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颈项透明层厚度超声联合无创 DNA 对孕妇胎儿染色体非整倍体异常诊断效能的影响 *

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摘要 目的：探讨颈项透明层(nuchal translucency，NT)厚度超声联合无创 DNA 对孕妇胎儿染色体非整倍体异常诊断效能的影响。**方法：**2018 年 7 月到 2020 年 4 月选择在本院进行产前筛查的孕妇 120 例，所有孕妇都给予 NT 厚度超声联合无创 DNA 检查，采用羊水穿刺分析检测结果为阳性的胎儿情况。**结果：**120 例胎儿的 NT 厚度为 0.8~10 mm，平均厚度为 1.57±0.41 mm；不同孕妇年龄的 NT 厚度对比差异无统计学意义 (*P*>0.05)。以羊水穿刺检测结果为金标准，120 例胎儿中检出染色体非整倍体异常 7 例，NT 超声检出 12 例，无创 DNA 检出 13 例，联合检出 14 例。NT 超声、无创 DNA 与联合诊断的染色体非整倍体异常敏感性为 57.1%、85.7%和 100.0%，特异性为 92.9%、93.8%和 93.8%。检测结果为阳性的 14 例胎儿中，还包括 3 例淋巴水囊瘤，2 例单脐动脉伴胎儿宫内发育迟缓，1 例胎儿双肾畸形，1 例胎儿并腿畸形。**结论：**颈项透明层厚度超声联合无创 DNA 在孕妇胎儿染色体非整倍体异常中的诊断具有操作简便、无创伤等特点，诊断敏感性与特异性都比较高，可对临床医生遗传咨询有一定的参考价值。

关键词：颈项透明层；超声；无创 DNA；染色体非整倍体异常；联合诊断

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Effect of Ultrasound on Thickness of Neck Transparent Layer Combined with Noninvasive DNA on Diagnosis of Abnormal Chromosomal Aneuploidy*

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ABSTRACT Objective: To investigate the effect of the thickness of the nuchal translucency (NT) ultrasound combined with non-invasive DNA on the diagnostic efficiency of chromosomal aneuploidy in pregnant women and fetuses. **Methods:** A total of 120 pregnant women, who went to Shaanxi Provincial People's Hospital for prenatal screening from July 2018 to April 2020, were chosen as research subjects. All the pregnant women were given NT thickness ultrasound combined with non-invasive DNA examination, and the fetuses with positive results were given amniocentesis analysis. **Results:** The NT thickness of 120 fetuses was 0.8-10mm, and the average thickness was 1.57±0.41mm. There were no statistically significant differences in NT thickness of different pregnant women (*P*>0.05). Take the results of amniocentesis as the gold standard, in the 120 fetuses,chromosomal aneuploidy was detected in 7 cases, 12 cases were detected by NT ultrasound, 13 cases were detected by non-invasive DNA, and 14 cases were detected in combination. The sensitivity of NT ultrasound, non-invasive DNA and combination diagnosis of chromosomal aneuploidy were 57.1%, 85.7% and 100.0%, and the specificity were 92.9%, 93.8% and 93.8%. In the 14 fetuses with positive test results of combination diagnosis, there were 3 cases of lymphatic cystoma, 2 cases of single umbilical artery with intrauterine growth delay, 1 case of fetal kidney abnormalities, and 1 case of fetal sirenomelia. **Conclusion:** In the diagnosis of chromosomal aneuploidy abnormalities of pregnant women and fetuses, the cervical transparent layer thickness ultrasound combined with noninvasive DNA has the characteristics of simple operation and non-invasiveness. The sensitivity and specificity of the diagnosis are relatively high, which can be used for genetic consultation of clinicians.

Key words: Nuchal translucency; Ultrasound; Non-invasive DNA; Chromosomal aneuploidy abnormality; Combined diagnosis

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前言

胎儿畸形尤其染色体异常是危害新生儿生长发育与智力发育的严重疾病，其中新生儿染色体异常的发生率约为 1/160，主要包括数目异常和结构异常[1,2]，使得新生儿出现生长缓慢、出生缺陷、功能异常等，严重影响新生儿的预后[3,4]。常见的非整倍体异常包括 21、13、X、Y 等，其中 21- 三体综合征最常见，其次是 13- 三体综合征、三倍体等[5]，且一旦发生，无有效治疗手段[6,7]。DNA 检测为染色体非整倍体异常为常见检测方法，虽然为无创性，但是诊断效应有待提高[8]。胎儿颈项透明层(nuchal translucency，NT)厚度与染色体异常等有关，并且超声监测具有经济高效、可重复性强、检出率高等，并且颈项透明层超声检查还可筛查心脏畸形等结构异常，在胎儿染色体异常筛查中具有重要价值[9,10]。本研究显示颈项透明层厚度超声联合无创 DNA 对孕妇胎儿染色体非整倍体异常诊断效能的重要影响，希望有助于推动早孕期联合筛查的广泛开展。

1 资料与方法

1.1 研究对象

2018 年 7 月到 2020 年 4 月选择在本院进行产前筛查的孕妇 120 例，纳入标准：单胎妊娠；医院伦理委员会批准了此次研究；孕妇年龄 20~45 岁；婚姻状态稳定；孕妇知情同意本研究；孕周 11 周 +6 天 ~28 周；临床资料完整；头臀长 45~84 mm。排除标准：非自然受孕孕妇；孕妇或配偶染色体易位、倒位者；存在先天畸形家族史。

年龄最小 21 岁，最大 38 岁，平均年龄 29.47±2.48 岁；孕周 11 周 +6 天 ~28 周，平均 18.27±2.18 周；孕次最少 1 次，最多 6 次，平均 3.78±1.22 次；产次最少 0 次，最多 3 次，平均 3.22±0.13 次；平均受教育年限 15.20±1.28 岁。

1.2 超声检查

所有孕妇都给予 NT 厚度超声检查，使用 GE voluson E10 的彩色多普勒超声诊断仪，配有腹部低频凸阵探头，探头频率为 1~5 MHz，选择胎儿检查程序。孕妇取仰卧位，在胎儿伸展仰卧位时测量胎儿的顶臀长，顺序检查胎儿结构情况，核实超声孕周。取得胎儿正中矢状切面图，同时显示胎儿的鼻骨、间脑、腭部及脊柱等结构，在胎儿自然姿势下进行测量 NT 值。连续测量 3 次，并记录测量的最大值。

1.3 无创 DNA 检测

抽取孕妇的外周血 8 ml 左右，抗凝后静置 30 min，2000 rpm 离心 10 min，取上层血浆组织，提取游离 DNA 片段并进行测序，分析测序结果。

1.4 调查资料

调查所有孕妇的建档号、年龄、孕周、孕次、姓名、产次、受教育年限，随访 NT 超声联合无创 DNA 检测结果为阴性的胎儿情况，采用羊水穿刺分析检测结果为阳性的胎儿情况。

1.5 统计方法

应用 SPSS21.00，计量资料用($\bar{x}\pm s$)表示，计数资料以%表示，对比为 t 检验与 χ^2 分析，多组间对比为方差分析，P<0.05 具有统计学意义。

2 结果

2.1 NT 厚度超声结果

120 例胎儿的 NT 厚度为 0.8~10 mm，平均厚度为 1.57±0.41 mm；不同孕妇年龄的 NT 厚度对比差异无统计学意义(P>0.05)，见表 1。

表 1 不同孕妇年龄的 NT 厚度超声结果对比(mm，$\bar{x}\pm s$)

Table 1 Comparison of ultrasound results of NT thickness of different pregnant women (mm, $\bar{x}\pm s$)

Age of pregnant	n	NT thickness	F	P
21~25 years	14	1.52±0.22	0.127	0.882
26~29 years	76	1.58±0.14		
30~35 years	22	1.59±0.28		
36~38 years	8	1.57±0.18		

2.2 诊断结果

120 例胎儿中检出染色体非整倍体异常 7 例，NT 超声检出 12 例，无创 DNA 检出 13 例，联合检出 14 例，见表 2。

2.3 诊断敏感性与特异性

在 120 例胎儿中，NT 超声、无创 DNA 与联合诊断的染色体非整倍体异常敏感性为 57.1 %、85.7 %和 100.0 %，特异性为 92.9 %、93.8 %和 93.8 %，见表 3。

表 2 NT 超声联合无创 DNA 对胎儿染色体非整倍体异常的诊断结果(例，%)

Table 2 Diagnostic results of NT ultrasound combined with non-invasive DNA for fetal chromosomal aneuploidy (n,%)

Amniocentesis	NT ultrasound		Non-invasive DNA		Combined diagnosis		Total
	Positive	Negative	Positive	Negative	Positive	Negative	
Positive	4	3	6	1	7	0	7
Negative	8	105	7	106	7	106	113
Total	12	108	13	107	14	106	120

表 3 NT 超声联合无创 DNA 对胎儿染色体非整倍体异常的诊断敏感性与特异性(例,%)

Table 3 The diagnostic sensitivity and specificity of NT ultrasound combined with non-invasive DNA for fetal chromosomal aneuploidy abnormalities (n,%)

Diagnostic method	Sensibility	Specificity
NT ultrasound	57.1%(4/7)	92.9%(105/113)
Non-invasive DNA	85.7%(6/7)	93.8%(106/113)
Combined diagnosis	100.0%(7/7)	93.8%(106/113)
F	4.324	0.097
P	0.115	0.953

2.4 随访结果

NT 超声联合无创 DNA 检测结果为阴性 106 例胎儿中，随访至产后未见明显异常。检测结果为阳性的 14 例胎儿中,包括染色体非整倍体异常 7 例 (21- 三体综合征 4 例、13- 三体综合征 2 例、三倍体 1 例),3 例淋巴水囊瘤,2 例单脐动脉伴胎儿宫内发育迟缓,1 例胎儿双肾畸形,1 例胎儿并腿畸形。

3 讨论

染色体非整倍体异常是导致出生缺陷最常见的遗传病之一,是由于染色体数目减少或增多,使得新生儿与胎儿出现异常[11,12]。到目前为止预防染色体非整倍体异常胎儿的出生目前主要还是进行产前筛查,羊水穿刺的诊断准确率比较高,但是对孕妇与胎儿都有一定的创伤,且检测周期比较长[13,14],为此在临床上需要寻找更好的诊断方法。

在孕 10~14 周期胎儿颈部淋巴管与颈静脉窦相互连通[15]。不过在相通之前有少量的淋巴液积聚在胎儿颈部,可形成暂时性的颈部透明带。而随着妊娠的进展,胎儿淋巴系统可将积聚在颈部后的淋巴液引流至颈内静脉,让颈项透明层逐渐消退[16,17]。NT 为胎儿颈后部皮下组织内液体积聚的厚度,是指胎儿颈椎水平矢状切面皮肤至皮下软组织之间的厚度[18]。本研究显示 120 例胎儿的 NT 厚度为 0.8~10 mm，平均厚度为 1.57±0.41 mm；不同孕妇年龄的 NT 厚度对比差异无统计学意义。NT 增厚胎儿中可伴随有染色体异常,最常见的为 21- 三体综合征、13、三体综合症等、囊状淋巴瘤、先天性心脏病[19]。特别是染色体异常胎儿的细胞外间质的成分出现转变,透明基质的间隔内吸附了大量的细胞外液,使胎儿颈部皮肤细胞外透明基质增加,使颈部皮肤发生海绵样改变,从而导致 NT 增厚[20]。不过部分胎儿 NT 超声检查为一过性异常,导致在异常胎儿的诊断中也有一定的不足[21]。

胎儿染色体非整倍体异常是由于遗传因素、环境因素或两者共同作用,引起胎儿在发育过程中发生染色体异常,对胎儿进行染色体非整倍体异常筛查,对控制胎儿出生畸形具有重要作用[22]。NT 超声检查对胎儿 NT 进行测量,从而可间接反映染色体情况[23]。孕妇血浆中胎儿游离 DNA 为胎儿基因物质的重要来源,也具有孕早中期可检、易提取、高灵敏度、无流产风险、含量高等特点,从而为无创 DNA 的检测提供了条件,也可判断胎儿染色体有无非整倍体变化[24-26]。本研究显示以羊水穿刺检测结果为金标准,120 例胎儿中检出染色体非整倍体异常 7 例,NT 超声检出 12 例，无创 DNA 检出 13 例，联合检出 14 例;NT 超声、无创 DNA 与联合诊断的染色体非整倍体异常敏感性为 57.1 %、85.7 %和 100.0 %，特异性为 92.9 %、93.8 %和 93.8 %，表明 NT 超声联合无创 DNA 筛查胎儿染色体非整倍体异常的敏感性为更高。本研究显示联合诊断检测结果为阳性的 14 例胎儿中,包括染色体非整倍体异常 7 例,3 例淋巴水囊瘤,2 例单脐动脉伴胎儿宫内发育迟缓,1 例胎儿双肾畸形,1 例胎儿并腿畸形。从机制上分析,NT 增厚可使不良妊娠结局的风险增加,包括胎儿发育不良、胎儿死亡、遗传综合征、自发性流产等 [27,28]。但 NT 增厚并不等于胎儿异常，一旦排除无创 DNA 筛查异常，多数 NT 增厚的孕妇可分娩健康新生儿[29,30]。本研究也存在一定的不足,调查的孕妇数量比较少,且没有进行不同孕周孕妇 NT 增厚的分析,将在后续研究中进行探讨。

总之，颈项透明层厚度超声联合无创 DNA 在孕妇胎儿染色体非整倍体异常中的诊断具有操作简便、无创伤等特点,诊断敏感性与特异性都比较高,可对临床医生遗传咨询具有一定的参考价值。

参 考 文 献(References)

[1] 王一鹏,王成,李珊珊,等.无创产前筛查在胎儿性染色体非整倍体产前筛查及诊断中的应用[J].中国医刊, 2020, 55(6): 672-674

[2] 田瑞丽,张敏,崔莹莹.NT 超声联合无创 DNA 对接受产前筛查孕妇胎儿染色体非整倍体异常诊断效能的影响 [J]. 河南医学研究, 2020, 29(8): 1484-1485

[3] 张舫,曲冬颖.无创产前检测在高龄孕妇中的临床应用[J].中国妇幼健康研究, 2020, 31(1): 74-77

[4] Gao S, Wu Z, Kajigaya S, et al. Screening for fetal chromosomal and subchromosomal disorders[J]. Blood, 2018, 23(2): 85-93

[5] Gil MM, Accurti V, Santacruz B, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis [J]. Ultrasound Obstet Gynecol, 2017, 50(3): 302-314

[6] Levy B, Wapner R. Prenatal diagnosis by chromosomal microarray analysis[J]. Fertil Steril, 2018, 109(2): 201-212

[7] Nicolaides KH, Redaelli S, Maitz S, et al. Refining the Phenotype of Recurrent Rearrangements of Chromosome 16 [J]. Ultrasound Obstet Gynecol, 2019, 20(5): 114-119

[8] Zhao X. Single-cell RNA-seq reveals a distinct transcriptome signature of aneuploid hematopoietic cells [J]. Int J Mol Sci, 2017, 130(25): 2762-2773

[9] 罗丽双,孟繁杰,郝冬梅,等.4204 例高龄孕妇的无创产前基因检测结果分析[J].生殖医学杂志, 2020, 29(4): 532-535

[10] 李晓洲,史云芳,琚端,等.应用孕妇血浆中胎儿游离 DNA 进行产前筛查的临床研究进展[J].天津医药, 2020, 48(8): 796-800

[11] Armour CM, Dougan SD, Brock JA, et al. Practice guideline: joint CCMG-SOGC recommendations for the use of chromosomal microarray analysis for prenatal diagnosis and assessment of fetal loss in Canada[J]. J Med Genet, 2018, 55(4): 215-221

[12] Beulen L, Faas BHW, Feenstra I, et al. Clinical utility of non-invasive prenatal testing in pregnancies with ultrasound anomalies [J]. Ultrasound Obstet Gynecol, 2017, 49(6): 721-728

[13] Choy KW, Wang H, Shi M, et al. Prenatal Diagnosis of Fetuses With Increased Nuchal Translucency by Genome Sequencing Analysis[J]. Front Genet, 2019, 10(13): e761

[14] Cuckle H. Re: Cut-off value of nuchal translucency as indication for chromosomal microarray analysis. I. Maya, S. Yacobson, S. Kahana, J. Yeshaya, T. Tenne, I. Agmon-Fishman, L. Cohen-Vig, M. Shohat, L. Basel-Vanagaite and R. Sharony. Ultrasound Obstet Gynecol 2017; 50: 332-335[J]. Ultrasound Obstet Gynecol, 2017, 50(3): 293-294

[15] Egloff M, Hervé B, Quibel T, et al. Diagnostic yield of chromosomal microarray analysis in fetuses with isolated increased nuchal translucency: a French multicenter study [J]. Ultrasound Obstet Gynecol, 2018, 52(6): 715-721

[16] Goutte-Gattat D, Horovitz J, Saura R, et al. Early Evaluation of the Fetal Heart[J]. PLoS One, 2017, 42(3): 161-173

[17] Hellmuth SG, Pedersen LH, Miltoft CB, et al. Increased nuchal translucency thickness and risk of neurodevelopmental disorders[J]. Ultrasound Obstet Gynecol, 2017, 49(5): 592-598

[18] Li L, Fu F, Li R, et al. Prenatal diagnosis and pregnancy outcome analysis of thickened nuchal fold in the second trimester [J]. Ultrasound Obstet Gynecol, 2018, 97(46): e13334

[19] Li Y, Xie X, Lin Y, et al. Prenatal diagnosis of pathogenic genomic imbalance in fetuses with increased nuchal translucency but normal karyotyping using chromosomal microarray [J].Mol Genet Genomic Med, 2019, 25 Suppl 5(4): 30-32

[20] Lord J, Mcmullan DJ, Eberhardt RY, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study [J]. Lancet, 2019, 393 (10173): 747-757

[21] Maya I, Kahana S, Yeshaya J, et al. Chromosomal microarray analysis in fetuses with aberrant right subclavian artery[J]. Ultrasound Obstet Gynecol, 2017, 49(3): 337-341

[22] Nicolaides KH, Toutain J. Confined placental mosaicism revisited: Impact on pregnancy characteristics and outcome [J]. Ultrasound Obstet Gynecol, 2018, 13(4): e0195905

[23] Roozbeh N, Azizi M, Darvish L. Pregnancy Outcome of Abnormal Nuchal Translucency: A Systematic Review [J]. J Clin Diagn Res, 2017, 11(3): Qc12-qc16

[24] Santorum M, Wright D, Syngelaki A, et al. Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13[J]. Ultrasound Obstet Gynecol, 2017, 49(6): 714-720

[25] Socolov D, Socolov R, Gorduza VE, et al. Increased nuchal translucency in fetuses with a normal karyotype-diagnosis and management: An observational study[J]. Medicine (Baltimore), 2017, 96(29): e7521

[26] Su L. Clinical application of chromosomal microarray analysis in fetuses with increased nuchal translucency and normal karyotype[J]. Ultrasound Obstet Gynecol, 2019, 7(8): e811

[27] Sulaiman B, Shehu CE, Panti AA, et al. Prevalence and outcome of increased nuchal translucency in usmanu danfodiyo university teaching hospital, Sokoto, Nigeria: A cohort study [J]. Niger J Clin Pract, 2020, 23(6): 864-869

[28] Syngelaki A. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11-13?weeks' gestation [J]. Prenat Diagn, 2019, 54(4): 468-476

[29] Syngelaki A, Guerra L, Ceccacci I, et al. Impact of holoprosencephaly, exomphalos, megacystis and increased nuchal translucency on first-trimester screening for chromosomal abnormalities[J]. Ultrasound Obstet Gynecol, 2017, 50(1): 45-48

[30] Vogel I, Petersen OB, Christensen R, et al. Chromosomal microarray as primary diagnostic genomic tool for pregnancies at increased risk within a population-based combined first-trimester screening program [J]. Ultrasound Obstet Gynecol, 2018, 51(4): 480-486

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[24] Cullum D, Lucas M. Minimally Invasive Extraction Site Management With Dehydrated Amnion/Chorion Membrane: Immediate Implant Placement With Dynamic Navigation [J]. Compend Contin Educ Dent, 2019, 40(10): 646-650

[25] Grassi FR, Grassi R, Rapone B, et al. Dimensional changes of buccal bone plate in immediate implants inserted through open flap, open flap and bone grafting and flapless techniques: A cone-beam computed tomography randomized controlled clinical trial [J]. Clin Oral Implants Res, 2019, 30(12): 1155-1164

[26] Soni R, Priya A, Yadav H, et al. Bone augmentation with sticky bone and platelet-rich fibrin by ridge-split technique and nasal floor engagement for immediate loading of dental implant after extracting impacted canine[J]. Natl J Maxillofac Surg, 2019, 10(1): 98-101

[27] Lee J, Kim S, Koo KT, et al. Histologic Analyses of Immediate Implant Placement in Infected and Noninfected Sockets: An Experimental Pilot Study in Beagle Dogs [J]. Int J Oral Maxillofac Implants, 2019, 34(3): 575-584

[28] Araú jo MG, Silva CO, Souza AB, et al. Socket healing with and without immediate implant placement [J]. Periodontol, 2019, 79(1): 168-177

[29] Norcia A, Cicciù M, Matacena G, et al. Dental implant positioning by using the root way. A predictable technique for postextractive surgery [J]. Minerva Stomatol, 2016, 65(6): 393-402

[30] Silva KC, Zenóbio EG, Souza PEA, et al. Assessment of Dental Implant Stability in Areas Previously Submitted to Maxillary Sinus Elevation[J]. J Oral Implantol, 2018, 44(2): 109-113