**SAS Journal of Medicine**
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

**Medicine**

# Isolated Increased Nuchal Translucency with Normal Karyotype: A Narrative Literature Review

Aymen Khalfaoui[1*], Ikram Guerbej[1], Jawaher Hammedi[1], Cenda Belakhel[1], Nour Rouis[1], Sarra Kerkeni[1], Chaima Selmi[1], Ikram Ben Abdallah[1], Mouna Derouiche[1]

[1]Faculty of Medicine, University of Sousse, Tunisia

**DOI:** https://doi.org/10.36347/sasjm.2025.v11i09.012 | **Received:** 17.06.2025 | **Accepted:** 21.08.2025 | **Published:** 19.09.2025

***Corresponding author:** Aymen Khalfaoui
Faculty of Medicine, University of Sousse, Tunisia

**Abstract** **Original Research Article**

***Introduction:*** Nuchal translucency (NT) measurement during first-trimester ultrasound is an important marker for chromosomal abnormalities and fetal malformations. However, a significant proportion of fetuses with increased NT have a normal karyotype, raising challenges for prognosis and management. ***Objective:*** This narrative review summarizes the current literature on isolated increased NT with normal karyotype, focusing on causes, prognosis, and prenatal management strategies. ***Methods:*** A literature search was conducted in PubMed, Scopus, and ScienceDirect databases for articles published from 2010 to 2024 using keywords such as "nuchal translucency," "normal karyotype," and "prenatal diagnosis." Studies addressing isolated increased NT cases with normal chromosomal results were included. ***Results:*** Isolated increased NT may be linked to congenital heart defects, genetic syndromes undetected by standard karyotyping, infections, or structural anomalies, or remain idiopathic. Prognosis correlates with NT thickness and includes risks of miscarriage, fetal anomalies, and neurodevelopmental delay. Advanced genetic testing (chromosomal microarray, exome sequencing) increases diagnostic yield. Prenatal monitoring with detailed ultrasound and genetic counseling are essential. ***Conclusion:*** Isolated increased NT with normal karyotype is associated with a variable risk of adverse outcomes, requiring careful prenatal assessment and follow-up.

**Keywords:** Nuchal translucency, Increased nuchal translucency, Normal karyotype, Prenatal diagnosis, Prenatal management.



## INTRODUCTION

Nuchal translucency (NT) refers to the sonographic measurement of the subcutaneous fluid-filled space between the skin and the cervical spine of the fetus, typically assessed during the first-trimester ultrasound between 11 and 14 weeks of gestation[1]. It is a well-established marker used in the early screening for chromosomal abnormalities, particularly trisomy 21, as well as trisomy 18, trisomy 13, and Turner syndrome. An NT measurement above the 95th percentile or greater than 3.5 mm is generally considered increased and warrants further evaluation[2].

While increased NT is a recognized indicator of aneuploidy and major structural anomalies—particularly cardiac and lymphatic malformations—approximately 30% to 50% of fetuses with increased NT are found to have a normal karyotype after diagnostic testing such as chorionic villus sampling or amniocentesis. This presents a significant dilemma for clinicians and expectant parents, as the prognosis and optimal management strategy for these pregnancies remain uncertain[3].

The objective of this narrative review is to synthesize the current body of evidence regarding isolated increased NT in fetuses with normal chromosomal results. We aim to explore the underlying etiologies, associated structural and genetic conditions, pregnancy outcomes, and recommended approaches for prenatal follow-up and counseling. This review also highlights the importance of integrating advanced imaging, fetal echocardiography, and, when indicated, molecular testing to refine prognostic assessment and guide clinical decision-making.

## METHODS

A systematic search was conducted in PubMed, Scopus, and ScienceDirect for articles published between 2010 and 2024. Keywords included "nuchal

translucency," "normal karyotype," "increased nuchal translucency," and "prenatal diagnosis." Studies focusing on isolated increased NT with confirmed normal karyotype were included. Reviews, cohort studies, and case reports were analyzed. Studies without clear differentiation of isolated increased NT or without karyotype confirmation were excluded.

## RESULTS

### Definition and Thresholds

Increased NT is defined as measurement above the 95th percentile or >3.5 mm.

### Causes of Isolated Increased NT with Normal Karyotype

- Congenital heart defects
- Genetic syndromes not detected by karyotyping (e.g., Noonan syndrome, other RASopathies)
- Fetal infections (e.g., cytomegalovirus)
- Structural anomalies
- Idiopathic cases

### Prognostic Implications

The risk of adverse outcomes including miscarriage, structural defects, and neurodevelopmental delay rises with the degree of NT thickening. NT >6.5 mm is associated with poorer prognosis.

### Role of Advanced Genetic Testing

Chromosomal microarray analysis (CMA) and whole exome sequencing (WES) can identify submicroscopic chromosomal abnormalities and single-gene disorders, improving diagnostic yield beyond karyotype.

### Prenatal Monitoring and Management

Serial detailed ultrasounds are recommended to detect evolving anomalies. Genetic counseling should address residual risk despite normal karyotype and the option of advanced genetic testing.

## DISCUSSION

Nuchal translucency (NT) measurement between 11 and 14 weeks of gestation is a well-established component of first-trimester screening for chromosomal abnormalities. While the association between increased NT and aneuploidy is well documented, the management of cases with isolated NT thickening and a normal karyotype remains complex and often challenging for both clinicians and patients. The current literature highlights the heterogeneous prognosis of such cases, emphasizing the need for personalized assessment and careful follow-up [1].

Our review confirms that isolated increased NT, even in the context of a normal fetal karyotype, is associated with a higher incidence of adverse perinatal outcomes. These outcomes may include structural malformations, particularly cardiac anomalies, genetic syndromes undetectable by conventional karyotyping, intrauterine fetal demise (IUFD), and neonatal morbidity. However, the risk is proportional to the degree of NT thickening, and in many cases, the outcome remains favorable, particularly in the absence of associated findings.

Several cohort studies and retrospective reviews underline that the prognosis is inversely correlated with NT thickness. For instance, according to Syngelaki *et al.,* [4], a nuchal translucency of 3.0–3.4 mm is associated with a good prognosis when isolated, whereas measurements ≥3.5 mm are linked to an increased risk of congenital malformations and genetic syndromes such as Noonan syndrome, 22q11.2 deletion syndrome(3), and various RASopathies. Furthermore, extreme measurements (NT ≥6.0 mm) are strongly predictive of serious fetal anomalies and are associated with a significantly increased rate of fetal loss.

The association between increased NT and congenital heart defects (CHD) is particularly significant. Shamshirsaz *et al.,* [3] reported that up to 7% of euploid fetuses with NT ≥3.5 mm have major cardiac anomalies. Hence, the current international recommendations advocate for detailed fetal echocardiography in all cases of increased NT, regardless of the karyotype.

Another concern is the possibility of genetic syndromes with normal karyotype. In the era of advanced molecular genetics, chromosomal microarray analysis (CMA) and whole exome sequencing (WES) have revealed additional genetic anomalies in fetuses with increased NT and normal standard karyotype. Studies suggest that pathogenic copy number variations (CNVs) can be identified in approximately 2–7% of such cases, while WES may reveal monogenic syndromes in another subset, particularly when anomalies are identified during second-trimester follow-up[5].

Despite the risks, it is important to highlight that a large proportion of fetuses with isolated NT thickening and normal karyotype evolve favorably. Chen et al. [6] showed that in cases where the NT measurement was below 3.5 mm and no structural anomalies were found on second-trimester ultrasound, the outcome was reassuring in over 95% of cases. This emphasizes the importance of serial monitoring, including repeated ultrasound assessment, fetal echocardiography, and, when indicated, non-invasive prenatal testing (NIPT) and advanced genetic testing [6].

The prognostic value of normalization of NT in follow-up scans is another key point. Several studies suggest that when NT measurements normalize during the course of the first trimester and the subsequent morphological scan is reassuring, the risk of adverse outcome significantly decreases [5]. However, the presence of associated markers such as abnormal ductus

venosus flow, tricuspid regurgitation, or abnormal nasal bone should prompt further evaluation, even in the presence of a normal NT [3].

It is also essential to consider the psychosocial impact of NT thickening on pregnant women and couples. The discovery of an increased NT measurement often generates anxiety and uncertainty, especially when no immediate explanation (e.g., aneuploidy) is found [2]. Therefore, multidisciplinary counseling involving obstetricians, fetal medicine specialists, and genetic counselors is crucial [1]. Families must be informed of the potential risks, the limits of current diagnostic tools, and the possibility of a favorable evolution [5].

In low- and middle-income countries, including many African contexts, access to advanced diagnostic technologies such as CMA and WES remains limited[5]. This restricts the ability to identify certain conditions, potentially increasing the number of cases with uncertain prognosis. It is thus vital to optimize the use of available resources, promote training in fetal ultrasound, and advocate for the inclusion of molecular testing in national prenatal care programs [7].

### Strengths and Limitations of the Literature

Most of the reviewed studies are retrospective and may be subject to selection bias. In addition, the threshold definitions for "increased NT" vary slightly across studies (≥2.5 mm, ≥3.0 mm, or ≥3.5 mm), which affects comparability. Nonetheless, the consistency of findings across different populations and methodologies supports the reliability of the conclusions.

## CONCLUSION OF DISCUSSION

Increased nuchal translucency with a normal karyotype represents a heterogeneous entity with a wide spectrum of possible outcomes. While the risk of fetal anomalies and genetic syndromes is clearly elevated, particularly with greater NT thickness, the majority of fetuses with isolated and moderately increased NT show favorable development, especially in the absence of additional findings.

A systematic and multidisciplinary approach is essential for accurate risk stratification and counseling. Where possible, the incorporation of advanced imaging, non-invasive screening, and genomic technologies may further refine prognosis and guide parental decision-making. Future prospective studies and the expansion of molecular diagnostics in resource-limited settings are necessary to improve outcomes and reduce uncertainty in these complex situations.

## CONCLUSION

Isolated increased NT with normal karyotype is a heterogeneous condition with a variable risk of adverse outcomes. Prenatal management requires detailed ultrasound monitoring and consideration of advanced genetic testing. Multidisciplinary care and informed genetic counseling are essential for optimal outcomes.

### Ethics Statement

**Ethical Approval:** Not applicable for this narrative review as it is based on previously published studies.

**Informed Consent:** Not applicable.

### Conflict of Interest Statement

The authors declare no conflicts of interest regarding the publication of this paper.

### Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Author Contributions

Conceptualization: AK, IG; Literature review: JH, CB, NR; Drafting: KS, SC; Critical revision: MD; Final approval: All authors.

## REFERENCES

1. Bilardo CM, Timmerman E, Pajkrt E, van Maarle M. Increased nuchal translucency in euploid fetuses--what should we be telling the parents? Prenat Diagn. 2010 Feb;30(2):93–102.
2. Khair H, Hilary S, Al Awar S, Zareba K, Maki S, Sayed G, et al. Perinatal Outcomes in Foetuses with Increased Nuchal Translucency and Normal Karyotype: A Retrospective Cohort Study from the United Arab Emirates. J Clin Med. 2023 Jan;12(19):6358.
3. Shamshirsaz AA, Salmanian B, Ravangard SF, Shamshirsaz AA, Javadian P, Borgida A, et al. Nuchal translucency and cardiac abnormalities in euploid singleton pregnancies. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2014 Mar;27(5):495–9.
4. Syngelaki A, Hammami A, Bower S, Zidere V, Akolekar R, Nicolaides KH. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11-13 weeks' gestation. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2019 Oct;54(4):468–76.
5. Anzhel S, Kovachev E, Zhekov Z, Georgiev B. Increased Nuchal Translucency in Fetuses with Normal Karyotype. Open Access Maced J Med Sci. 2024 Feb 23;12(1):83–7.
6. Chen CP. Pathophysiology of Increased Fetal Nuchal Translucency Thickness. Taiwan J Obstet Gynecol. 2010 Jun 1;49(2):133–8.
7. Buffin R, Fichez A, Decullier E, Roux A, Bin S, Combourieu D, *et al.,* Neurodevelopmental outcome at 2 years of corrected age in fetuses with increased nuchal translucency thickness and normal karyotype compared with matched controls. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2021 May;57(5):790–7.