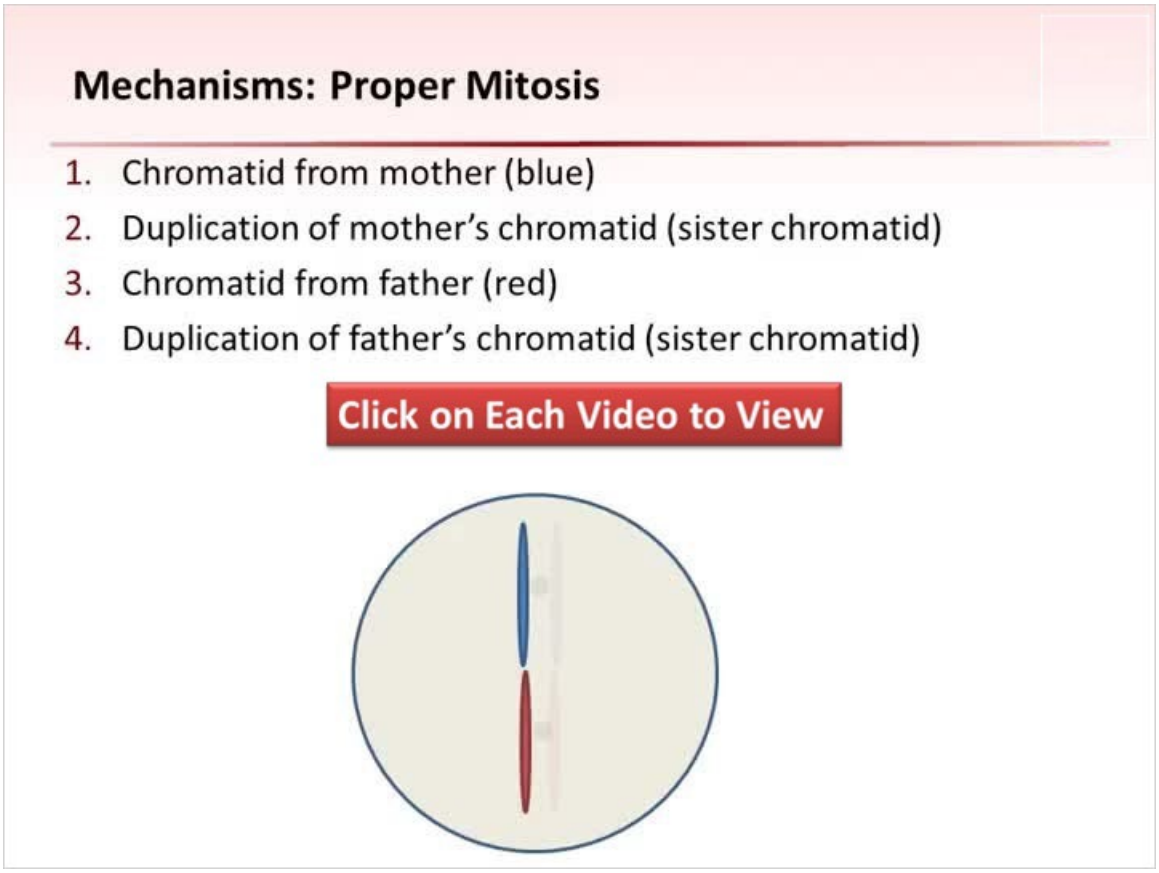
1.12 Mechanisms of Mosaicism



Notes:

The next section will focus on the mechanisms by which mosaicism arises.

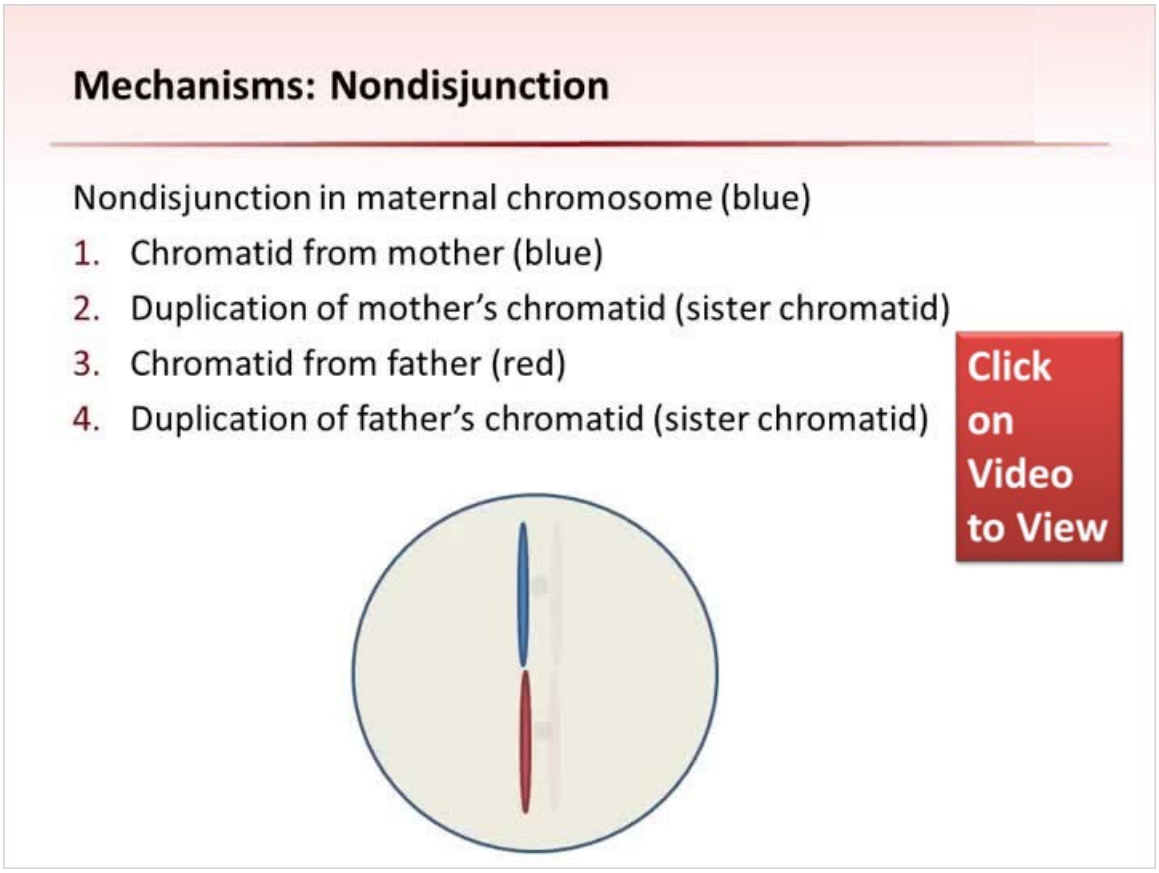
1.13 Mechanisms: Proper Mitosis



Notes:

How do chromosomes segregate? A normal cell has 2 sets of chromosomes. The chromosomes from the mother and father are represented as blue and red, respectively. Each chromosome contains 2 chromatids, a chromatid from the mother or father and a duplication of that chromatid. During division, also known as mitosis, the spindle apparatus (represented by black lines) develops and attaches itself to the chromosomes at a site known as the kinetochore (represented as a black dot). The spindle pulls the chromosomes apart and each chromatid goes to opposite poles. The cell then divides, creating 2 identical cells. Unfortunately, mitosis does not always occur as planned, leading to aneuploidy and subsequent mosaicism.

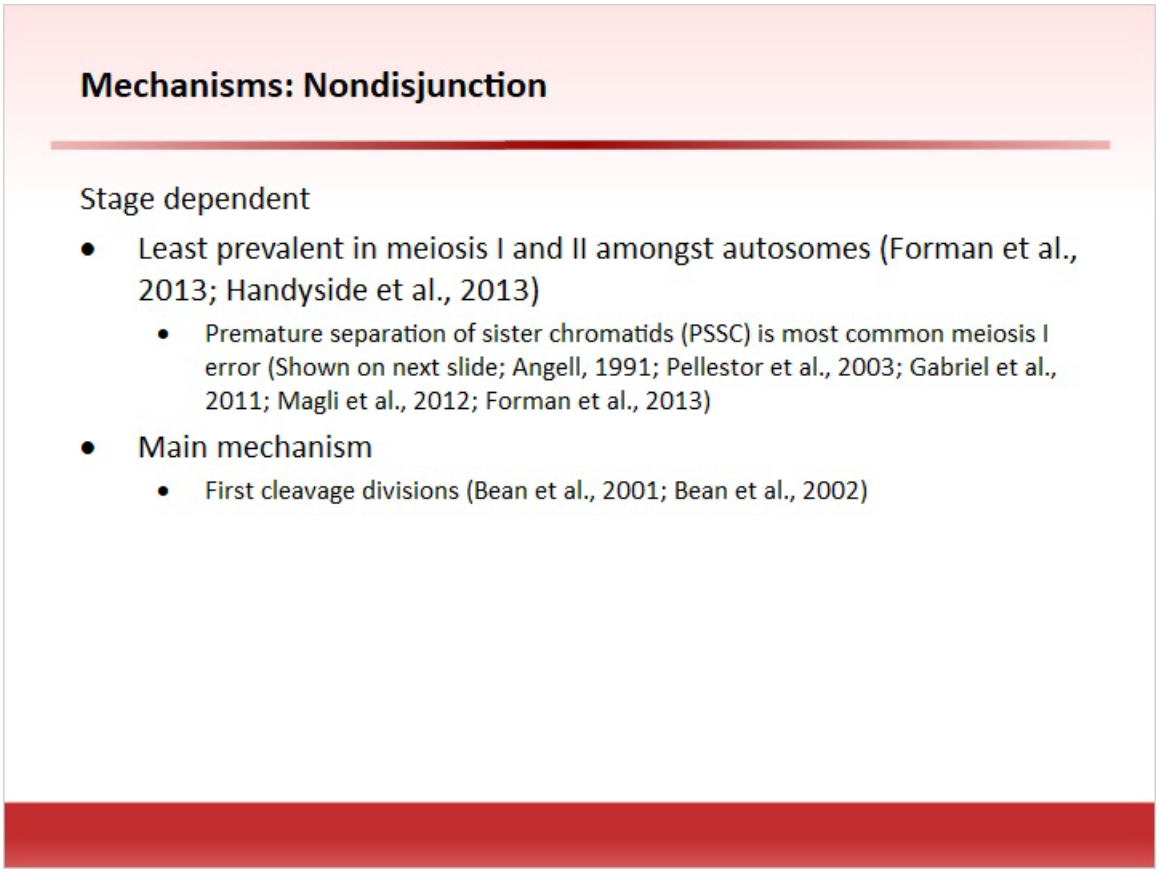
1.14 Mechanisms: Nondisjunction



Notes:

One mechanism by which mosaicism occurs is referred to as nondisjunction. Here again is the same cell with 2 sets of chromosomes, the spindle apparatus, and the kinetochore. Instead of each chromatid migrating to opposite poles, 1 chromosome fails to separate and the entire chromosome (both chromatids) are forced to the same pole. This creates a gain (referred to as a trisomy) in 1 cell, and a loss (or monosomy) in the other cell.

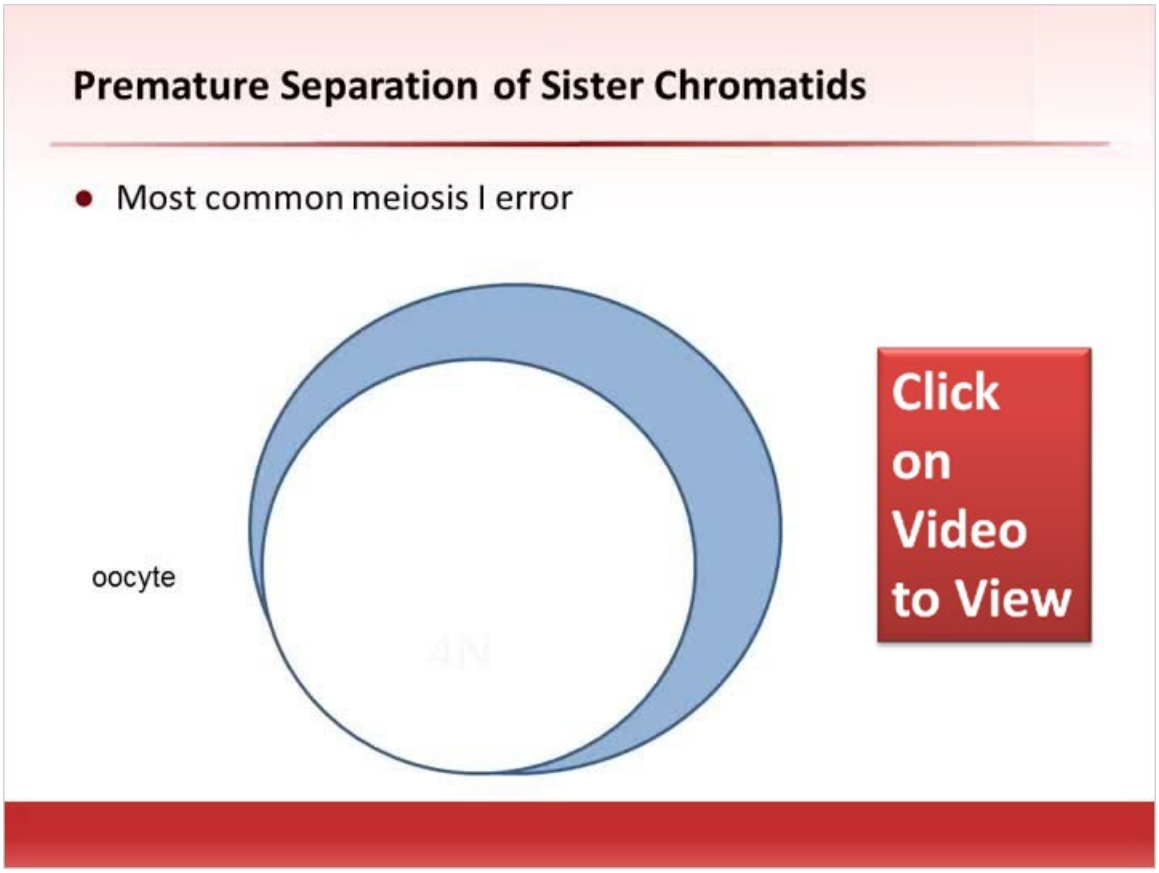
1.15 Mechanisms: Nondisjunction



Notes:

Nondisjunction is not necessarily the most prominent mechanism by which errors occur. Nondisjunction seems more prevalent at certain stages, particularly meiosis I and II among the autosomes. The first cleavage division seems especially prone to nondisjunction.

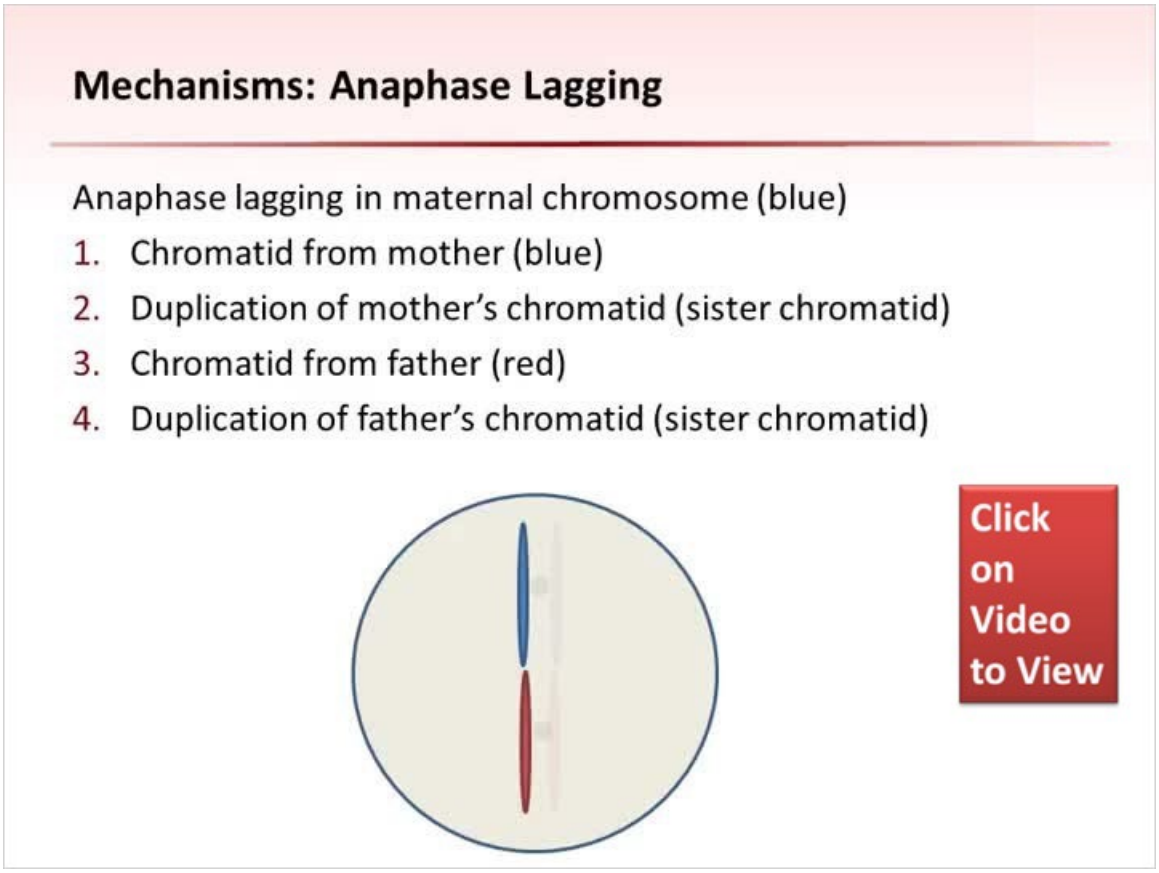
1.16 Premature Separation of Sister Chromatids



Notes:

This is the oocyte surrounded by the zona pellucida. The oocyte must undergo two reduction divisions (meiosis) to get from 4N to 1N. During normal meiosis, the first division results in the reduction of chromosomes from 4N to 2N. The second division results in the reduction of the oocyte from 2N to 1N. However, even meiosis doesn't go as planned. The most common error at this stage is premature separation of sister chromatids which results in the first reduction division of 1 chromosome, as opposed to the usual 2 chromosomes. Ironically, oocytes that undergo premature separation of sister chromatids, can make up for the error in the subsequent MII reduction division. Euploid embryos have been diagnosed from oocytes that have undergone premature separation of sister chromatids (Forman et al., 2013).

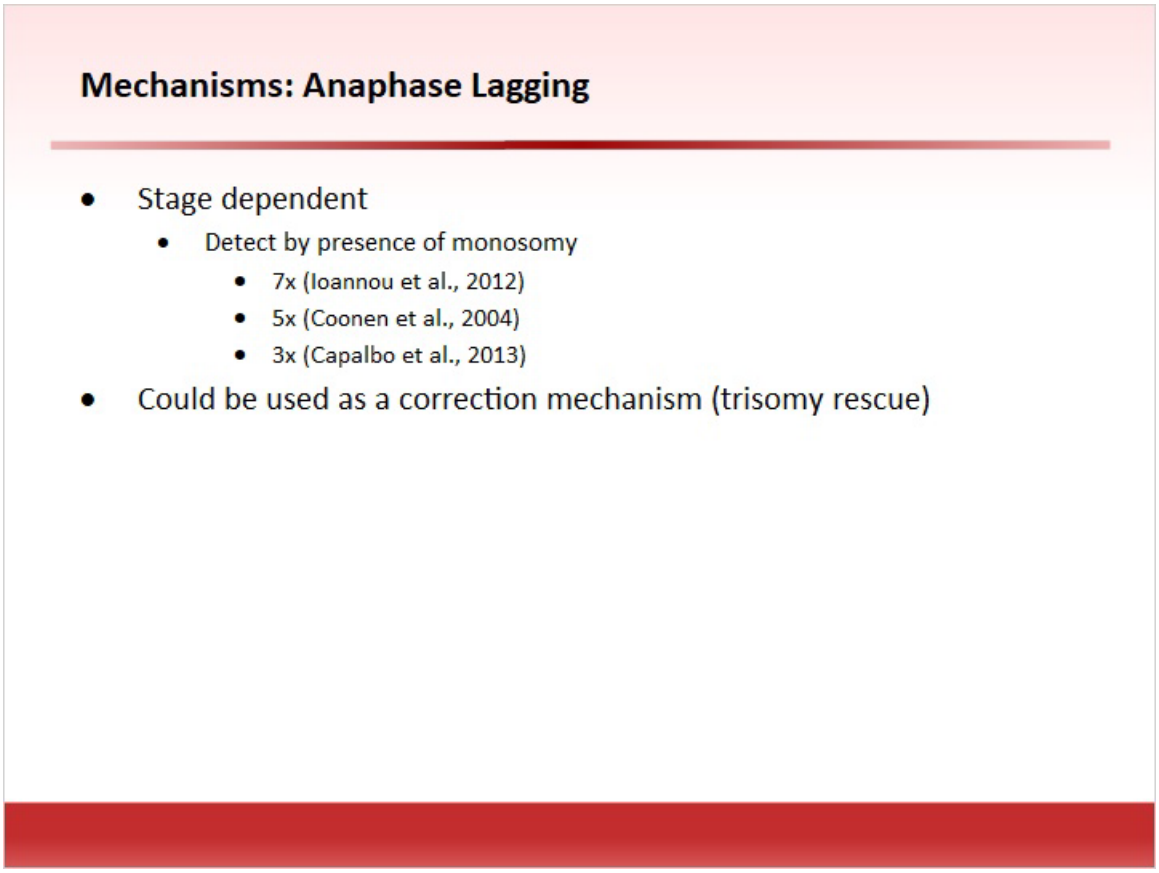
1.17 Mechanisms: Anaphase Lagging



Notes:

Another mechanism is referred to as anaphase lagging. Once again, there are 2 sets of chromosomes (1 from the mother, 1 from the father), the spindle apparatus, and the kinetochore. During anaphase lagging, a single chromatid fails to be incorporated into the nucleus. This creates 1 cell with the proper number of chromosomes and another cell with a loss or monosomy.

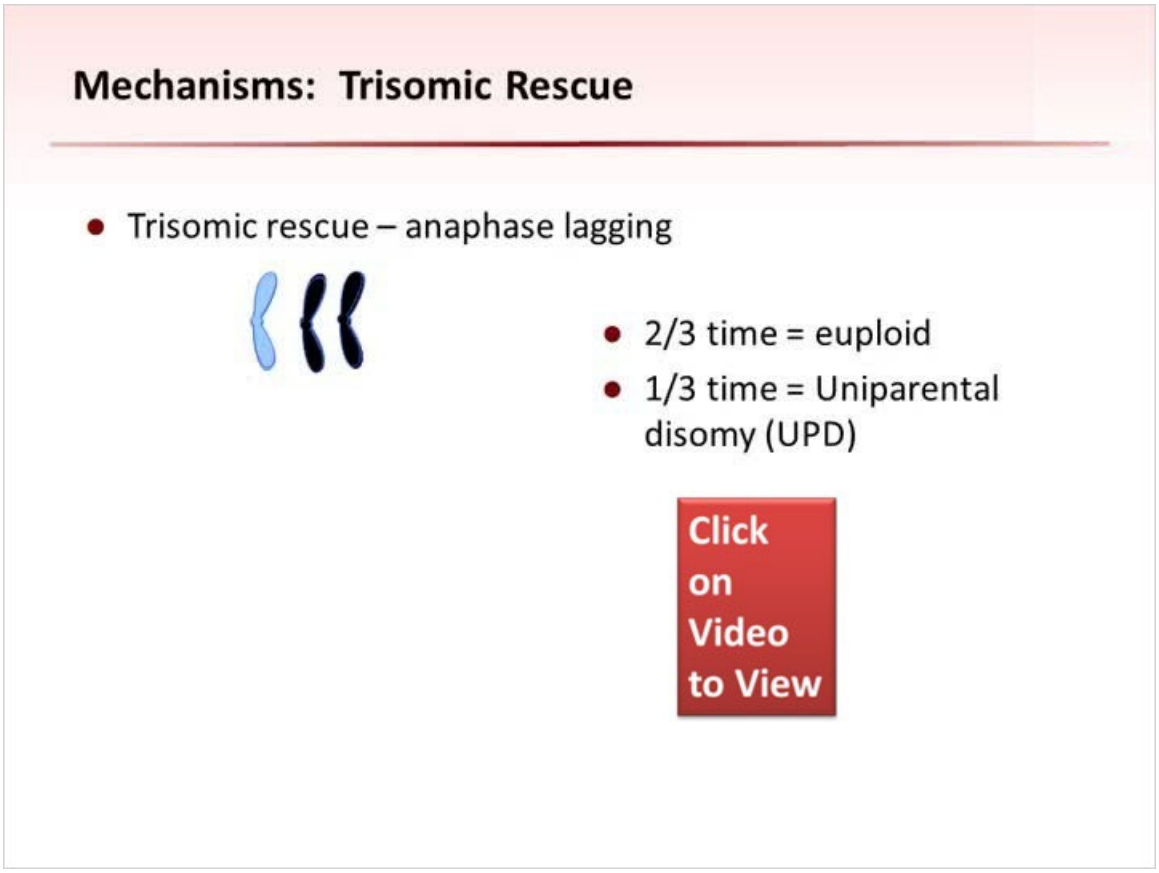
1.18 Mechanisms: Anaphase Lagging



Notes:

Much like nondisjunction, anaphase lagging is also stage dependent. Anaphase lagging is detected by the presence of a single monosomy. Research has indicated that monosomies tend to be more prevalent than trisomies, somewhere in the range of 3-7 times. However, note that fluorescence in-situ hybridization (FISH) was used in these studies and that this procedure does have drawbacks which will be discussed later. Lastly, anaphase lagging can create an aneuploid cell line; however, it can also "correct" a trisomy cell line back to euploid status, a phenomenon known as trisomy rescue.

1.19 Mechanisms: Trisomic Rescue



Notes:

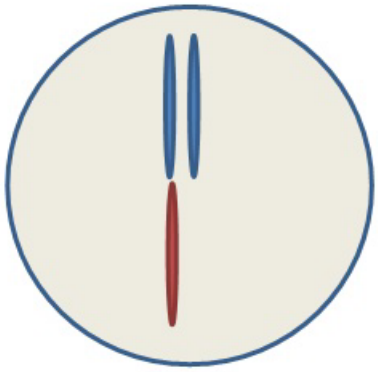
What if an anaphase lagging event occurs on a chromosome that has 3 copies? In this example, there are 3 copies of chromosome 5. If an anaphase lagging event occurs, 1 of the copies of the chromosome fails to be incorporated into the nucleus, thereby creating 2 euploid cells from a trisomic cell. Two-thirds of the time, this will result in a euploid and corrected cell line, and one-third of the time this process will result in uniparental disomy.

1.20 Mechanisms: Endoreplication

Mechanisms: Endoreplication

Endoreplication in maternal chromosome (blue)

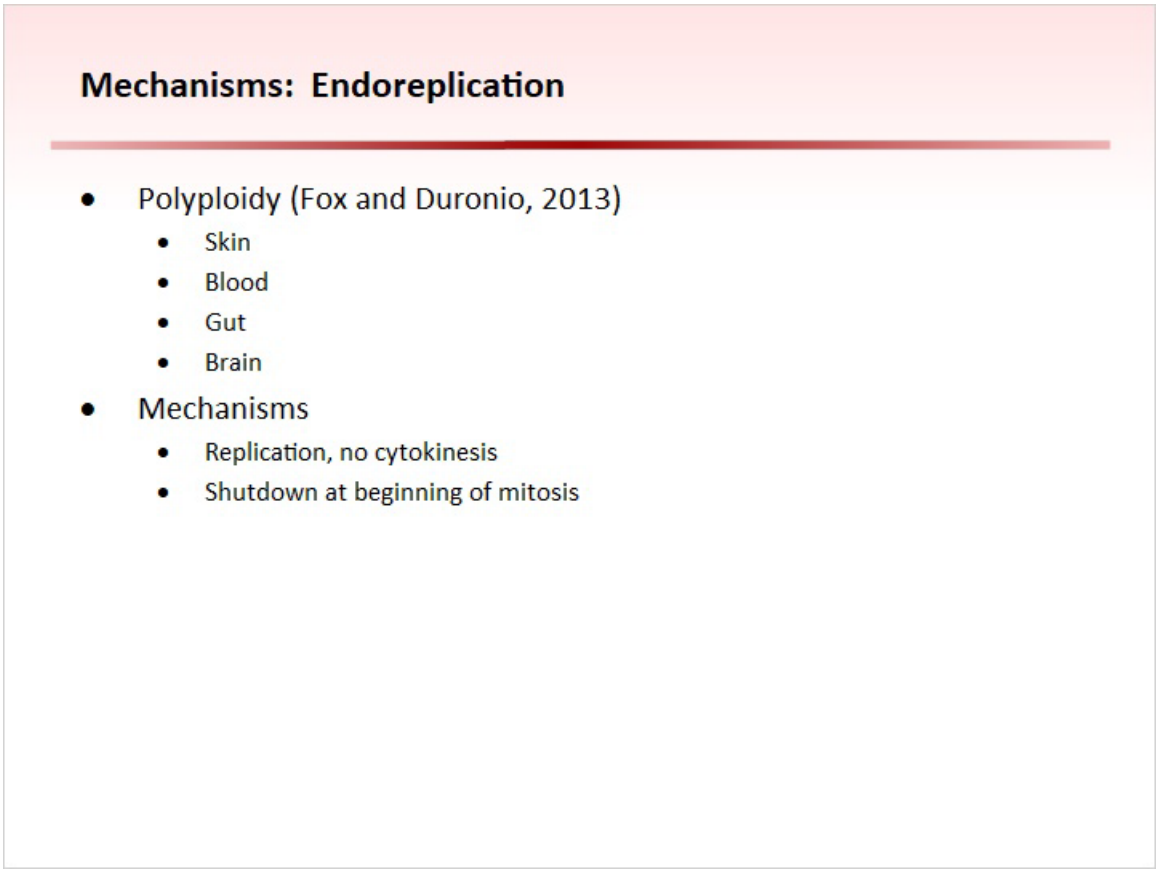
1. Chromatid from mother (blue)
2. Duplication of mother's chromatid (sister chromatid)
3. Chromatid from father (red)



Notes:

Endoreplication does occur, although to a much lesser extent than anaphase lagging and nondisjunction. In essence, endoreplication is chromosome replication without division.

1.21 Mechanisms: Endoreplication



Notes:

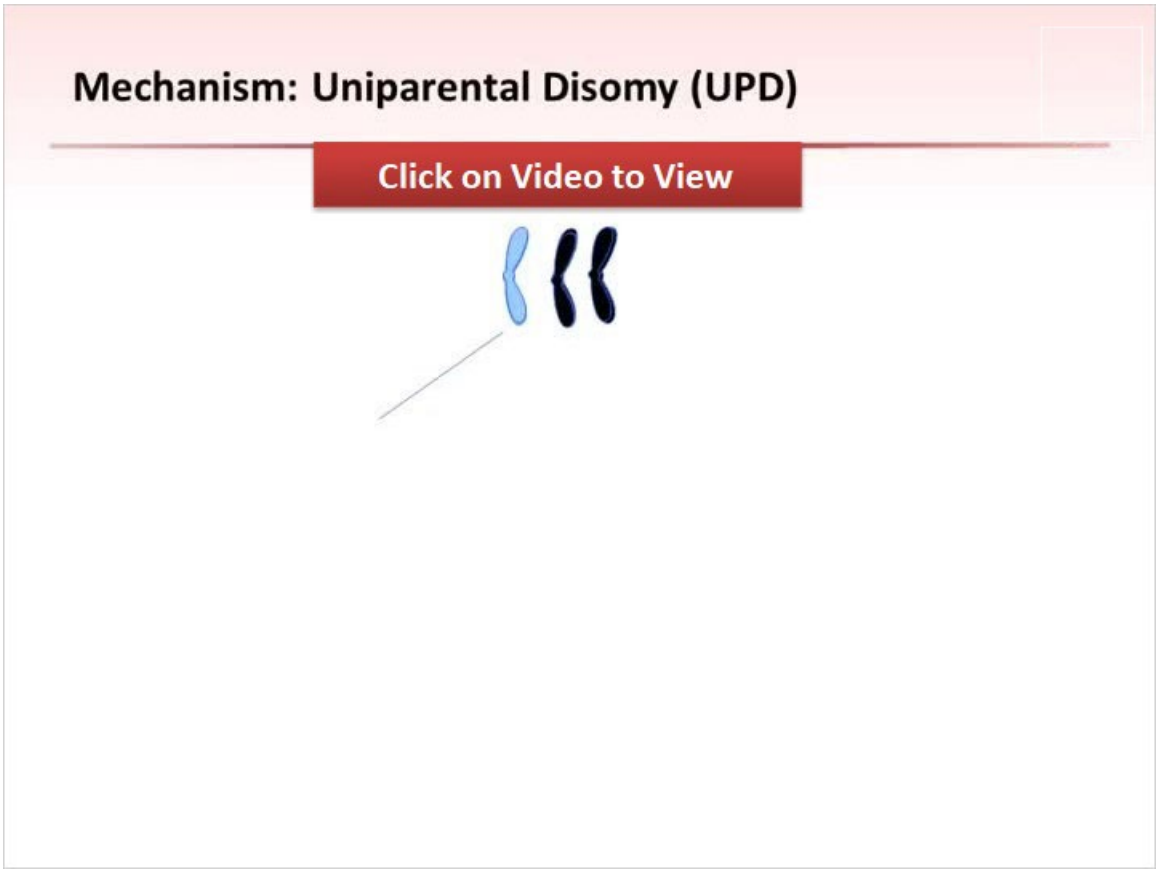
Another name for endoreplication is polyploidy. Endoreplication has been found in the skin, blood, gut, and brain, among other places.

It is believed to derive from 2 mechanisms:

1)A cell-cycle malfunction in which a chromosome is replicated without subsequent cytokinesis.

2)Mitosis is initiated but is shut down shortly thereafter, resulting in a duplicated chromosome.

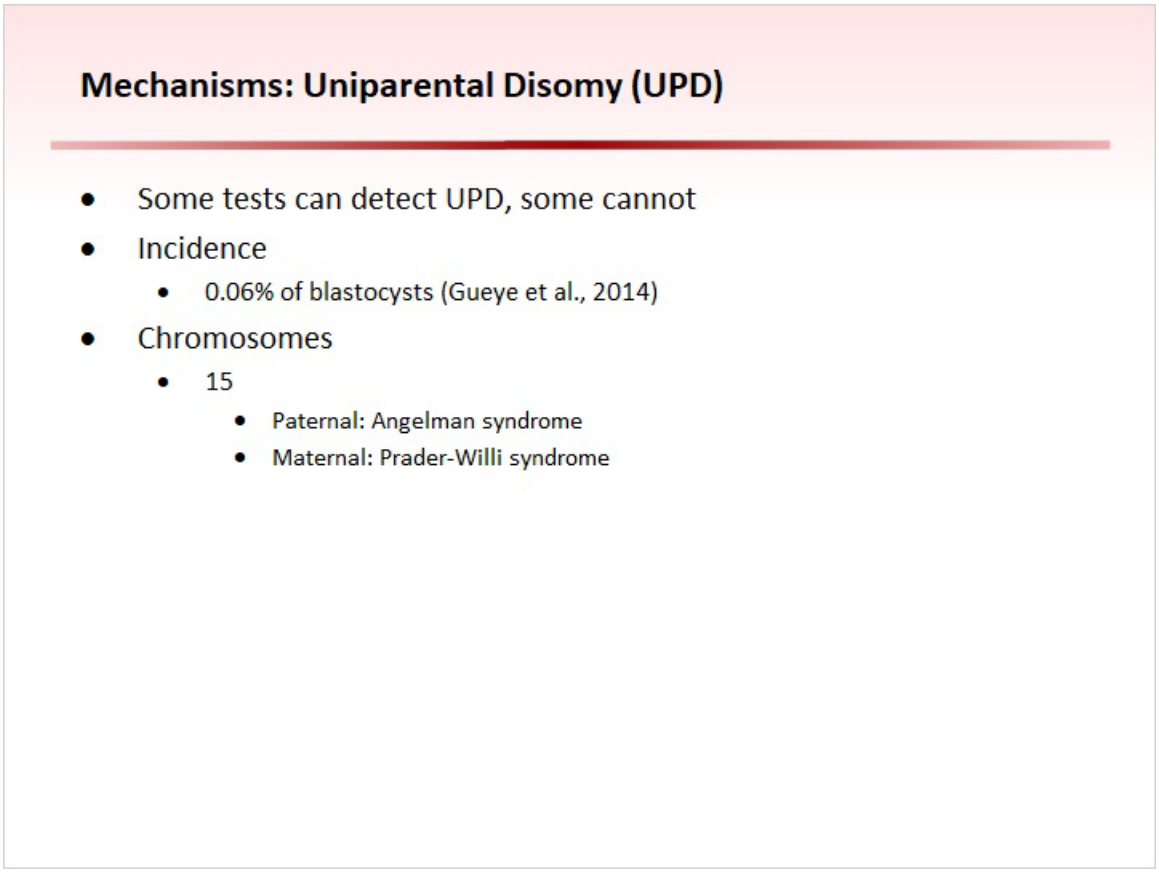
1.22 Mechanism: Uniparental Disomy (UPD)



Notes:

So far this module has reviewed mechanisms in which there are improper numbers of chromosomes. It is possible for a cell line to be mosaic even though it contains the proper chromosome number (46): a phenomenon known as uniparental disomy (UPD). Simply put, instead of a copy of a chromosome from each parent (1 from the mother and 1 from the father), the chromosome in question gets 2 copies, both from 1 parent. Shown here is a trisomic rescue that leads to UPD.

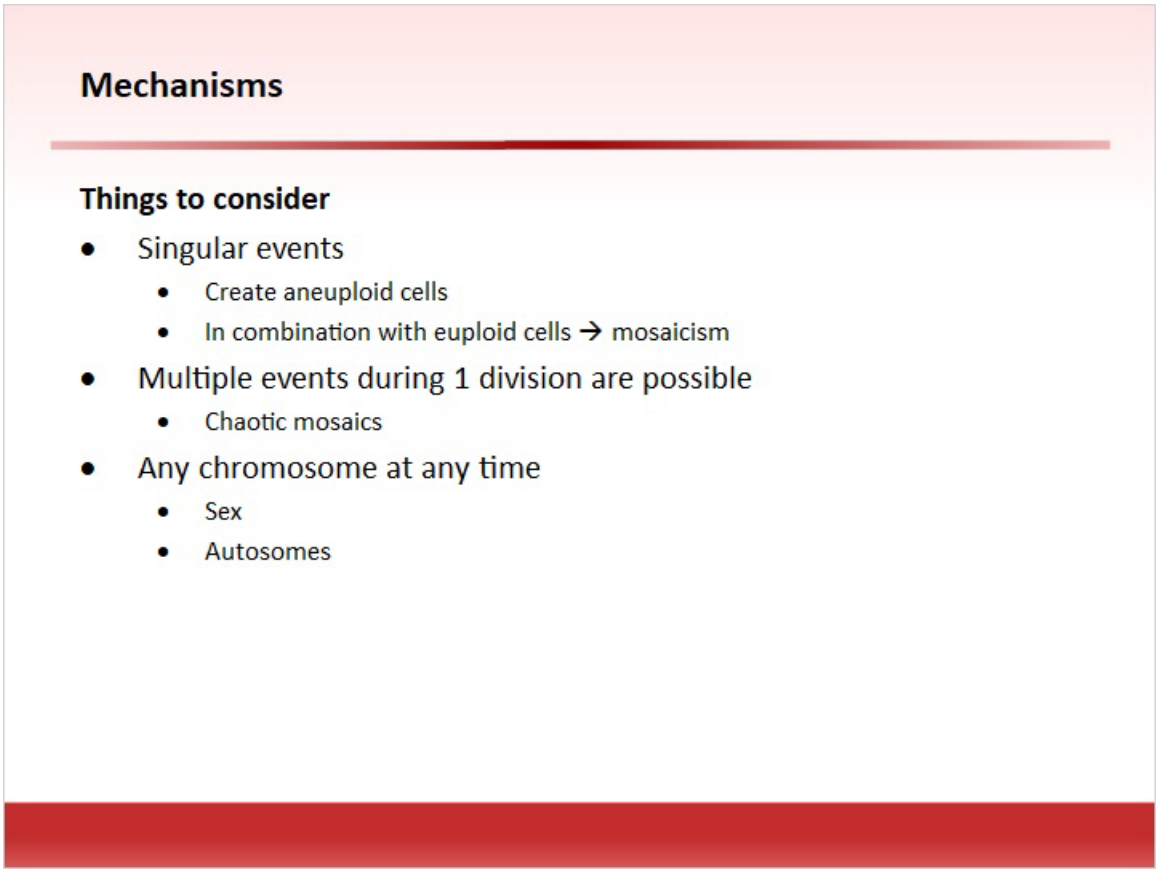
1.23 Mechanisms: Uniparental Disomy (UPD)



Notes:

Some tests can detect UPD, some cannot. However, the incidence during preimplantation development seems to be relatively low, <1%. UPD can lead to live births. For example, paternal UPD of chromosome 15 is referred to as Angelman syndrome, and maternal UPD of chromosome 15 is referred to as Prader-Willi syndrome.

1.24 Mechanisms

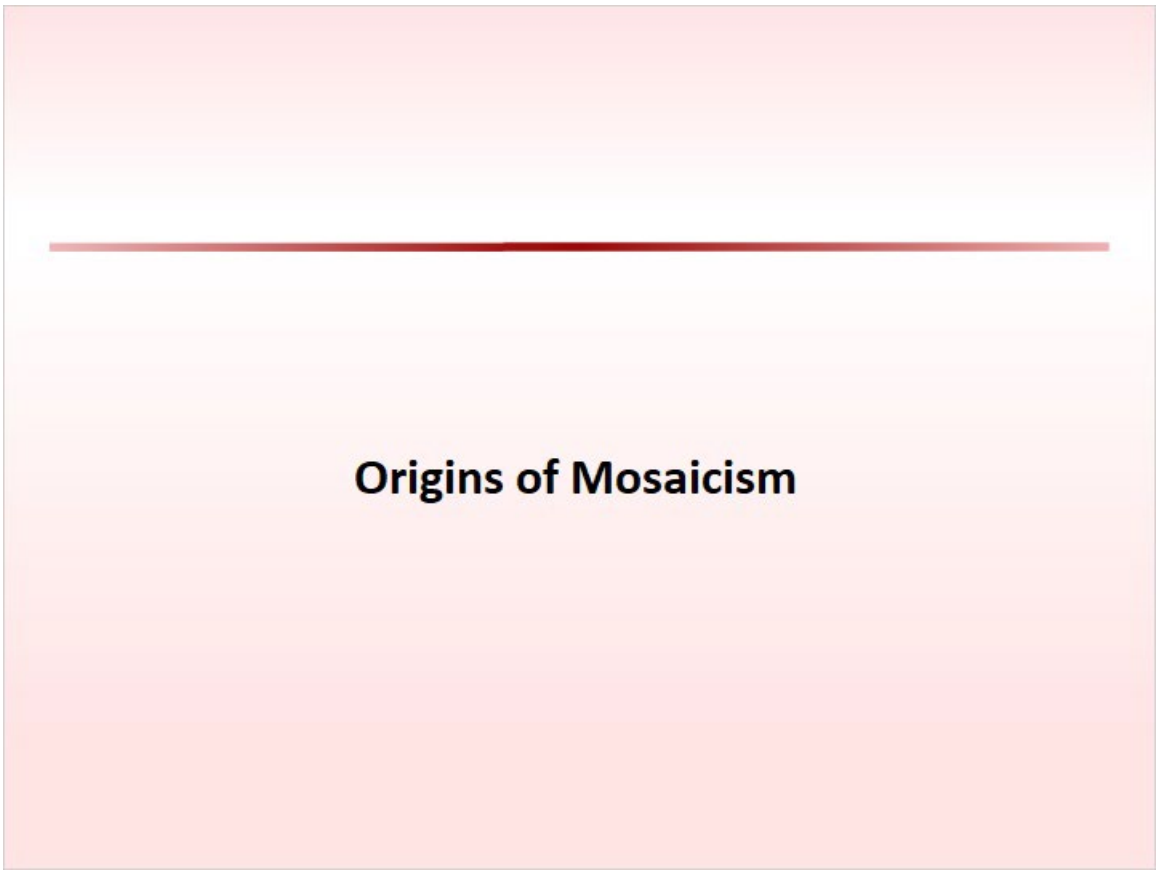


Notes:

The mechanisms described previously are singular events taking place on individual chromosomes. There are multiple chromosomes and multiple events can take place during 1 division. When this occurs, cells are created with multiple chromosomal abnormalities. When an embryo has multiple cells with multiple abnormalities, it is referred to as a chaotic mosaic. This is the most common form of mosaicism at the cleavage stage. However, as the embryo progresses to the blastocyst stage, the incidence of chaotic mosaicism decreases.

Errors can occur on every chromosome at any time. The timing of the error and the ability of the error to propagate determine the influence of mosaicism. For example, if 1 cell from an 8-cell embryo experiences a nondisjunction event, then 6 cells would be euploid, 1 cell would have a gain, and 1 cell would have a loss of a chromosome. At this point, the embryo is a general mosaic (because the entire individual has 3 cell lines). However if the euploid cell lines propagate and the chromosomally abnormal cells become atretic, the embryo reverts back to euploid status. The chromosomally abnormal cell lines must propagate in order to have an impact on development.

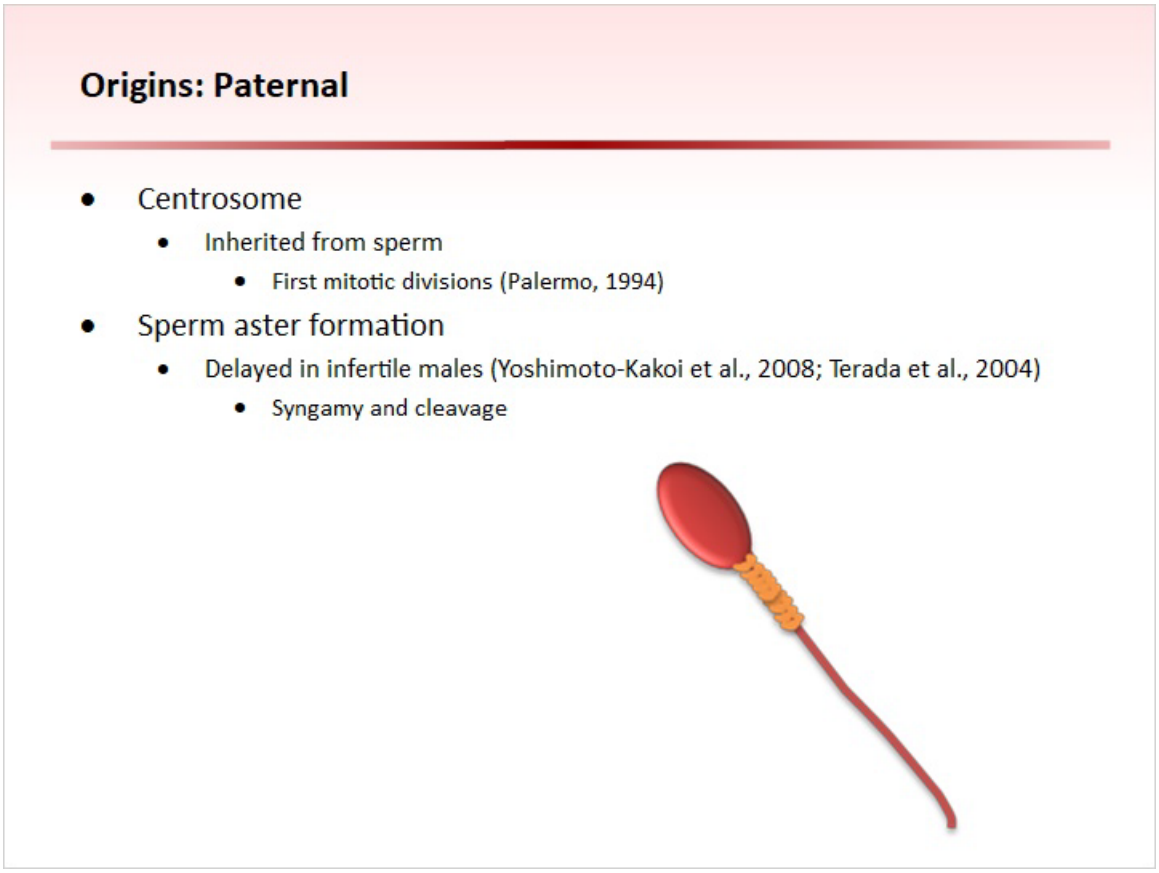
1.25 Origins of Mosaicism



Notes:

This section will address the origins of mosaicism: paternal, maternal, and external.

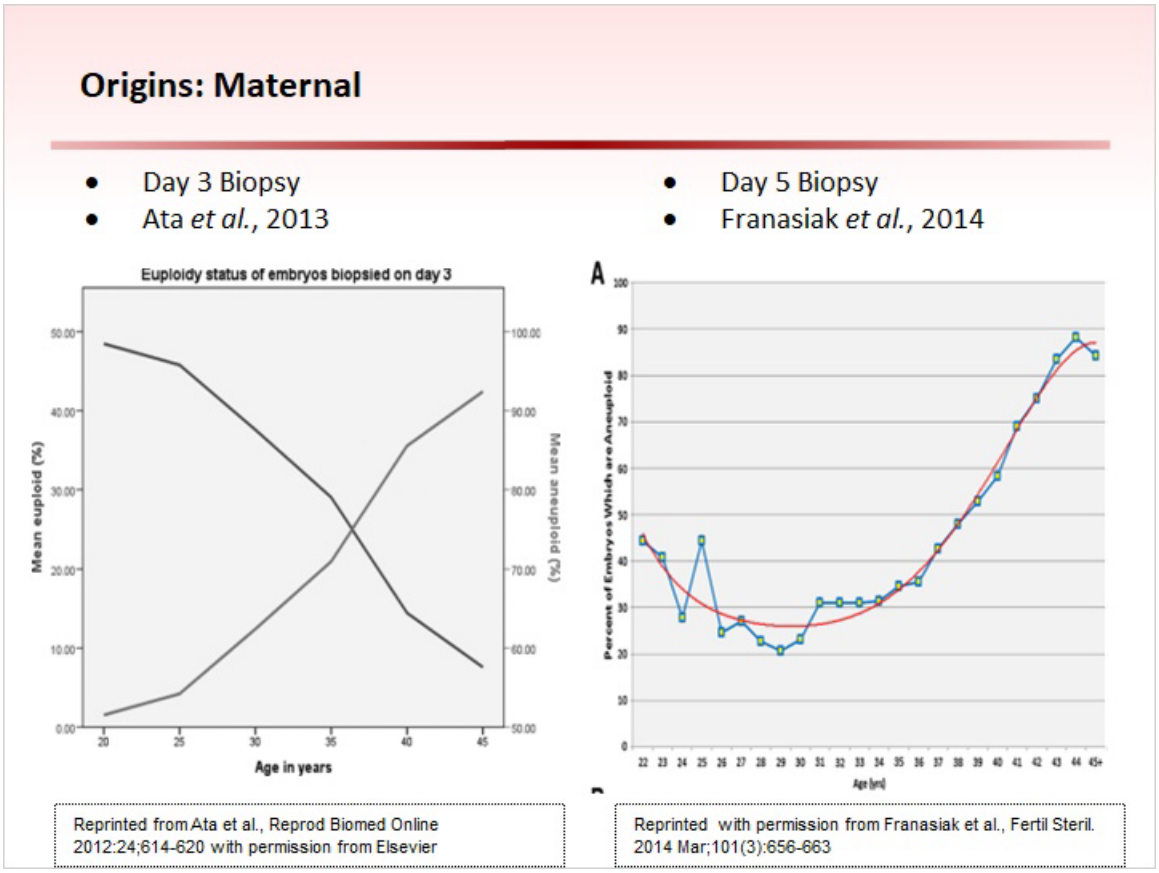
1.26 Origins: Paternal



Notes:

The centrosome is inherited from the sperm and is responsible for the first mitotic division within the human embryo. Therefore, any disruption of the sperm centrosome can theoretically produce mosaicism in the preimplantation embryo. Sperm aster formation has been shown to be delayed in infertile males when compared with fertile male controls. This could cause a delay in syngamy and subsequent cleavage and possibly induce aneuploidy and mosaicism. There are several studies that suggest aneuploidies are more prevalent in men with severe male factor infertility, indicating the importance of a functional sperm centrosome in the first mitotic divisions. If aneuploidies are more common in men with severe male factor infertility, then it is possible that mosaicism may also be more prevalent during preimplantation development in this group of patients.

1.27 Origins: Maternal



Notes:

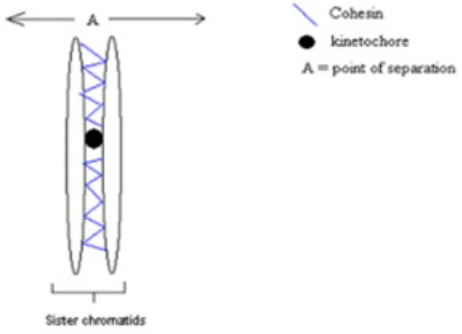
The incidence of aneuploidy increases with maternal age. This graph depicts the relationship between day of biopsy (day 3 and day 5) and maternal age and euploidy. With increasing maternal age is seen the increase in percentage of aneuploidy. Although there is no relationship between maternal age and mosaicism, maternal factors can still influence chromosomal division. As previously discussed, the centrosome is paternally inherited, while the mitochondria and mRNA stores necessary for proper chromosome division originate from the oocyte. Indeed, research has indicated that mitochondrial function is affected by maternal age, possibly influencing chromosome segregation (Wilding et al., 2001; Schon et al., 2000).

1.28 Origins: Maternal

Origins: Maternal

Maternal age

- Reactive oxygen species (ROS)
- Environmental factors
- Cohesion (Duncan et al., 2012; Hodges et al., 2005)
- Down-regulation of mitosis genes (Ly et al., 2000)
- Spindle abnormalities (Battaglia et al., 1996)

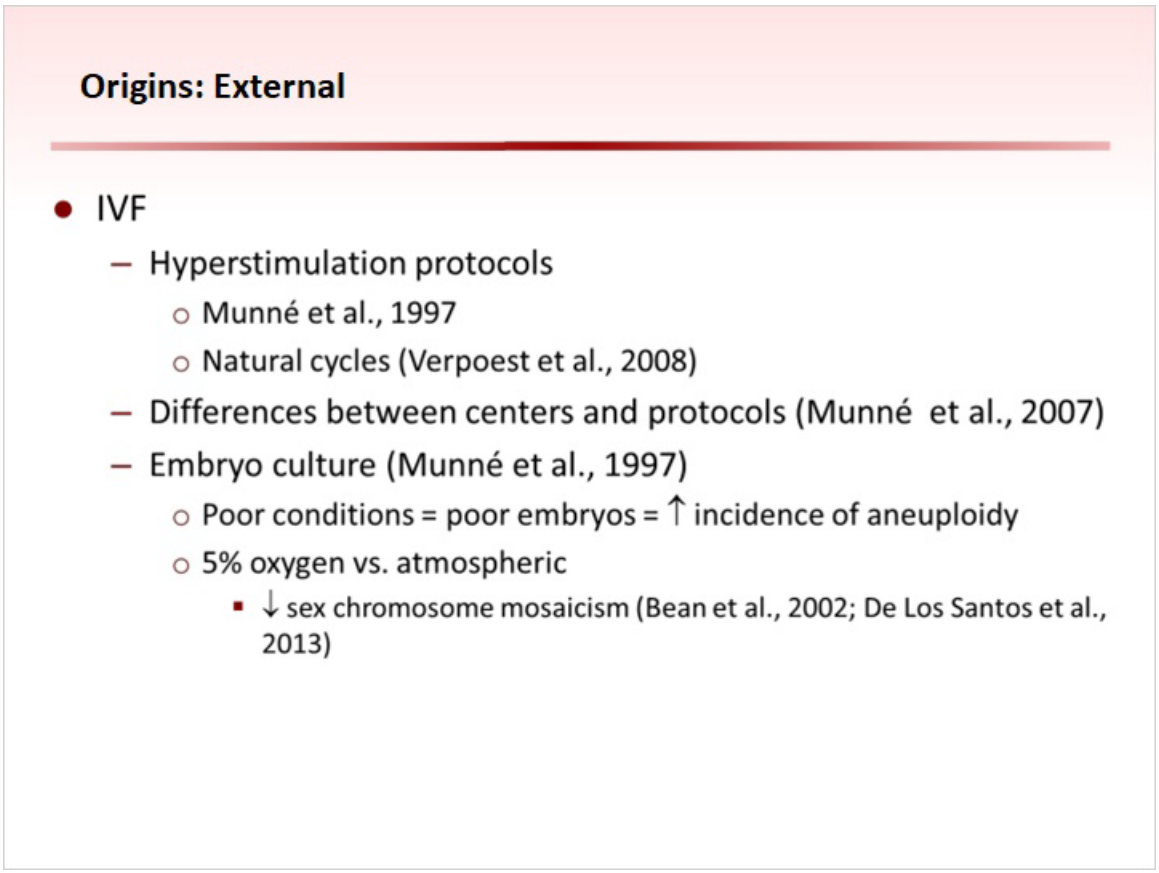


Notes:

Oocytes have been arrested at prophase since prenatal development. As women age, so too does the oocyte's length of exposure to reactive oxygen species (ROS) and environmental factors that may have negative effects during embryological development. An increase in maternal age correlates to a loss in cohesion that is responsible for binding the sister chromatids together. If cohesion is decreased in older women, this could cause an unequal separation of chromosomes leading to aneuploidy. Further, genes necessary for mitosis are down-regulated in fibroblasts from older patients when compared with younger ones. Abnormally shaped meiotic spindles seem to be more prevalent in older women compared with younger women. Although the meiotic spindle does not directly influence mitotic chromosome segregation, perhaps the presence of an abnormal meiotic spindle suggests that the process of chromosome segregation is flawed from the onset. Lastly, studies have shown an increase in mitotic spindle abnormalities in arrested and poor quality embryos compared with blastocysts. If abnormal mitotic spindles are present within the human embryo, then one would expect a higher incidence of mosaicism. Aneuploidy has also been shown to be prominent in young and fertile women (Munne et al., 2006; Baart et al., 2006; Fragouli et al., 2009; Ata et al., 2012). This would indicate that aneuploidy and possibly

mosaicism may be a pathological phenomenon during human preimplantation development.

1.29 Origins: External

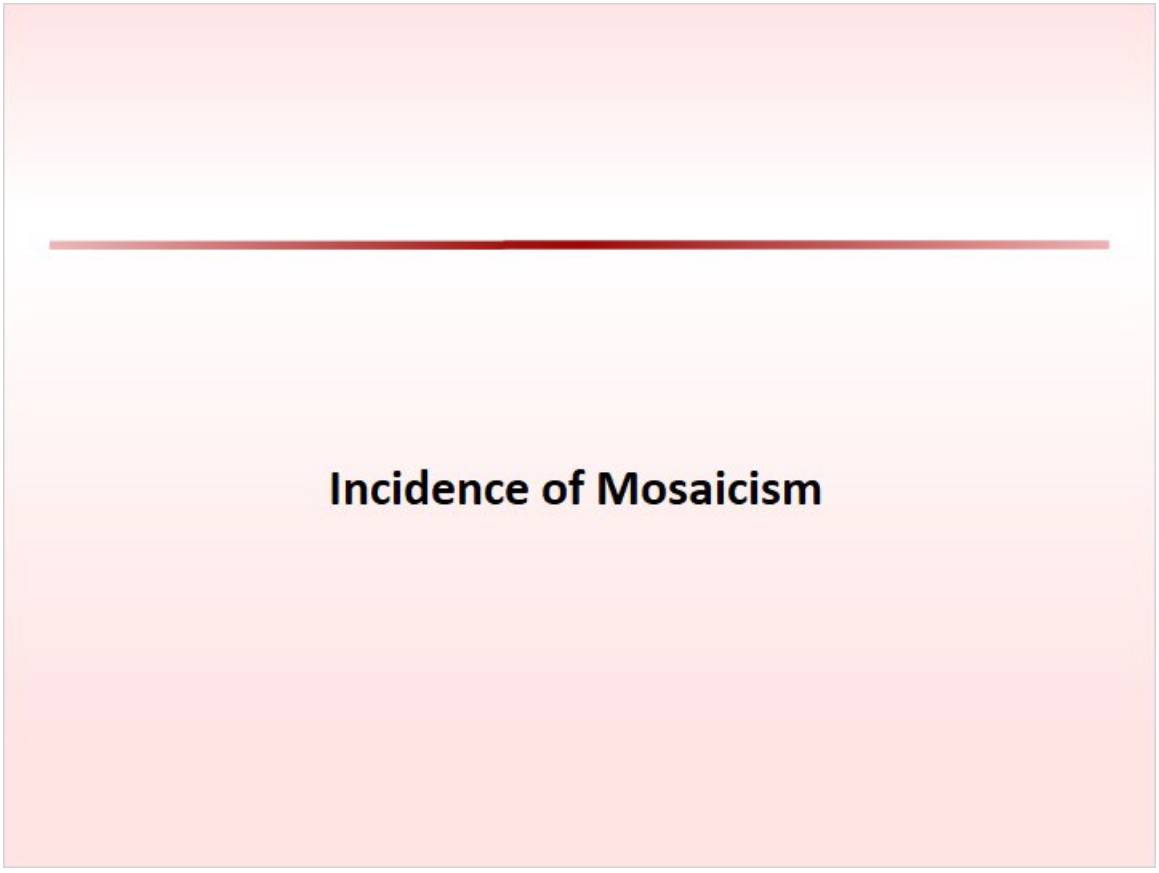


Notes:

External factors also contribute to mosaicism. For example, the production of oocytes for IVF requires the stimulation of ovaries by follicle-stimulating hormone (FSH). Hyperstimulation has been implicated in increased rates of cleavage-stage aneuploidy. Research shows, however, that even embryos derived from unstimulated ovaries produce similar rates of chromosomal aneuploidies. Munne and colleagues (1997) demonstrated different mosaicism rates between IVF centers, suggesting different stimulation protocols as a potential reason. Improper culture conditions may influence mosaicism and lead to compromised embryo quality. Bean and colleagues found that embryo culture in 5% oxygen as opposed to atmospheric oxygen levels improved embryo quality and decreased sex chromosome mosaicism. Proper embryo culture is essential for embryo development, and poorer quality embryos tend to have higher rates of chromosomal abnormalities (Munne et al., 2007). Thus, it is plausible to

conclude that embryo culture may increase aneuploidy and subsequent mosaicism in the human preimplantation embryo (Beyer et al., 2009). However, one could argue that in vitro blastocysts have lower rates of aneuploidy when compared with cleavage-stage embryos (Fragouli et al., 2013). Although accurate, embryos that develop to the blastocyst stage have progressed further than cleavage-stage embryos, and the culture media may have less of an effect on chromosome segregation within those embryos that develop to the blastocyst stage.

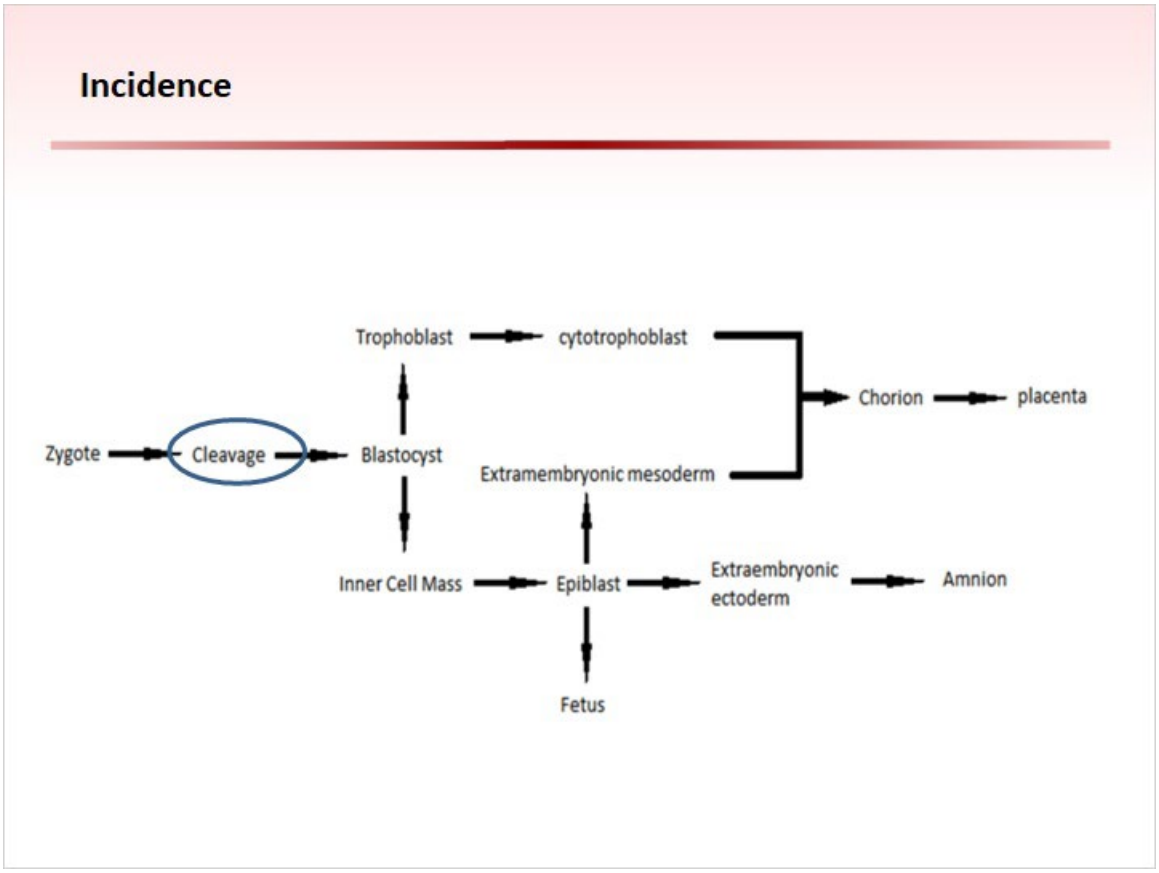
1.30 Incidence of Mosaicism



Notes:

This section will discuss the incidence of mosaicism during human pre- and postimplantation development.

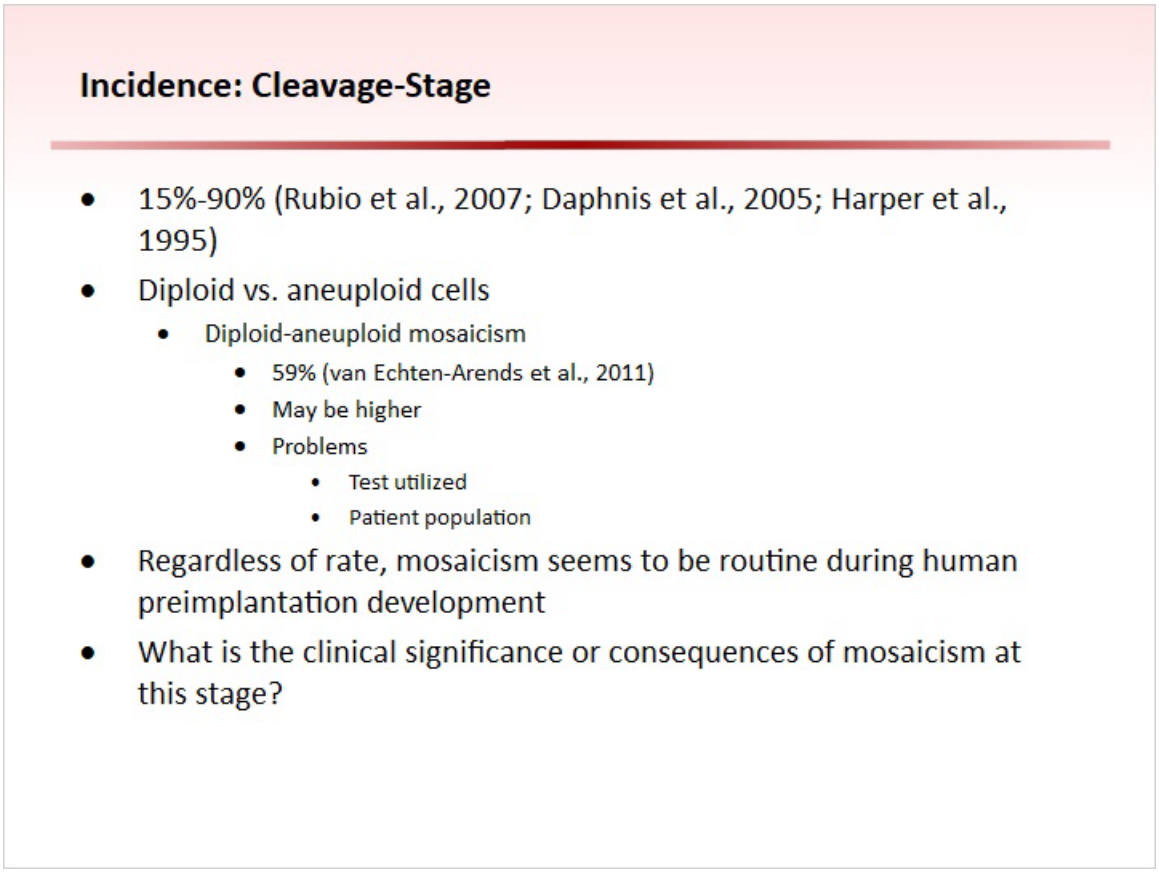
1.31 Incidence



Notes:

The first step in embryonic development to consider for the occurrence of mosaicism is the cleavage stage.

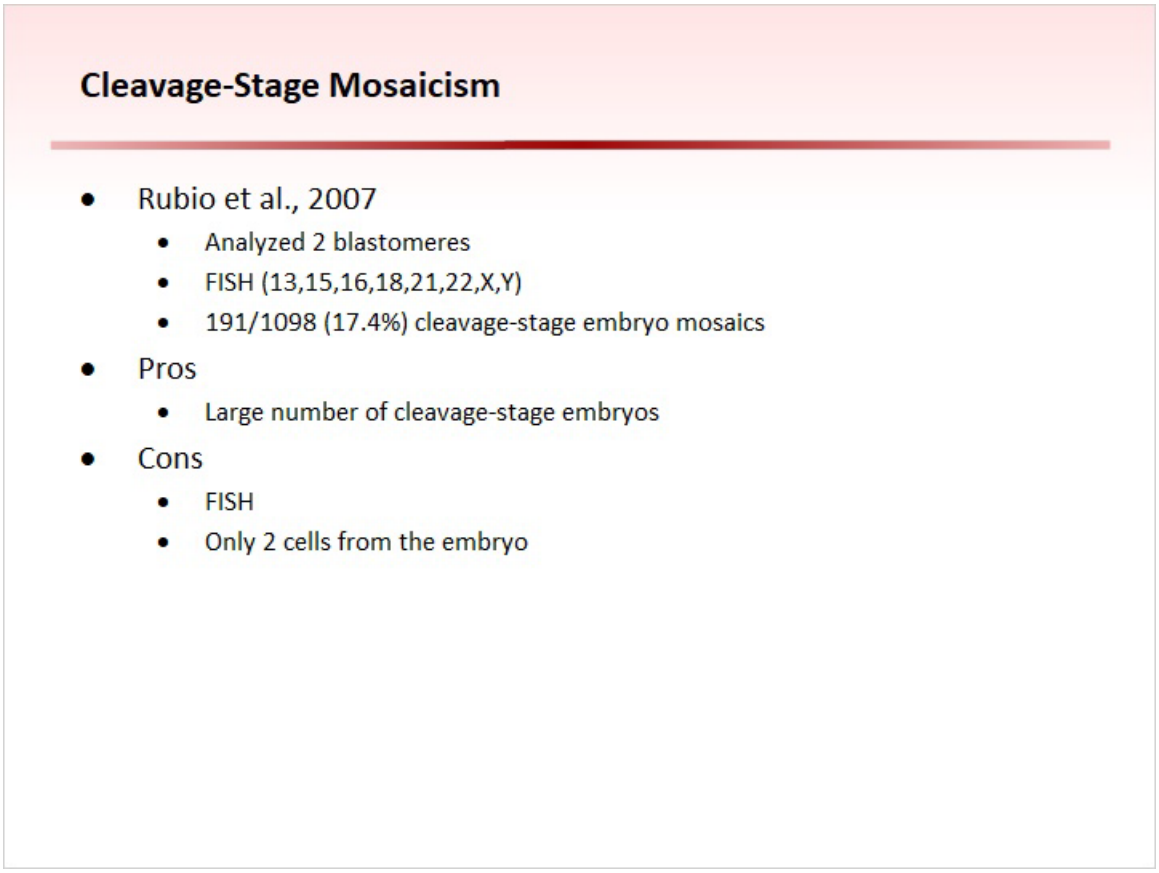
1.32 Incidence: Cleavage-Stage



Notes:

Mosaicism occurs in approximately 15%-90% of all cleavage-stage embryos. Although this is definitely a wide range, the percentage varies depending on a magnitude of variables such as maternal age, diagnosis, paternal age, what test was used to detect the abnormalities, and so on. One of the most common forms of mosaicism at the cleavage stage is diploid-aneuploid mosaicism. In essence, the embryo contains both euploid and aneuploid cell lines. Diploid-aneuploid mosaicism is believed to occur in approximately 59% of cleavage-stage embryos. Unfortunately, this percentage is based on data from a multitude of sources so the true incidence may be higher. Regardless, mosaicism seems to be routine during preimplantation development. The important question is not if mosaicism exists, but rather what is the threshold at which mosaicism becomes clinically relevant?

1.33 Cleavage-Stage Mosaicism

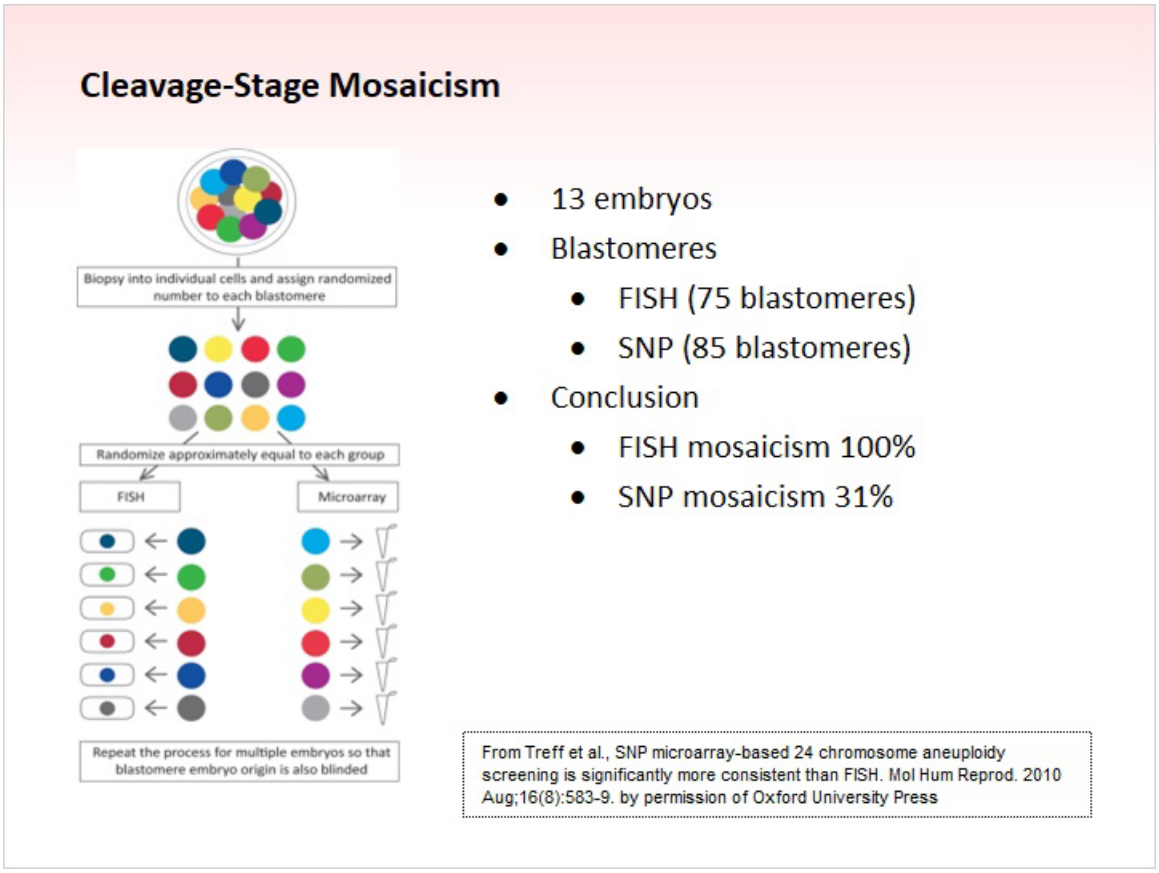


Notes:

There are numerous studies that examine cleavage-stage mosaicism; two will be covered here.

Rubio et al., (2007) examined 2 blastomeres from cleavage-stage embryos. Utilizing FISH for 8 chromosomes, they demonstrated approximately 17% mosaic rate. Although this study contained a large sample size, it was limited by the FISH and only examining 2 cells from the embryo. The mosaicism rate might have been higher if more chromosomes were incorporated or if more cells were analyzed.

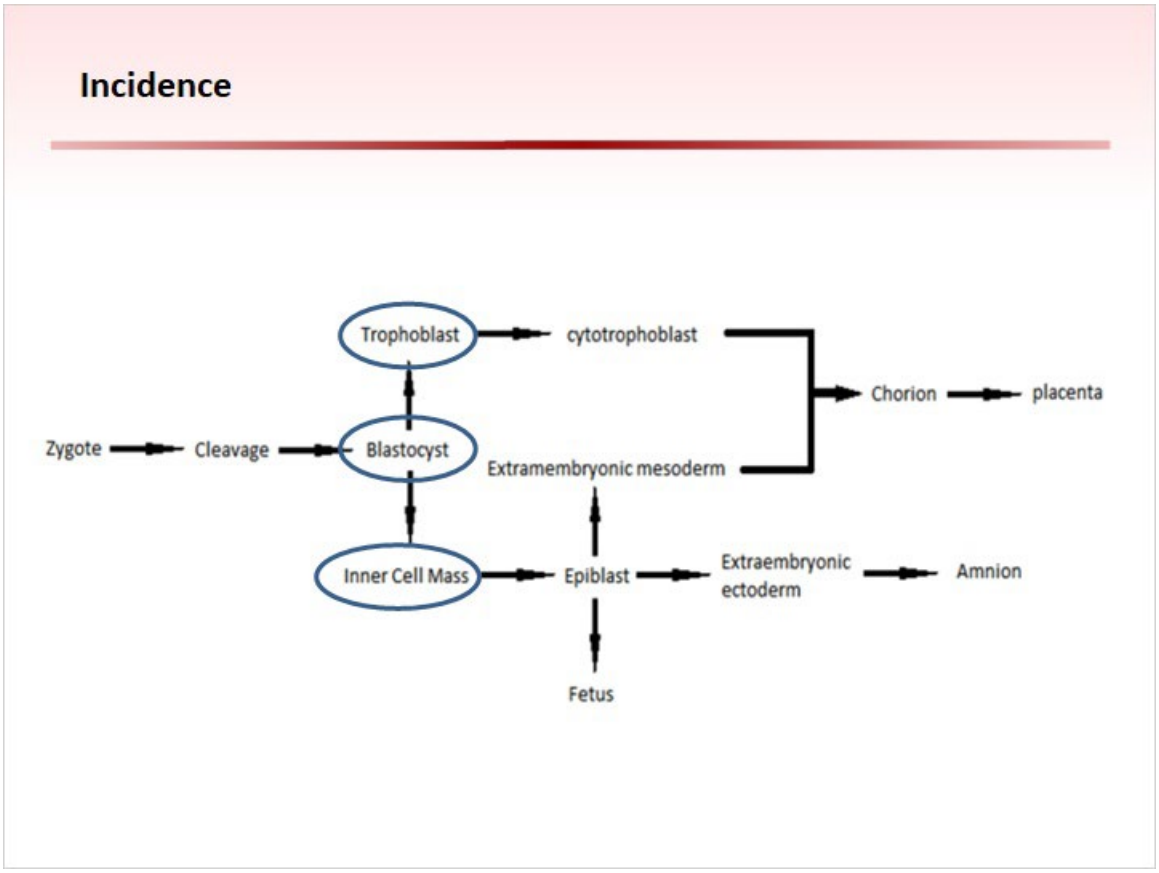
1.34 Cleavage-Stage Mosaicism



Notes:

Treff and colleagues (2010) randomized blastomeres from the same embryo to either FISH analysis or SNP microarray. They demonstrated that even though FISH examined less chromosomes than SNP, FISH found mosaicism in 100% of the embryos whereas SNP only found mosaicism in a approximately one-third of the embryos.

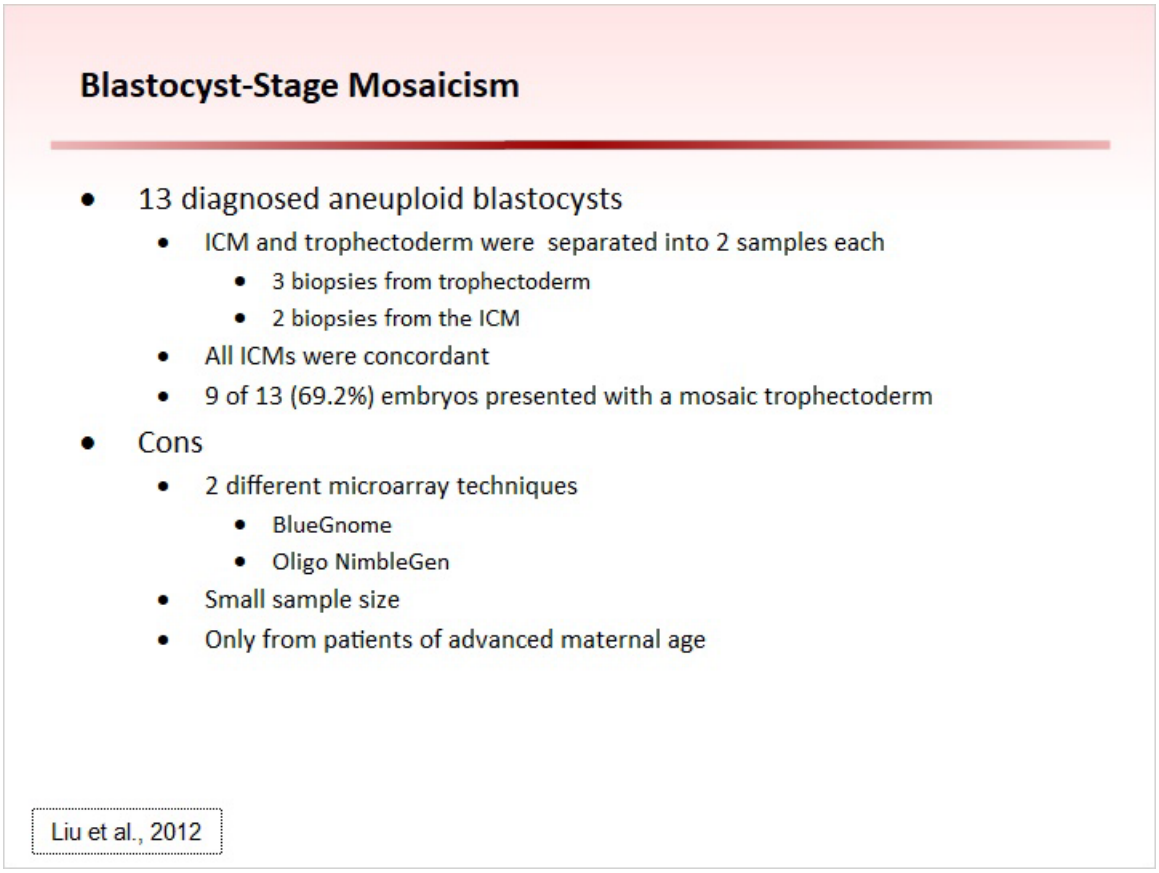
1.35 Incidence



Notes:

The blastocyst stage follows the cleavage stage. The blastocyst stage represents the first cellular differentiation into the trophoblast (which will become the placenta) and the inner cell mass (which will become the fetus).

1.36 Blastocyst-Stage Mosaicism

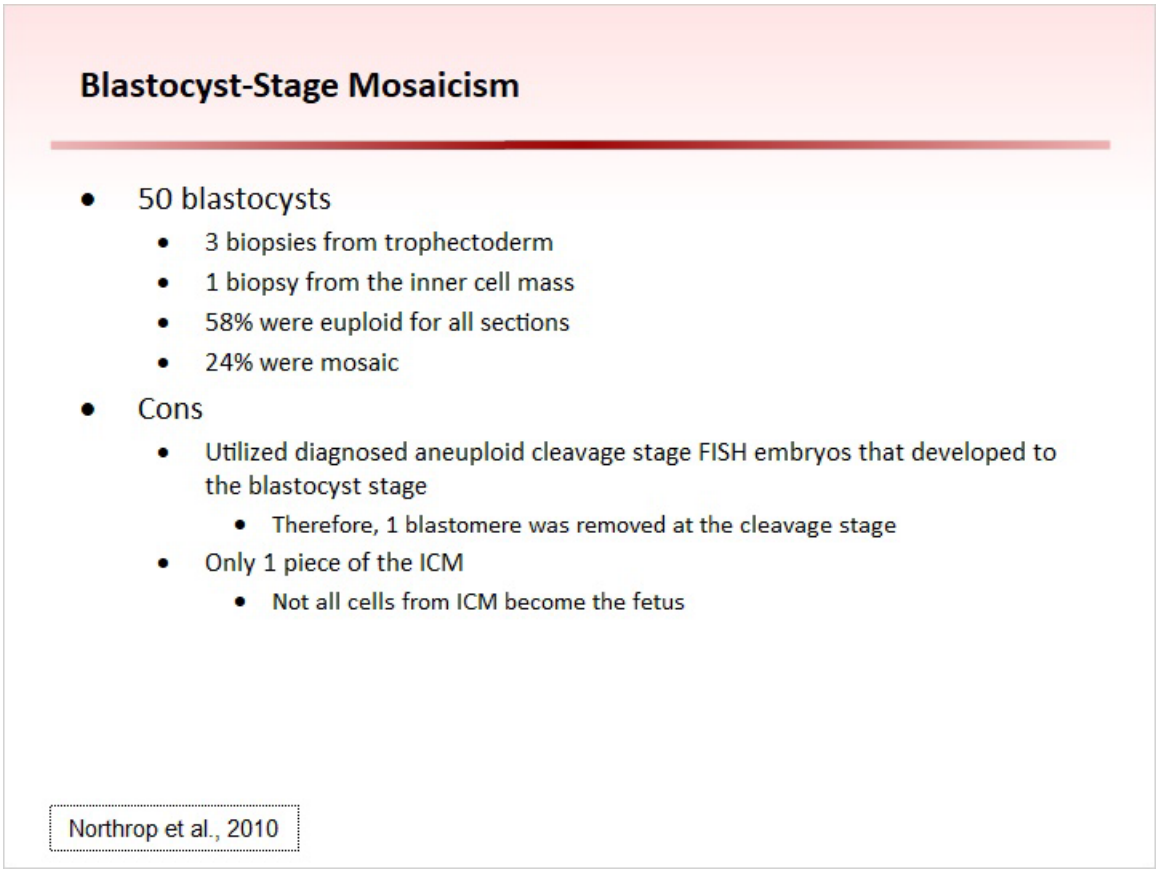


Notes:

Again, there are numerous studies that examine blastocyst-stage mosaicism and two will be examined here.

A study by Liu and colleagues (2012) utilized 13 previously diagnosed aneuploid blastocysts. This group rebiopsied the aneuploid blastocysts and ran 2 more trophectoderm samples and 2 ICM samples from each embryo. Therefore, there were 3 trophectoderm samples and 2 ICM samples from each embryo. All the ICMs produced identical results whereas 9 of 13 embryos were diagnosed as mosaic within the trophectoderm. Although this study utilized comprehensive chromosome screening, it was small in size and only included blastocysts from patients of advanced maternal age.

1.37 Blastocyst-Stage Mosaicism



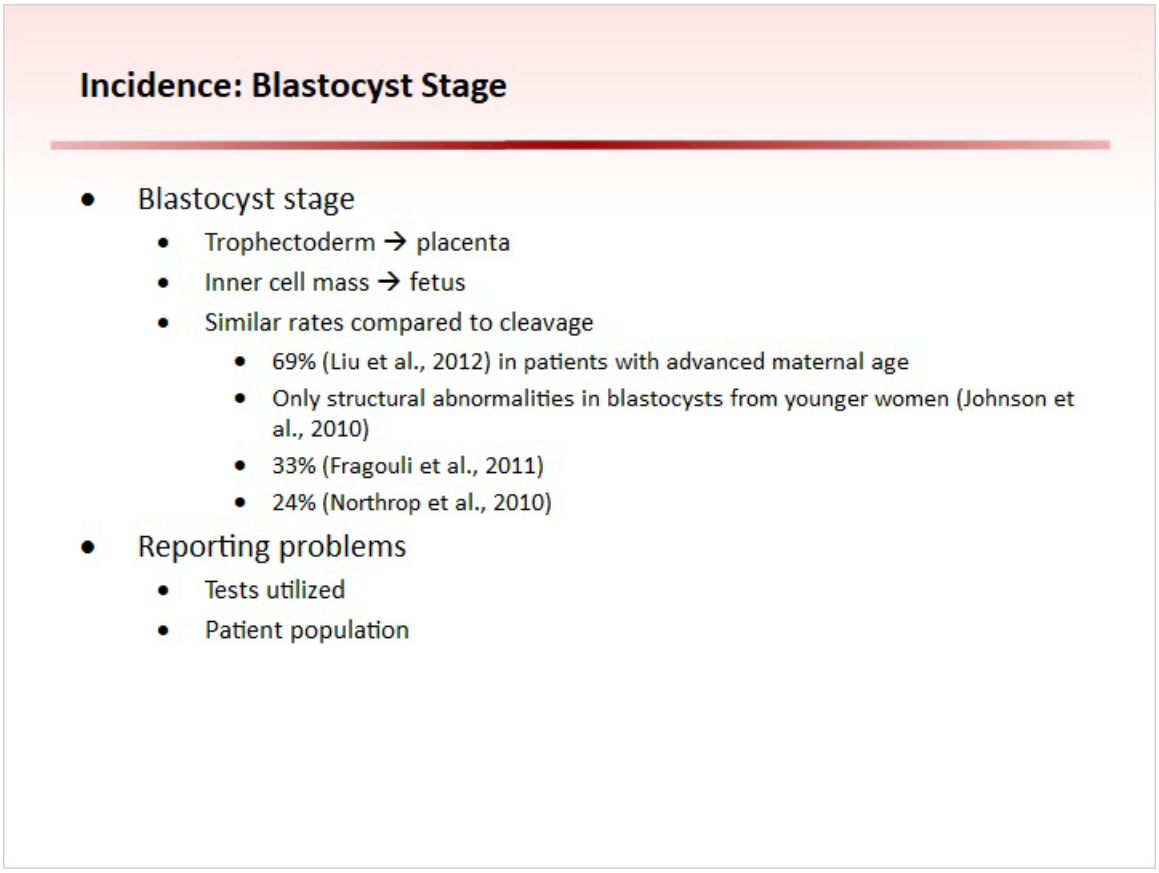
Notes:

Another study utilized blastocysts that were previously diagnosed as aneuploid by day-3 FISH.

50 blastocysts were separated into 4 sections: 3 biopsies from the trophectoderm and 1 from the ICM. SNP microarray analysis was performed on all pieces. They demonstrated that approximately 58% of the blastocysts were euploid for all sections, while 24% were mosaic.

Although a good study, it should be noted that blastocysts diagnosed as aneuploid at the cleavage stage by FISH were used. The embryo biopsy procedure at the cleavage stage could have removed a cell that could have propagated and influenced the chromosomal makeup of the blastocysts. Furthermore, not all the cells from the ICM become the fetus; therefore, it may be possible that aneuploid cell lines still exist within the ICM even though it is diagnosed as euploid.

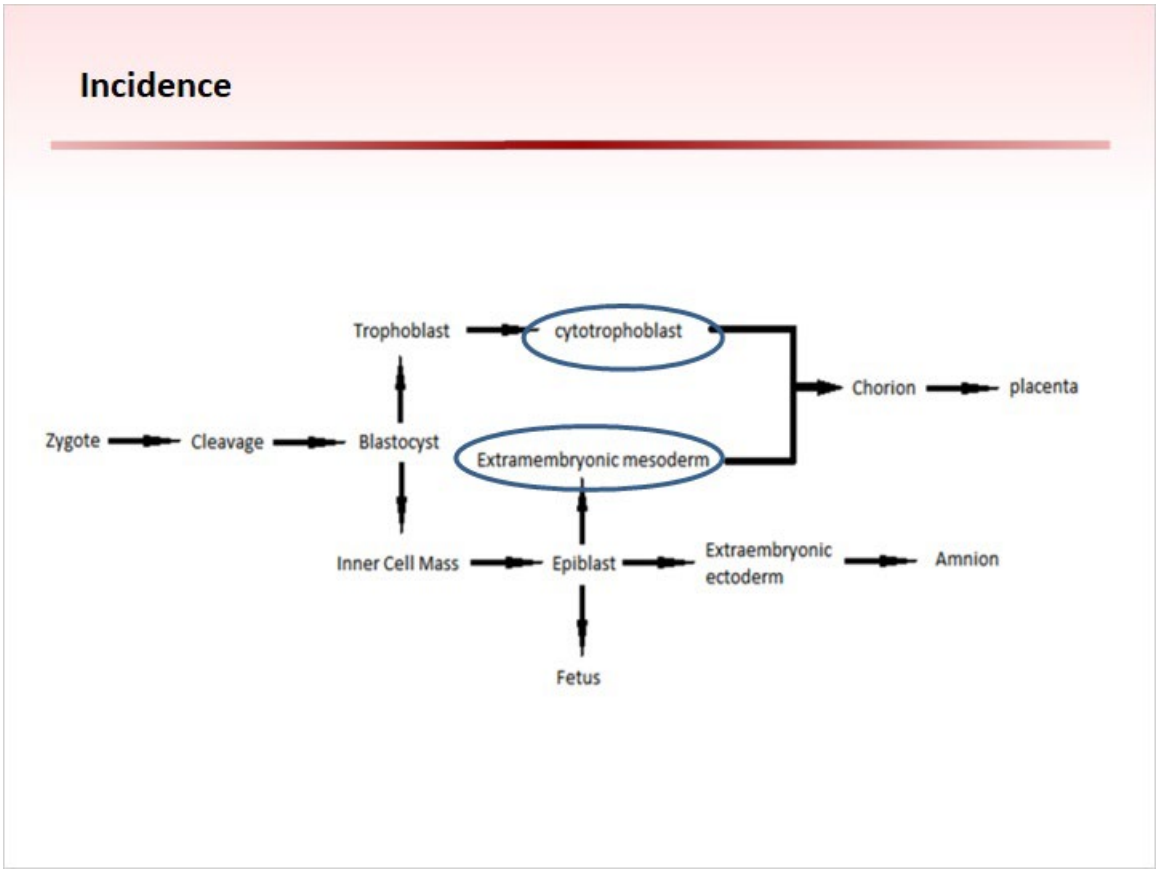
1.38 Incidence: Blastocyst Stage



Notes:

It is possible that the mosaic cell lines will be contained to either the trophoblast or the inner cell mass, making the 2 nonconcordant. However, research has indicated that this is not the case and at this stage of preimplantation development, the chromosome constitution of the trophectoderm mirrors the inner cell mass. Numerous studies report varying rates of mosaicism at the blastocyst stage. More than likely, this is due to the differences in the tests utilized and patient populations.

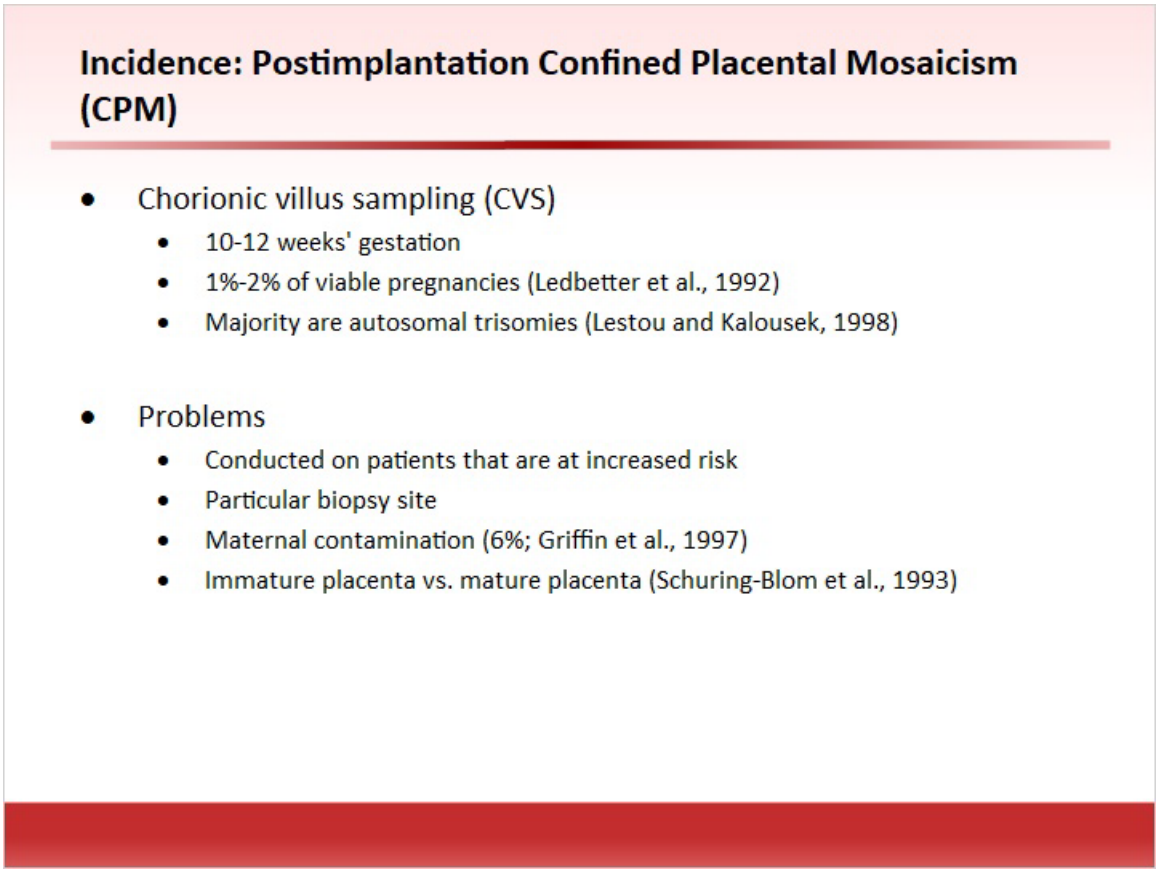
1.39 Incidence



Notes:

Next is a discussion of the incidence of mosaicism in postimplantation development. Specifically 2 different tissues will be examined: the cytotrophoblast, which is derived from the trophoblast, and the extraembryonic mesoderm, which is derived from the inner cell mass.

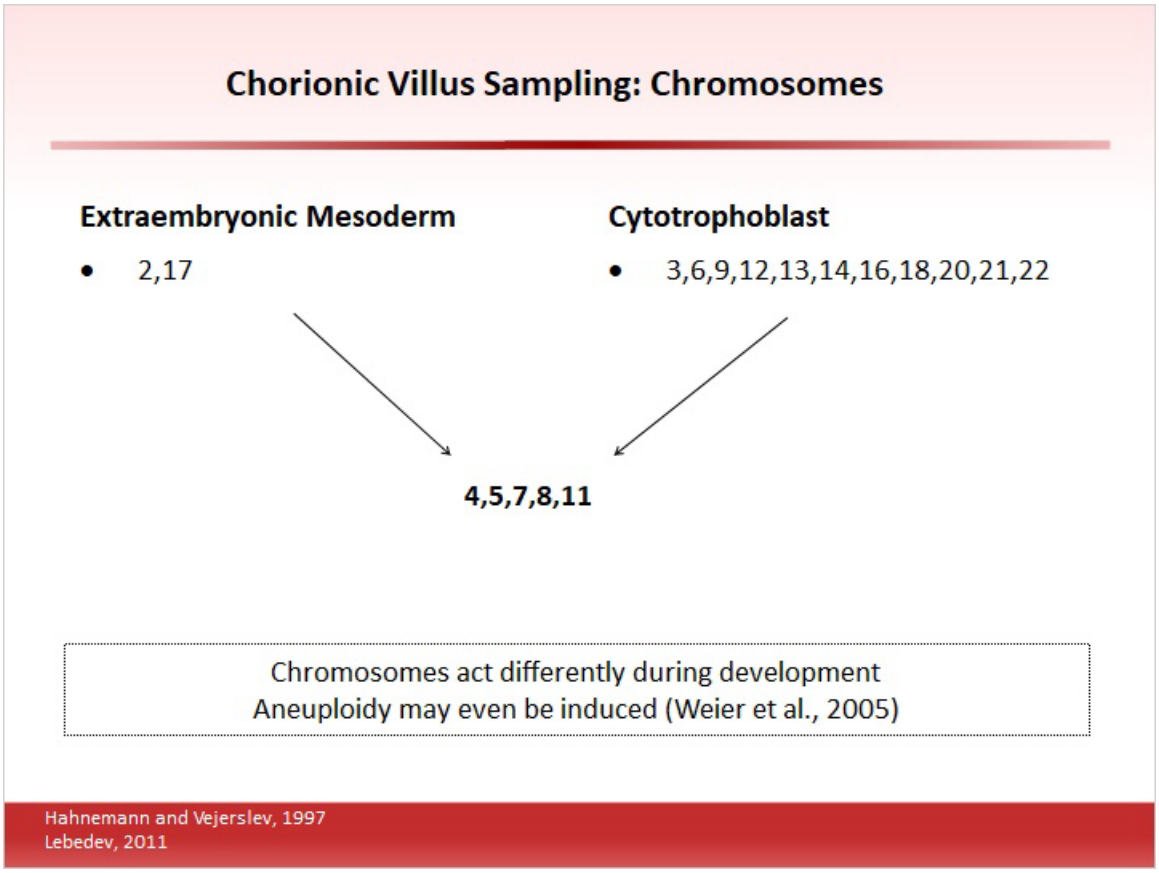
1.40 Incidence: Postimplantation Confined Placental Mosaicism (CPM)



Notes:

Confined placental mosaicism is detected via sampling of the chorionic villus typically at 10-12 weeks' gestation and is present in roughly 1%-2% of all viable pregnancies. The majority of autosomal abnormalities present as trisomies. The problem with confined placental mosaicism is that CVS is typically conducted on patients at an increased risk for abnormalities; therefore, there is bias in the patient population. Furthermore, the chorionic villus is sampled from a particular site, so the mosaic cell line could be present at that site and not others. Maternal contamination occurs in roughly 6% of all CVS samples. Also, as previously mentioned, CVS is done at 10-12 weeks' gestation when the placenta is not yet fully mature. An immature placenta may not be representative of the mature placenta.

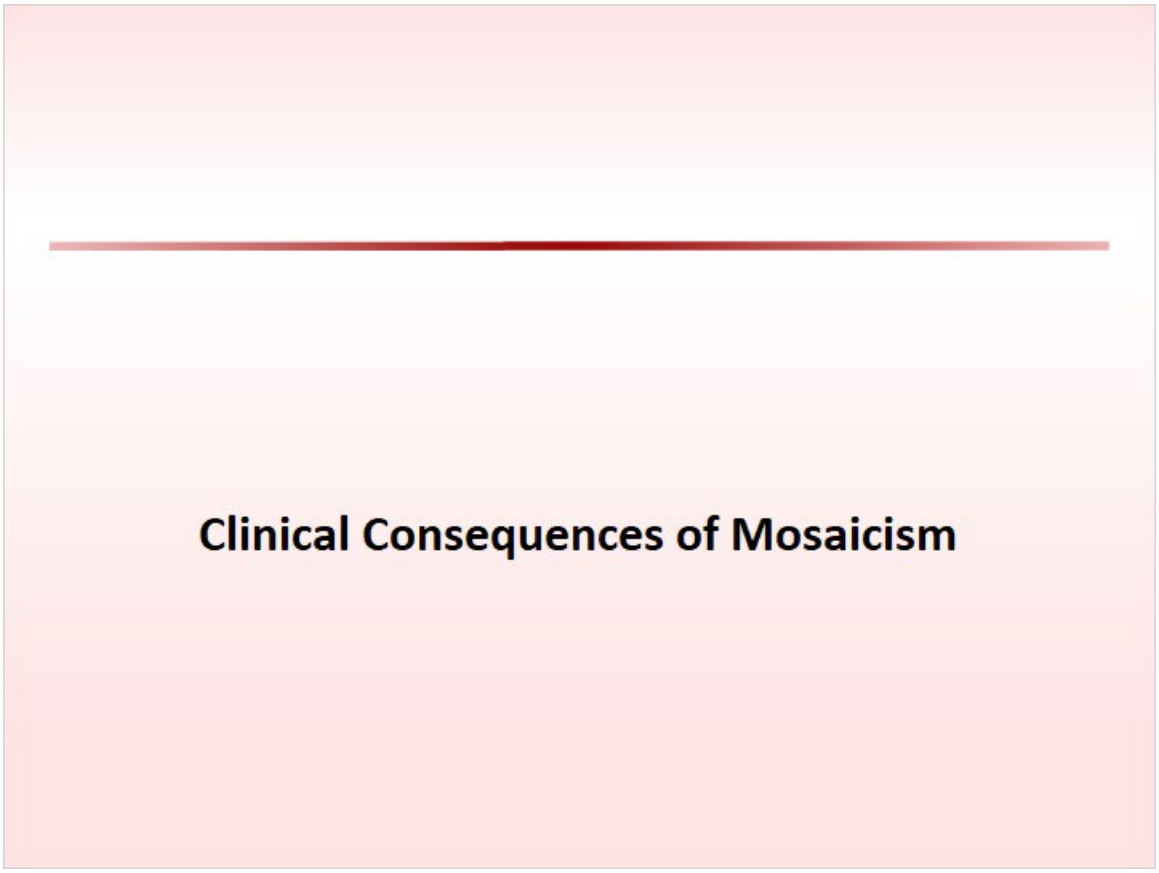
1.41 Chorionic Villus Sampling: Chromosomes



Notes:

CVS diagnoses chromosomal abnormalities from 2 different tissues: the extraembryonic mesoderm and cytotrophoblast. Evidence that chromosomes act differently during development is shown in the abnormalities within these 2 tissues. For example, in the extraembryonic mesoderm, trisomies 2 and 17 are the most prominent and in the cytotrophoblast, trisomies 3, 6, 9, 12, 13, 14, 16 ,18, 20, 21, and 22 are more prominent. Trisomies 4, 5, 7, 8, and 11 present equally between the 2 tissues. Interestingly, CPM may even be induced, indicating that postimplantation mosaicism may be routine and necessary for proper development.

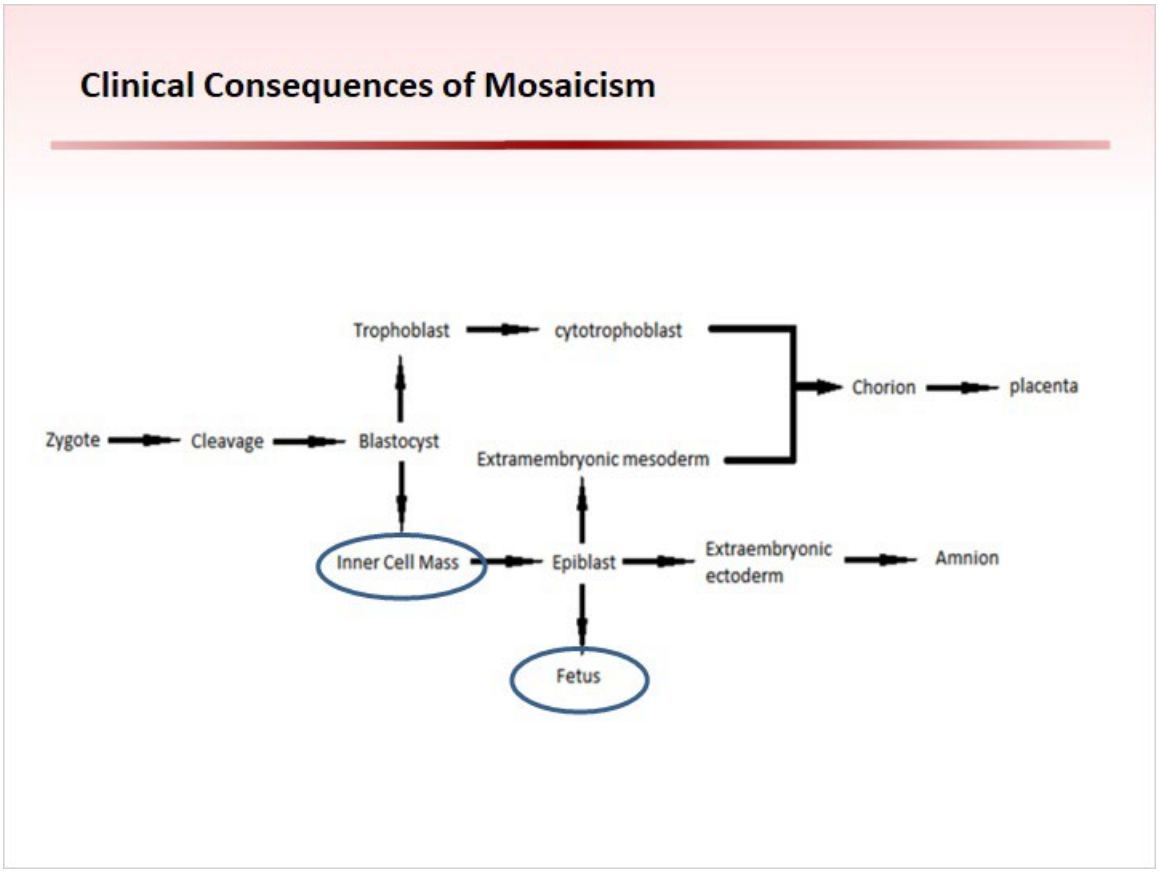
1.42 Clinical Consequences of Mosaicism



Notes:

This section will discuss when mosaicism is clinically relevant.

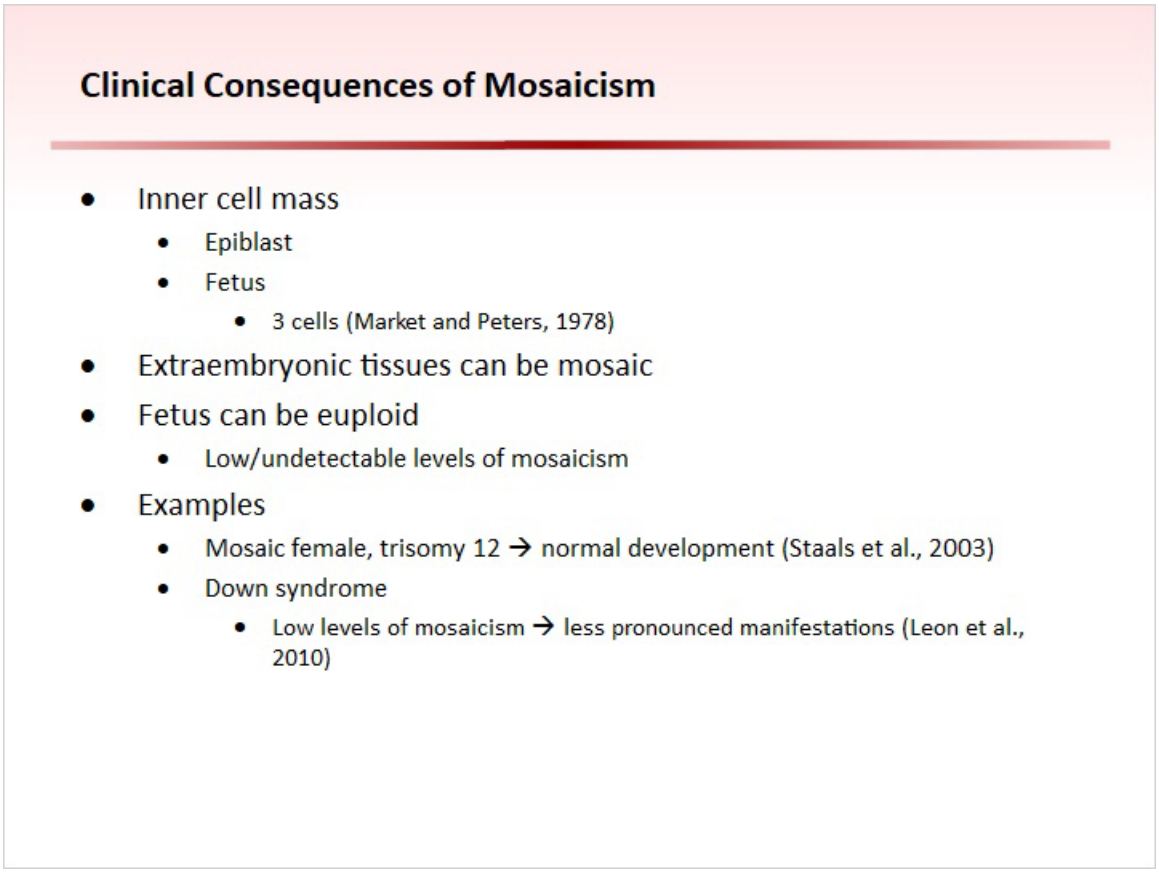
1.43 Clinical Consequences of Mosaicism



Notes:

The goal of assisted reproduction is a single euploid live birth. The goal of genetic testing is to determine the chromosomal constitution of the fetus. Although the fetus is derived from the inner cell mass, mosaicism in the trophoblast, cytotrophoblast, and placenta can affect the fetus.

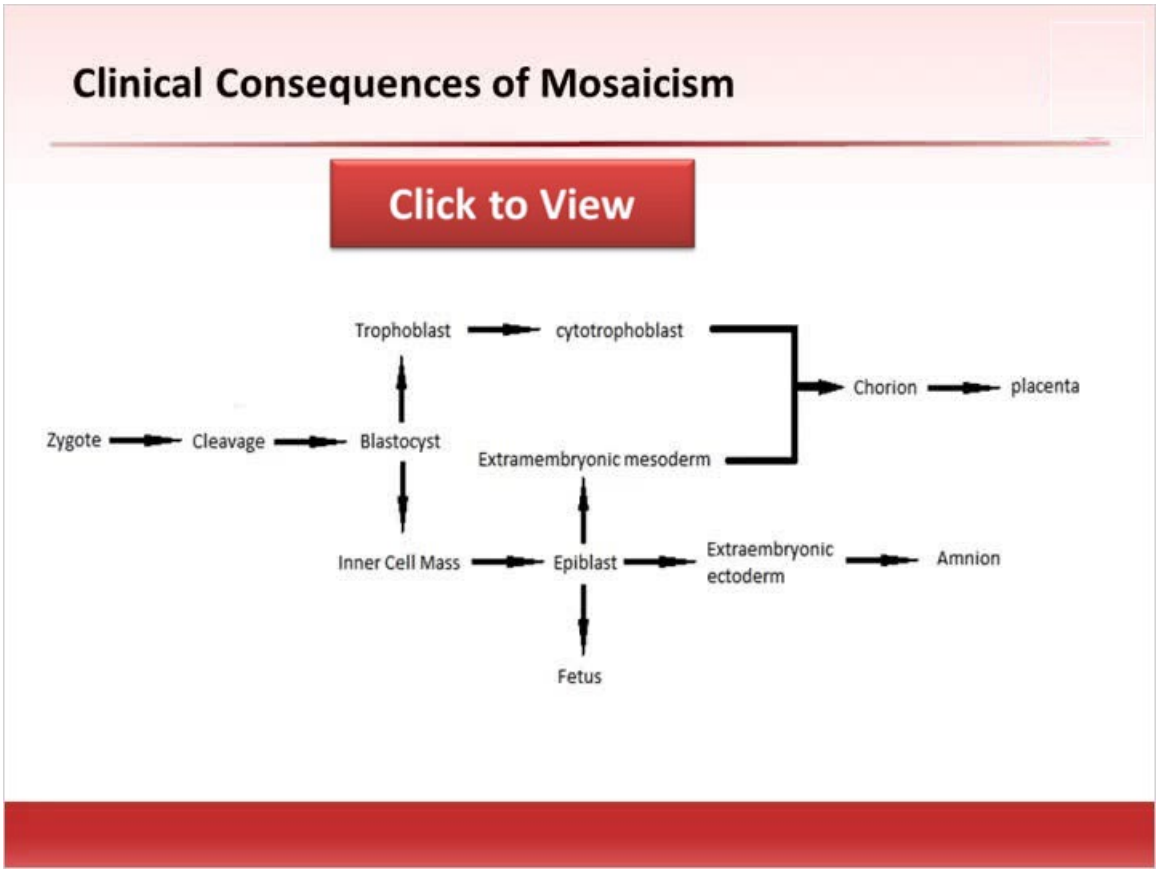
1.44 Clinical Consequences of Mosaicism



Notes:

The inner cell mass further differentiates into the epiblast and fetus. Research in the mouse has shown that the fetus is derived from as little as 3 cells. It is entirely possible that the extraembryonic tissues can be mosaic and the fetus remains euploid. Similarly, the fetus can present as phenotypically euploid but may contain low to undetectable levels of mosaicism. Examples of this include a case in which a mosaic trisomy 12 female presented with normal development. Also, patients who present as mosaic trisomy 21 (therefore, they are a general mosaic) have less pronounced manifestations than patients with nonmosaic trisomy 21.

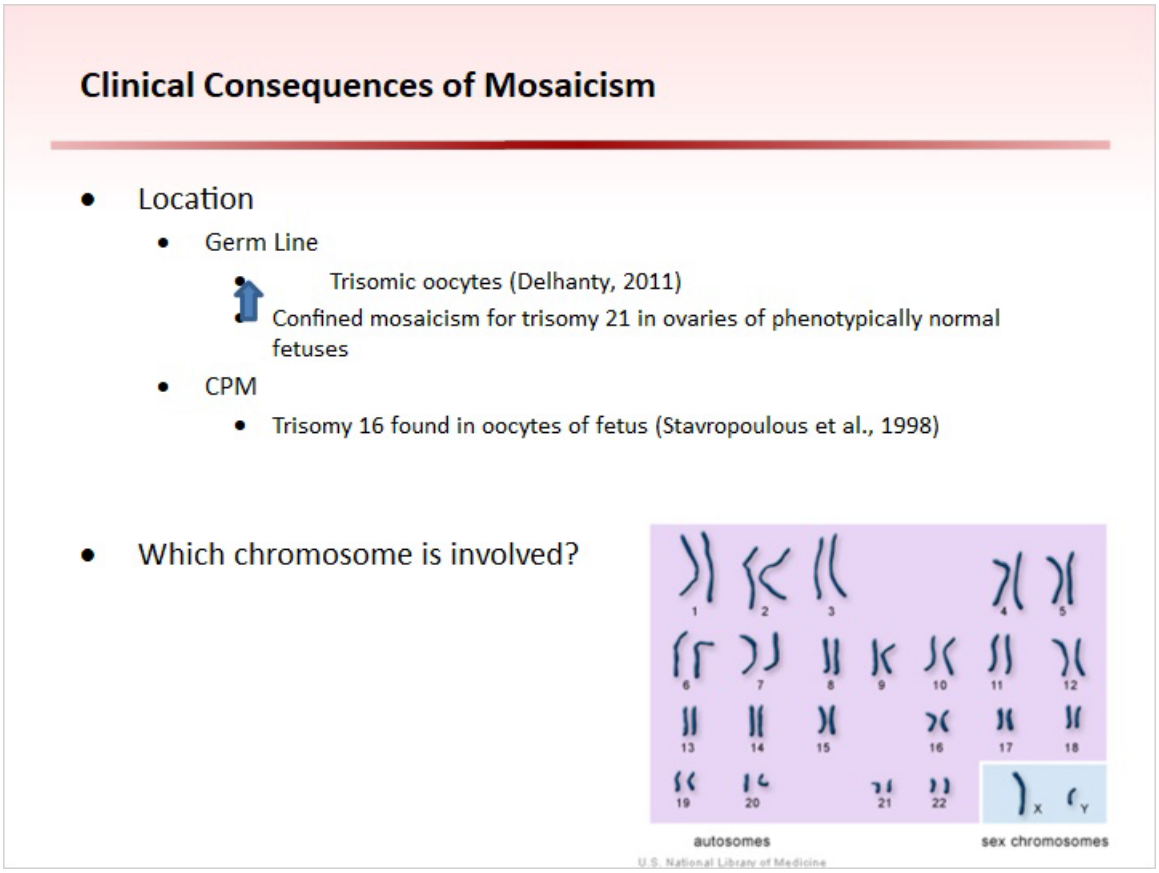
1.45 Clinical Consequences of Mosaicism



Notes:

So not only does the sheer number of mosaic cell lines play a role in the clinical consequences of mosaicism but also where and when the mosaic cell lines establish themselves. For example, if the aneuploid cell line establishes itself at the cleavage stage, then it is possible that it will propagate throughout the entire pregnancy. If the aneuploid cell line is established in the trophoblast, then it is possible that the fetus will remain euploid while the cytotrophoblast, chorion, and placenta will be aneuploid (hence confined placental mosaicism with a euploid fetus). Likewise, the inner cell mass can present with an aneuploid cell line that could propagate throughout the epiblast, fetus, and placenta. There may be mechanisms at each differentiation that prevent or support specific cell lines from propagating.

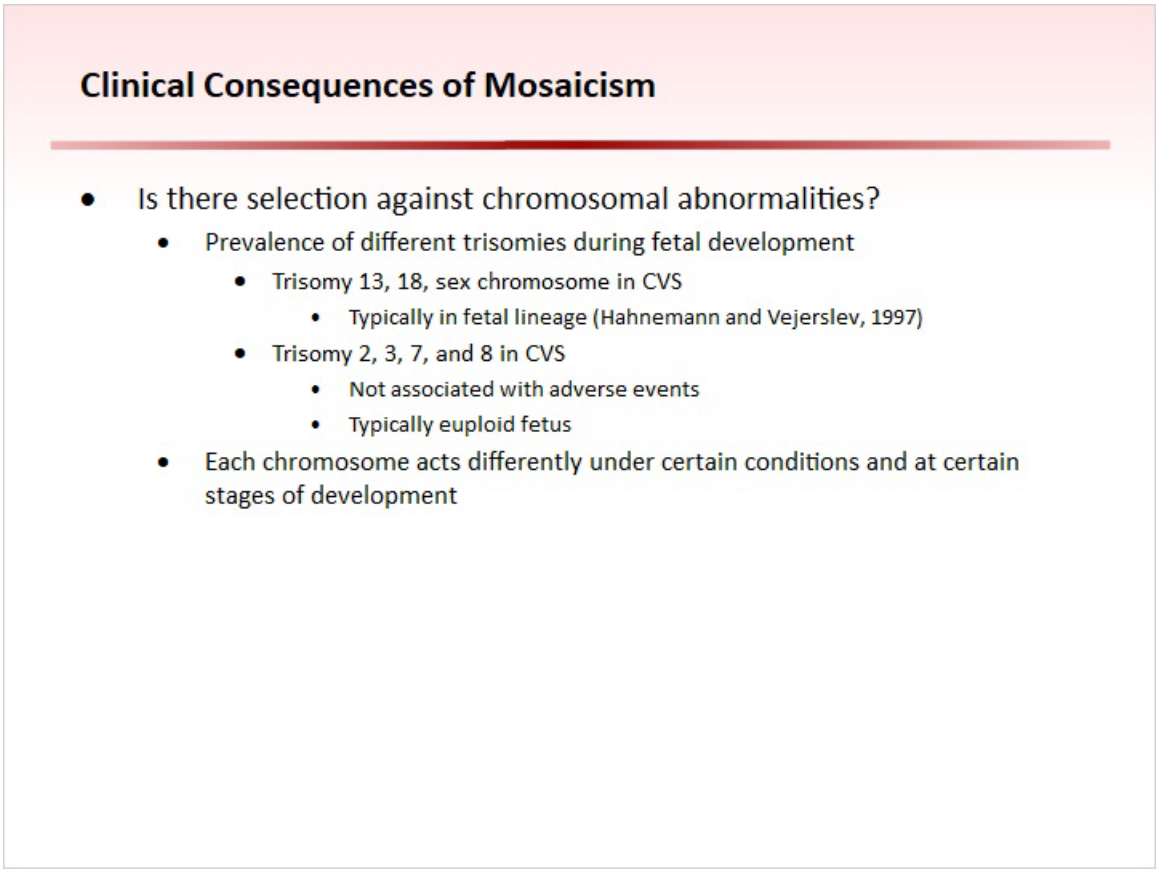
1.46 Clinical Consequences of Mosaicism



Notes:

The specific location of the mosaic cell line can also influence the consequences of mosaicism. There have been reports of an increase in trisomic oocytes from germ line mosaicism (mosaicism confined to ovaries). Reports also exist of a trisomy 21 cell line confined to the ovaries of an otherwise phenotypically normal fetus. If this were the case, the clinical consequences of the mosaic cell line could influence the next generation (by creating a fetus predisposed to Down syndrome). Along those same lines, trisomy 16 has been found in oocytes of a euploid fetus that presented with confined placental mosaicism. As one can see, the consequences are widespread and are dependent upon which stage the mosaic cell line takes hold and which chromosome(s) are involved.

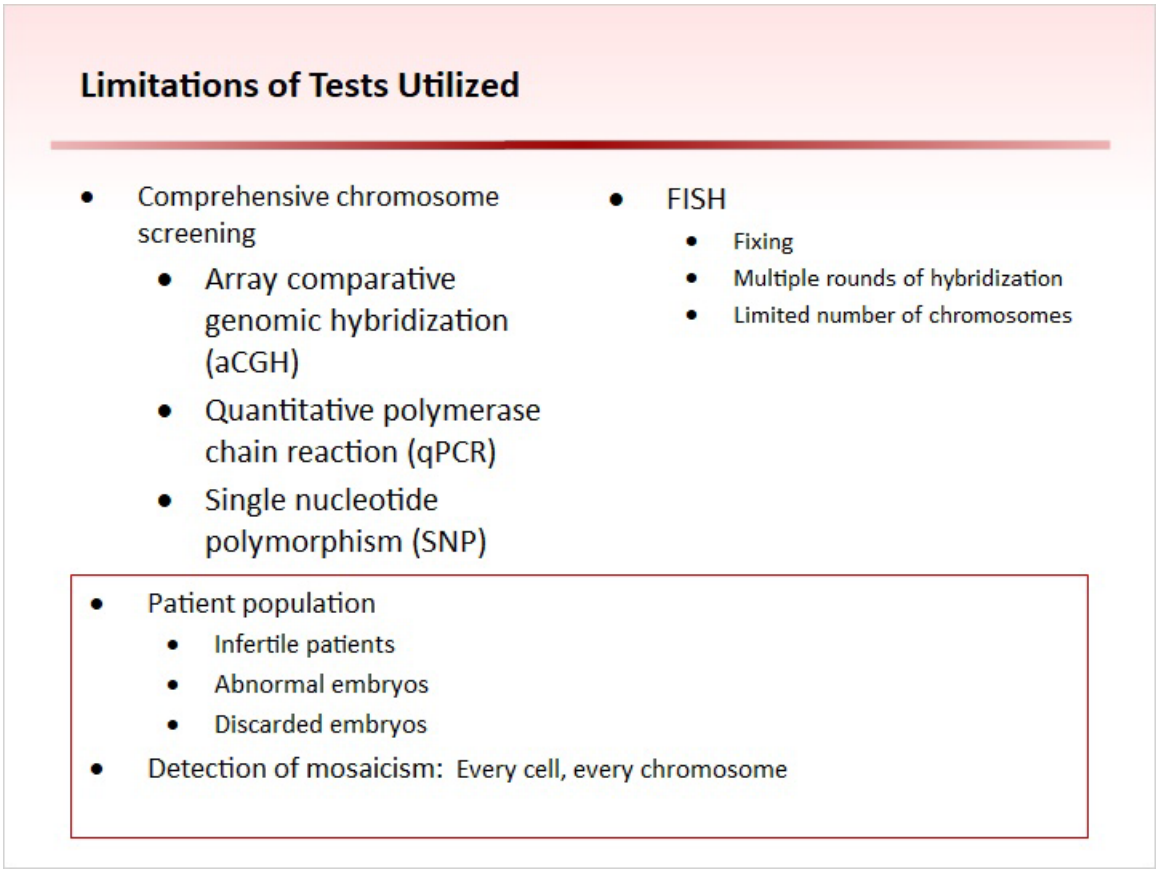
1.47 Clinical Consequences of Mosaicism



Notes:

The key here is that the clinical consequences of mosaicism are different for each and every incidence. Indeed there are mosaic cell lines that do not present with clinical consequences. For example, during CVS, if trisomy 13, 18, or sex chromosome abnormalities are detected, these will typically be present in the fetus as well. If trisomy 2, 3, 7, and 8 are present in the CVS, this is typically not associated with any clinical consequences and the fetus is usually euploid. Therefore, mosaicism may not always have a clinical consequence. In essence, each chromosome acts differently under certain conditions and at certain stages of development and it may even be patient specific.

1.48 Limitations of Tests Utilized



Notes:

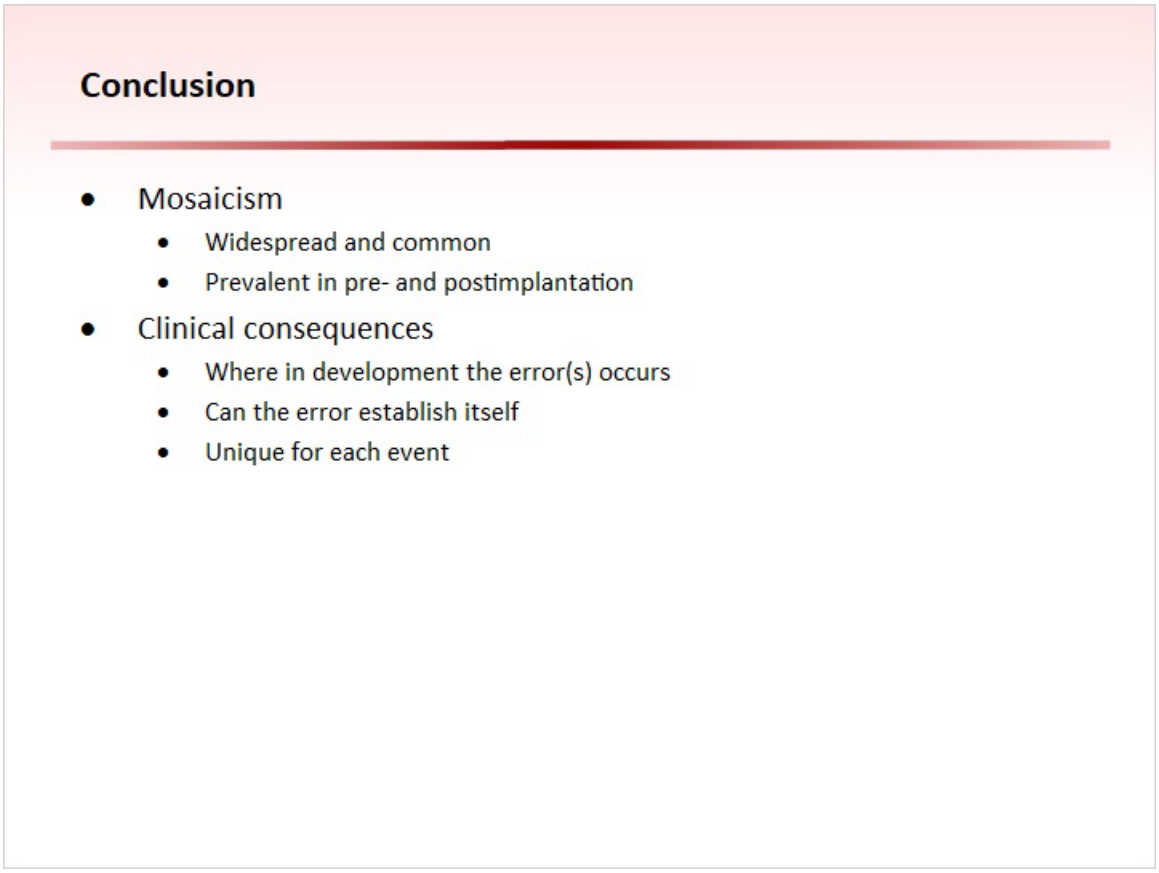
Although this module discusses chromosomal mosaicism in humans, there are some points to keep in mind. First, it is important to consider what test is being used to detect the chromosomes, as each test has its own limitations. For example, FISH requires fixing the nucleus to a slide. The nucleus can become lost or fragmented during the fixing process, possibly losing chromosomes. Also, to add chromosomes, rounds of hybridization are needed. Each round of hybridization increases the number of chromosomes analyzed and also increases the error rate of the procedure. Lastly, FISH is limited to a certain number of chromosomes, although 24-chromosome FISH has been reported. There are 3 different comprehensive chromosome screening techniques: array comparative genomic hybridization (aCGH), quantitative polymerase chain reaction (qPCR), and single nucleotide polymorphism (SNP). Each technique has its own pros and cons.

Another limitation is that knowledge gained from studies in infertile patients is inferred to the general, fertile population. Also, research material is difficult to come by, so embryos diagnosed as abnormal or discarded are typically utilized. This presents its own problems as these embryos are typically of poor quality. Do results obtained from

studies utilizing poor quality embryos from infertile patients relate to the general, fertile population?

Lastly, in order to determine which mechanism is used to generate mosaicism, every cell and every chromosome must be examined. Obviously this is not possible without destroying the embryo. Knowledge of chromosomes, specifically during pre- and postimplantation, is hindered by numerous variables.

1.49 Conclusion



Notes:

In conclusion, mosaicism is widespread and common in humans, and is specifically prevalent in pre- and postimplantation development. The clinical consequences of mosaicism depend on where and when the error(s) occurs during development and if the error can establish itself. Indeed, the clinical consequences are unique for each event and circumstance.

1.50 Thank you!

Notes:

Thank you for participating in this educational activity.