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Increased nuchal translucency with normal karyotype and anomaly scan: What next?

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Over the years, it has become clear that increased nuchal translucency is a marker for chromosomal abnormalities, and it is also associated with a wide spectrum of structural anomalies, genetic syndromes, a higher risk of miscarriage, and intrauterine fetal death. These risks are all proportionally related to the degree of nuchal translucency enlargement.

After the initial assessment of increased nuchal translucency, parents should be counselled by the fetal medicine specialist about the possible outcomes and the value of additional karyotyping and array comparative genomic hybridisation. A detailed late first-trimester and subsequent 20-week scan should aim at identifying structural anomalies, with special focus on the fetal heart and subtle dysmorphic features. In the absence of structural anomalies or markers, the chance of a favourable outcome is high.

Introduction

In 1992, Nicolaides et al. [1] proposed nuchal translucency measurement as a marker for chromosomal abnormalities in the first trimester of pregnancy. Over the years, it has become clear that an increased nuchal translucency is also associated with a wide spectrum of structural anomalies, genetic syndromes, a higher risk of miscarriage, and intrauterine fetal death. These risks are all proportionally related to the degree of nuchal translucency enlargement [2,3].

At present, the most challenging part of managing pregnancies with increased nuchal translucency, after exclusion of chromosomal aberrations, is to establish an adequate diagnostic work up, and

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provide parents with realistic and correct information about outcome, especially long-term neurological outcome in the absence of structural anomalies [4–6].

In this chapter, we provide an overview of issues relating to nuchal translucency. We subsequently suggest a protocol for managing these pregnancies to aid parental counselling once a normal karyotype or genotype has been confirmed.

At present, nuchal translucency measurement is offered in most countries as part of first-trimester screening for Down's syndrome. Participation rates vary considerably per country, as its uptake is influenced by local policies, socioeconomic factors, attitude towards Down's syndrome screening, and termination of pregnancy [7–12]. When women are informed about first-trimester screening, the focus of counselling is primarily on the detection of Down's syndrome. They should, however, be informed that this type of screening may detect many other chromosomal anomalies, and an increased nuchal translucency is also a powerful marker for cardiac anomalies, other structural anomalies, and genetic syndromes [13,14]. Furthermore, fetuses with an increased nuchal translucency have an increased risk of adverse pregnancy outcome, such as fetal loss and developmental delay [2,3,15–18].

Increased nuchal translucency

Nuchal translucency is a subcutaneous accumulation of fluid behind the neck of the fetus and generally visible by ultrasound up to 15 weeks of gestation. The size of the nuchal translucency is influenced by gestational age and is part of normal development [19]. Nuchal translucency is considered abnormal only when it exceeds a certain cut-off [1]. Many different definitions and cut-offs for increased nuchal translucency have been used in the past [20]. Although debate continues about whether nuchal translucency should be regarded as an increase above the 95th or 99th centile, there is consensus that nuchal translucency above the 99th centile (3.5 mm) is definitely increased.

Nuchal translucency seems to be influenced by gender. Two studies have shown that male fetuses tend to have a slightly larger nuchal translucency than females, about 0.06–0.1 mm [21–24], but this finding could not be confirmed by another study [23]. Timmerman et al. [25]showed, that among fetuses with an increased nuchal translucency, significantly more male fetuses had a favourable outcome compared with females (adverse outcome male 20.1% compared with 35.9% in females). The favourable outcome was especially present in male fetuses, with a marginally increased nuchal translucency (between P95 and 99), suggesting that a different cut-off may be necessary in male fetuses.

Increased nuchal translucency and aetiology

The pathophysiology behind increased nuchal translucency is not yet fully understood, and many hypotheses about the cause of nuchal translucency and the pathophysiology behind an increased nuchal translucency have been forwarded [27–33]. One of the possible causes for increased nuchal translucency is a congenital heart defect, but it is difficult to explain the exact mechanism behind this possible relationship, as different types of congenital heart defects with their own corresponding haemodynamics are encountered. An alternative explanation could be heart failure [33–36], although at present the relationship between impaired cardiac function as the main cause of increased nuchal translucency has not yet been established by all research groups [31,32]. Bekker et al. [37] suggested that impaired endothelial development could be the link between increased nuchal translucency and congenital heart defects.

Another possibility is developmental delay of the lymphatic system. Lymphatic jugular sacs are part of the lymphatic system, and a delay in development of these sacs, could cause increased nuchal translucency owing to fluid accumulation [38]. A study by de Mooij et al. [39] showed that a disturbance in lymphatic endothelial differentiation is present in euploid fetuses, with increased nuchal translucency, and that this disturbance has a similar phenotype as aneuploid fetuses with enlarged jugular lymphatic sacs. More research, however, is needed to ascertain that this is a plausible explanation for all cases of increased nuchal translucency.

Changes in the extra-cellular matrix, owing to a higher concentration of hyaluronan, and as a result excessive hydration of the extracellular matrix and a perturbed function or migration of the neural