The ultrasound detection of chromosomal anomalies[1]

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Introduction

In a previous chapter (Fetal syndrome) we have reviewed several syndromes, a majority of which could be traced to genetic anomalies. In this chapter we will review syndromes and their associated findings that are due to chromosomal anomalies. Many references will be to a few standard textbooks[4,5,6,7,8,9,10] and sources[11, 12] that will not be repeated at each occurrence since these are considered basic and should be part of everyone library or tool.

Graph 1 represents the increase in frequency of aneuploidy with maternal age[13,14]. After 35 years of age the risk increase steeply not only for trisomy 21 but also for other aneuploidies in general. Some chromosomal anomalies are increased with the maternal age, and these include trisomy 13, trisomy 18 and trisomy 21, but not all chromosomal anomalies are increased with maternal age, and in particular triploidy and most of the sex chromosomal aneuploidies do not increased with maternal age.

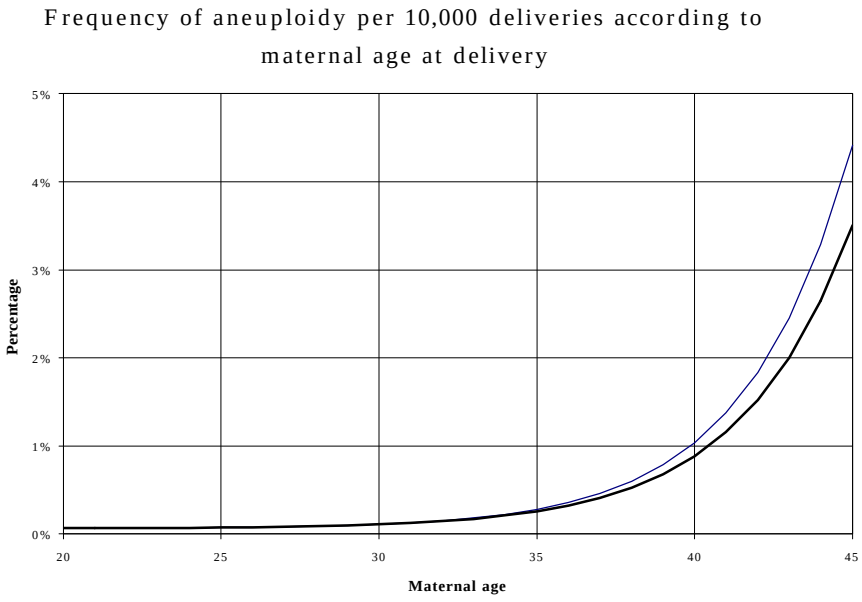

Figure 1: Frequency of aneuploidy per 10,000 deliveries according to maternal age at delivery (Adapted from [13] and [14]).

Fetuses that have structural anomalies often also have chromosomal anomalies. Wladimiroff[15] and Palmer[16] have demonstrated that between 10 and 30% of fetuses that have structural anomalies also have chromosomal anomalies. In their studies about ½ of the fetuses have a trisomy, a quarter have a monosomy, about 10-15% have a mosaic and the rest are a few triploidy and miscellaneous aneuploidies.

It has further been shown, by Nicolaides[17], that babies that have more than one anomaly are more likely to have chromosome anomalies, and this graph from his study clearly demonstrate this association.

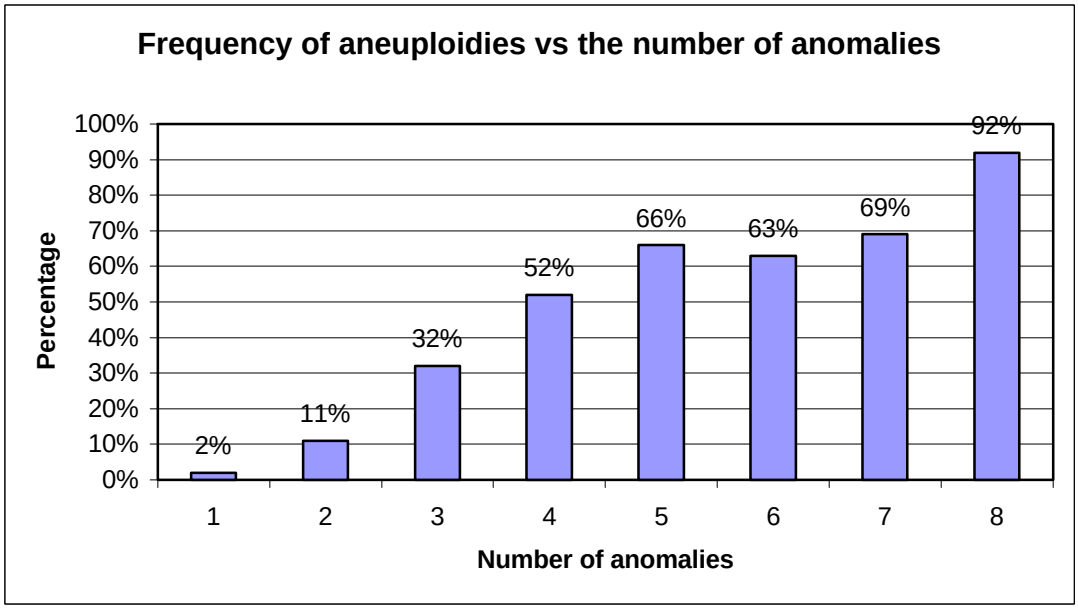

Figure 2: Frequency of aneuploidies vs the number of anomalies (Adapted from [22])

Anne Marie Plachot[18] at the INSERM in Paris, conducted a very interesting study in which she used some eggs from in vitro fertilization and tried to assess what was the frequency of chromosomal anomalies in the fertilized eggs. In her experiment 38 percent of those fertilized egg had an aneuploidy (26% were due to aneuploidy oocytes, 8% to an aneuploidy sperm, 2% to polyploidy and 6% to parthenogenesis). Yet we do not see 38% aneuploidies. So what happened to all these embryos? About a quarter them disappear and are not able to implant, and among those who implant only about half of them are able to go persist until the first trimester. Finally during the first trimester the majority of these embryos are lost to miscarriages and number decrease to about 1 percent aneuploidies in the second and third trimester.

Complementary investigations

The usual findings in aneuploidies include biochemical alterations, structural anomalies and growth restriction and we will review these topics in the next few pages. When a fetus is suspected to have an aneuploidy a karyotype is obtained either by chorionic villus sampling, amniocentesis, or fetal blood sampling. In the past we used to do echocardiography on these fetuses but now echocardiography is part of the normal examination

The triple screen

Biochemical alterations are commonly evaluated with a test called the “triple screen”. This is a maternal blood test in which maternal seric values are assessed and expressed as multiple of the median. The test tests 3 components: the alpha-fetoprotein, the beta-human chorionic gonadotropin, also called beta hCG,

and the unconjugated estriol. Abnormal combinations of these three values have predictive value in the detection of trisomy 21 and trisomy 18.

	Trisomy 21	Trisomy 18
α-fetoprotein	< 2.5 MoM	≤ 0.75 MoM
β-human-Chorionic Gonadotropin	≥ 2	≤ 0.6
Unconjugated Estriol	≤ 0.6	≤ 0.55

Figure 3 Abnormal combinations of the components of the triple screen have predictive value in the detection of trisomy 21 and trisomy 18

There are other markers that are being investigated. For instance the free beta hCG, the alpha hCG, the pregnancy associated plasma protein A or PAPPA. Other investigators are also trying to investigate urine tests, versus blood tests. Thus some report will be describing quadruple tests instead of triple tests, or other different combinations. About 5% of triple screen test are positive, of which 95% are falsely positive[19]. The triple screen test screens about 60% of trisomy 21 among women less than 35 years of age, almost a 100% for women greater than 35 years of age, 40% of the trisomy 18, 85% of the neural tube defects, and 75% of the abdominal wall defects. So that for a simple blood test one collects valuable information about the pregnancy. An important question that referring clinicians and patients will have is "How much does a normal ultrasound decreases the risk of the triple screen?". Unfortunately there is a lack of consistent data in the literature and the decrease in risk is quoted to be around 45% in David Nyberg's study[20] but around 800% in Bahado-Sing study[21]. We use the David Nyberg value when we talk to our patients. And therefore a patient that has a risk of 1:180 drops down to a risk of 1:270.

References

[1] Adapted from "The Ultrasound Detection of Chromosomal Anomalies—A multimedia Lecture" by Philippe Jeanty. ISBN (0-9667878-0-3) available at www.prenataldiagnosis.com and www.TheFetus.net
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