doi: 10.13241/j.cnki.pmb.2020.22.040

彩色多普勒超声检查对胎儿颅内畸形筛查的应用价值及染色体异常分析*

干书文[1] 曹引丽[2] 席如如[1] 亢 云[2] 侯小霞[1△]

（西北妇女儿童医院 1 医学超声中心;2 产一科 陕西 西安 710061）

摘要 目的:探讨彩色多普勒超声检查对胎儿颅内畸形筛查的应用价值,并进行染色体异常分析。**方法:**选择 2016 年 2 月至 2019 年 5 月本院收治的进行胎儿颅内畸形筛查的高危孕妇 120 例,所有孕妇都给予彩色多普勒二维超声与三维超声筛查,对超声筛查异常者进行染色体异常分析,记录预后情况。**结果:**在 120 例孕妇中,二维超声诊断为胎儿颅内畸形 12 例,三维超声诊断为 13 例(预后都确诊为胎儿颅内畸形)。染色体核型筛查检出胎儿颅内畸形 12 例,其中 21- 三体综合征 8 例,18- 三体综合征 3 例,13- 三体综合征 1 例。确诊为胎儿颅内畸形的孕妇超声 NT 值都显著高于非胎儿颅内畸形孕妇,差异都有统计学意义(P<0.05)。孕妇选择终止妊娠 10 例,选择继续妊娠 3 例,继续妊娠 3 例胎儿都最终死亡。**结论:**产前彩色多普勒超声结合染色体核型在胎儿颅内畸形筛查中具有很高的价值,两者可互相补充,共同发挥诊断与预后评估价值。

关键词:彩色多普勒超声;胎儿;颅内畸形;染色体

中图分类号:R714.53;R445.1 **文献标识码:**A **文章编号:**1673-6273(2020)22-4378-04

Application of Color Doppler Ultrasonography in Screening Fetal Intracranial Malformation and Analysis of Chromosomal Abnormalities*

GAN Shu-wen[1], CAO Yin-li[2], XI Ru-ru[1], KANG Yun[2], HOU Xiao-xia[1△]

(1 Medical Ultrasound Center; 2 Department of Production, Northwest Women and Children's Hospital, Xi'an, Shaanxi, 710061, China)

ABSTRACT Objective: To investigate the effects of color Doppler ultrasonography on the screening of fetal intracranial malformation and to analyze chromosomal abnormalities. **Methods:** From February 2016 to May 2019, 120 cases of high-risk pregnant women who were screened for fetal intracranial malformation were enrolled in the hospital. All pregnant women were given color Doppler two-dimensional ultrasound and three-dimensional ultrasound screening, and the abnormalities were analyzed for chromosomal abnormalities and the prognosis were recorded. **Results:** In the 120 pregnant women, 2D ultrasound were diagnosed as 12 cases of fetal intracranial malformation, and 13 cases were diagnosed by three-dimensional ultrasound (prognosis were diagnosed as fetal intracranial malformation). Chromosome karyotype screening detected 12 cases of fetal intracranial malformation, include 8 cases of 21-trisomy syndrome, 3 cases of 18-trisomy syndrome, and 1 case of 13-trisomy syndrome. The ultrasound NT value of pregnant women diagnosed as fetal intracranial malformation were higher than that of non-fetal intracranial malformation, and compared the difference were statistically significant (P<0.05). The pregnant woman chose to terminate the pregnancy in 10 cases, choose to continue the pregnancy in 3 cases, and continue to conceive 3 cases of the fetus will eventually die. **Conclusion:** Prenatal color Doppler ultrasound combined with karyotype is of great value in the screening of fetal intracranial malformation. The two can complement each other and play a diagnostic and prognostic value together.

Key words: Color Doppler ultrasound; Fetus; Intracranial malformation; Chromosome

Chinese Library Classification(CLC): R714.53; R445.1 Document code: A

Article ID: 1673-6273(2020)22-4378-04

前言

当前，每年出生的先天残疾儿童约占总出生人口总数的 5.0 %左右,也是新生儿死亡的最主要原因之一[1]。胎儿颅内畸形为比较常见的先天残疾疾病,主要表现为无脑儿、露脑畸形、脊柱裂、脑膜脑膨出等[2,3]。胎儿颅内畸形的具体发病机制目前还不明确,病因包括免疫溶血性疾病、感染性疾病、糖尿病、结缔组织疾病、遗传基因缺陷、丙酮尿症、慢性酒精中毒、不正常妊娠史、高龄孕妇等[4-6]。

孕期染色体检查是颅内畸形胎儿的常见筛查方法,但是有一定的创伤,筛查效果受到限制[7,8]。随着影像学仪器分辨率的不断提高及对胎儿病理生理知识认识的深化,在早孕期进行胎儿疾病的影像学筛查越来越广泛[9,10]。产前超声具有安全、简便、科学、有效、可重复等优点,也是胎儿畸形产前诊断的首选方

* 基金项目:中国疾病预防控制中心妇幼保健中心科研项目(2019FYH009)

作者简介:干书文(1986-),女,本科,住院医师,研究方向:妇产科超声,电话:18706805251,E-mail:sasuke08123@163.com

△ 通讯作者:侯小霞(1977-),女,硕士研究生,副主任医师,研究方向:产前超声诊断,电话:15891746859,E-mail:xiaoxia_hou@126.com

（收稿日期:2020-02-24 接受日期:2020-03-21）

法[11,12]。前三维超声能显示各平面的解剖学及病理学情况,提供所观察脏器的多维空间信息,并为孕妇提供适当的产前遗传咨询[13-15]。本研究主要探讨了彩色多普勒超声检查对胎儿颅内畸形筛查的应用价值,并进行了染色体异常分析,以促进早期检出胎儿颅内畸形。现报道如下。

1 资料与方法

1.1 研究对象

本院伦理委员会批准了此次研究。选择 2016 年 2 月至 2019 年 5 月本院收治的进行胎儿颅内畸形筛查的高危孕妇 120 例,纳入标准:孕周 11-14 周;单胎妊娠;临床、超声与随访资料完整,都能够追踪到引产或胎儿出生后预后的病例;孕妇年龄 30-40 岁,具有高危孕妇特征;孕妇知情同意本研究;无特殊病史。排除标准:临床资料缺乏者;具有超声检查禁忌者;外院引产或自然流产,无法确定最终诊断者;失访患者。

年龄最小 20 岁,最大 39 岁,平均年龄 28.76± 4.33 岁;平均孕周 12.11± 0.18 周; 平均孕次 2.44± 0.51 次; 平均产次 1.72± 0.33 次。

1.2 产前超声方法

1.2.1 超声仪器 采用 Voluson E8 型彩色多普勒超声诊断仪,分别配有三维容积探头(探头频率 4.0-8.0 MHz)和二维凸阵探头(探头频率 2.5-5.0 MHz)。

1.2.2 超声方法 孕妇取仰卧位,经腹扫查,确定胎儿的方位与测量生长指标,详细扫描胎儿特征。在三维超声中,根据胎儿体位选取合适的检查位置,对颅脑部位进行扫描检查,对超声数据进行后续处理。由产科诊断经验丰富的超声科医生严格按照测量流程操作完成胎儿颈项透明层(nuchal translucency,NT)测量,NT≥ 3.0 mm 为 NT 增厚。

1.3 染色体检查

对所有孕妇选择羊水穿刺、绒毛或胎儿脐血取样对胎儿染色体核型进行检查,分为染色体核型正常与异常,异常包括 21-三体、18- 三体与 13- 三体。对孕妇选择继续妊娠的胎儿进行随访监测并追踪妊娠结局。对引产后胎儿建议行尸检;若孕妇拒绝,则引产后行胸片检查。超声检查结合引产胎儿尸检、出生后影像学检查结果进行最终诊断。

1.4 统计学分析

选择 SPSS19.00 软件数据分析,计量数据以 " 均数± 标准差 " 表示,组间对比方法为 t 检验,计数数据以率的形式表示,组间对比为卡方 x^2 检验分析等,以 P<0.05 为差异有统计学意义。

2 结果

2.1 产前超声结果

在 120 例孕妇中,二维超声诊断为胎儿颅内畸形 12 例,其中无脑儿 6 例、露脑畸形 3 例、脊柱裂 2 例、脑膜脑膨出 1 例。三维超声诊断为胎儿颅内畸形 13 例,其中无脑儿 6 例、露脑畸形 4 例、脊柱裂 2 例、脑膜脑膨出 1 例。

2.2 染色体异常情况

三维超声诊断胎儿颅内畸形 13 例都进行了染色体核型筛查,其中绒毛取样 6 例,胎儿脐血取样 4 例,羊膜腔穿刺 3 例,检出胎儿颅内畸形 12 例, 其中 21- 三体综合征 8 例,18- 三体综合征 3 例,13- 三体综合征 1 例。

2.3 预后情况

在三维超声诊断胎儿颅内畸形 13 例的孕妇中, 孕妇选择终止妊娠 10 例,选择继续妊娠 3 例,继续妊娠 3 例胎儿都最终死亡,预后都确诊为胎儿颅内畸形。具体情况见表 1。

2.4 NT 增厚情况

在 120 例孕妇中,超声筛查检出胎儿 NT 增厚 11 例,增厚率为 9.2 %,平均 NT 厚度为 7.86± 1.24 mm。确诊为胎儿颅内畸形的孕妇超声 NT 值都高于非胎儿颅内畸形孕妇,差异都有统计学意义(P<0.05),具体情况见表 1。

表 1 胎儿颅内畸形的超声特征、NT 值、染色体异常情况、异常结果与预后情况(例,%)

Table 1 Ultrasound characteristics, NT values, chromosomal abnormalities, abnormal results and prognosis of fetal intracranial malformations (n,%)

Numbering	NT(mm)	Abnormal structure	Karyotype analysis	Prognosis
1	6.53	Spina bifida	21-trisomy syndrome	Death after continuing pregnancy
2	8.24	No brain	21-trisomy syndrome	Induction of labor
3	6.22	Meningocele	18-trisomy syndrome	Death after continuing pregnancy
4	2.09	No brain	18-trisomy syndrome	Induction of labor
5	7.59	No brain	13-trisomy syndrome	Induction of labor
6	7.14	Open brain malformation	21-trisomy syndrome	Induction of labor
7	8.44	Open brain malformation	21-trisomy syndrome	Induction of labor
8	2.14	No brain	21-trisomy syndrome	Induction of labor
9	7.39	No brain	21-trisomy syndrome	Induction of labor
10	1.94	Open brain malformation	21-trisomy syndrome	Induction of labor
11	8.92	Open brain malformation	18-trisomy syndrome	Induction of labor
12	2.03	No brain	Normal	Induction of labor
13	7.11	Spina bifida	21-trisomy syndrome	Death after continuing pregnancy

表 2 不同胎儿类型的孕妇超声 NT 值对比(mm, $\bar{x}\pm s$)

Table 2 Comparison of the ultrasound NT values of pregnant women with different fetal types (mm, $\bar{x}\pm s$)

Fetal type	n	NT
Fetal non-cranial malformation	107	3.67± 1.49
Fetal intracranial deformity	13	7.93± 1.92
t		6.793
P		0.002

3 讨论

出生缺陷即各种原因引起的胎儿在出生时所伴随的结构或功能异常,其极大的影响了人口素质的提高,也将影响社会的发展[16,17]。胎儿颅内畸形为出生缺陷的一种,也是一种严重的畸形,主要表现为脊柱裂、无脑儿、脑膨出等[18]。该病的病因不明,发病因素众多,在产前确诊胎儿颅内畸形,及时中止妊娠或产后及时治疗,对挽救患儿生命与改善产妇预后具有重要的临床价值和医学伦理意义[19]。

超声为筛查胎儿畸形的主要方法,不仅能清晰显示胎儿解剖结构,而且安全性好,对孕妇和胎儿无明显影响,也具有简便、可重复、科学、有效等优势[20]。当前胎儿畸形筛查的理想时间是 20-30 周,有助于孕妇早期决定妊娠结局[21]。本研究显示在 120 例孕妇中,二维超声诊断为胎儿颅内畸形 12 例,三维超声诊断为 13 例(预后都确诊为胎儿颅内畸形)。二维超声是胎儿畸形的重要筛查手段,一旦发现可疑颅内畸形,应当由有专门经验的超声医师进行更为详尽的胎儿超声检查,不过由于受到胎方位、羊水量、胎儿脊柱、肋骨遮挡、孕妇肥胖腹壁肥厚等多种因素的影响,导致诊断效果有待提高[22]。三维超声技术包括最大模式、多平面模式和表面模式等,能显示各平面的解剖学及病理学情况,提供所观察脏器的多位信息,有利于清晰显示可疑部位,有助于提高产前诊断胎儿颅内畸形的能力[23]。

胎儿染色体核型筛查是预测胎儿畸形的比较前沿的方法,最常见方式的是绒毛取样,若绒毛取样失败,则应进行脐带血管穿刺,但此为有创性检查,一般在发现 NT 增厚后才进行检测[24]。本研究显示三维超声诊断胎儿颅内畸形 13 例都进行了染色体核型筛查,其中绒毛取样 6 例,胎儿脐血取样 4 例,羊膜腔穿刺 3 例,检出胎儿颅内畸形 12 例,其中 21- 三体综合征 8 例,18- 三体综合征 3 例,13- 三体综合征 1 例。21- 三体综合征是临床最常见的染色体异常,NT 值越大,胎儿患 21- 三体综合征的风险也越大,测量时可结合胎儿头臀长测量 NT 值,可提高诊断敏感性。其他染色体异常如 18- 三体综合征、13- 三体综合征,除 NT 增厚外,超声显示还伴有其他畸形[25]。

NT 是胎儿颈后部皮下积聚的生理性液体的厚度,也为胎儿颈椎水平矢状切面皮肤至皮下软组织之间的最大厚度[26]。NT 增厚常常与胎儿染色体异常有关,孕早期胎儿 NT 增厚提示胎儿患染色体异常及结构畸形的风险增加,可为胎儿畸形的产前筛查提供较为准确且方便的筛查指标。但是也有研究显示染色体异常检出率并非会随 NT 厚度增加而成比例增长,临床上不应只根据 NT 厚度来判定胎儿染色体异常发生的几率[27]。本研究显示在 120 例孕妇中,超声筛查检出胎儿 NT 增厚 11 例,增厚率为 9.2 %,平均 NT 厚度为 7.86± 1.24 mm。确诊为胎儿颅内畸形的孕妇超声 NT 值都高于非胎儿颅内畸形孕妇。从机制上分析,随着胎儿颈部皮肤细胞外透明基质增加等因素的因素,在胚胎大约第 10 周时,淋巴系统开始发育,可于 14 周左右发育完善成为淋巴管,但是颈部静脉、淋巴管还不能完全相通,会有少量淋巴液集聚在颈后方形成 NT。如果出现颅内畸形,淋巴液未能被静脉引流或继续增加,则可导致超声 NT 值增加[28]。

由于各种因素的影响,当前我国出生缺陷儿呈增多趋势,给社会和家庭带来了沉重负担和精神痛苦。流行病学调查显示当前我国出生缺陷的发生率约占所有新生儿的 4 %,每年可能有 100 万例缺陷儿出生[29]。颅内畸形是复杂的多基因疾病,由遗传、环境因素共同作用所致,多需要及时进行引产。本研究显示在三维超声诊断胎儿颅内畸形 13 例的孕妇中,孕妇选择终止妊娠 10 例,选择继续妊娠 3 例,继续妊娠 3 例胎儿都最终死亡。主要在于三维超声技术有助于检查过程中更为直观地对颅内组织进行立体观察,提高诊断胎儿颅内畸形的准确性[30]。本研究也存在一定的不足,病例样本数量较少,导致诊断效果还有待继续优化提供。

总之,产前彩色多普勒超声结合染色体核型在胎儿颅内畸形筛查中具有很高的价值,两者可互相补充,共同发挥诊断与预后评估的价值。

参 考 文 献(References)

[1] Tripathi M, Ahuja CK, Mukherjee KK, et al. The Safety and Efficacy of Bevacizumab for Radiosurgery - Induced Steroid - Resistant Brain Edema; Not the Last Part in the Ship of Theseus [J]. Neurol India, 2019, 67(5): 1292-1302

[2] Furey CG, Timberlake AT, Nelson-Williams C, et al. Xp22.2 Chromosomal Duplication in Familial Intracranial Arachnoid Cyst [J]. JAMA Neurol, 2017, 74(12): 1503-1504

[3] Grossfeld P. Brain hemorrhages in Jacobsen syndrome: A retrospective review of six cases and clinical recommendations [J]. Am J Med Genet A, 2017, 173(3): 667-670

[4] Hebbar M, Kanthi A, Shrikiran A, et al. p.Arg69Trp in RNASEH2C is a founder variant in three Indian families with Aicardi-Goutieres syndrome[J]. Am J Med Genet A, 2018, 176(1): 156-160

[5] Hori YS, Ohkura T, Ebisudani Y, et al. Hypertensive Cerebral Hemorrhage in a Patient with Turner Syndrome Caused by Deletion in the Short Arm of the X Chromosome[J]. Pediatr Neurosurg, 2018, 53(3): 167-170

[6] Kilcoyne S, Luscombe C, Scully P, et al. Language Development, Hearing Loss, and Intracranial Hypertension in Children With TWIST1-Confirmed Saethre-Chotzen Syndrome[J]. J Craniofac Surg,

2019, 30(5): 1506-1511

[7] Lin A, Ching C RK, Vajdi A, et al. Mapping 22q11.2 Gene Dosage Effects on Brain Morphometry[J]. J Neurosci, 2017, 7(26): 6183-6199

[8] Poulton C, Baynam G, Yates C, et al. A review of structural brain abnormalities in Pallister-Killian syndrome [J]. Mol Genet Genomic Med, 2018, 6(1): 92-98

[9] Roux T, An-Gourfinkel I, Bertrand A, et al. Astrocytic tumor with large cells and worrisome features in two patients with tuberous sclerosis: drastically different diagnoses and prognoses [J]. Clin Neuropathol, 2017, 36 (2017)(3): 102-107

[10] Schoeppe F, Rossi A, Levin J, et al. Increased cerebral microbleeds and cortical superficial siderosis in pediatric patients with Down syndrome[J]. Eur J Paediatr Neurol, 2019, 23(1): 158-164

[11] Boudaouara Y, Aoun K, Maatoug R, et al. Congenital Toxoplasmosis in Tunisia: Prenatal and Neonatal Diagnosis and Postnatal Follow-up of 35 Cases[J]. Am J Trop Med Hyg, 2018, 98(6): 1722-1726

[12] Issa R, Barakat A, Salman R, et al. Vein of Galen Malformation, a cause of Intracranial Calcification: Case Report and Review of Literature[J]. J Radiol Case Rep, 2019, 13(3): 13-18

[13] Goergen SK, Alibrahim E, Govender N, et al. Diagnostic assessment of foetal brain malformations with intra-uterine MRI versus perinatal post-mortem MRI[J]. Neuroradiology, 2019, 61(8): 921-934

[14] Griffiths PD, Mousa HA, Finney C, et al. An integrated in utero MR method for assessing structural brain abnormalities and measuring intracranial volumes in fetuses with congenital heart disease: results of a prospective case-control feasibility study[J]. Neuroradiology, 2019, 61(5): 603-611

[15] Katsuragi S, Yoshimatsu J, Tanaka H, et al. Management of pregnancy complicated with intracranial arteriovenous malformation[J]. J Obstet Gynaecol Res, 2018, 44(4): 673-680

[16] Radhakrishnan R, Merhar SL, Burns P, et al. Fetal brain morphometry on prenatal magnetic resonance imaging in congenital diaphragmatic hernia[J]. Pediatr Radiol, 2019, 49(2): 217-223

[17] Radhakrishnan R, Merhar SL, Su W, et al. Prenatal Factors Associated with Postnatal Brain Injury in Infants with Congenital Diaphragmatic Hernia[J]. AJNR Am J Neuroradiol, 2018, 39(3): 558-562

[18] Wang M, Liu C, Li X, et al. Isolated periventricular pseudocysts do not affect white matter microstructure development in neonatal stage: A retrospective case-control diffusion tensor imaging study [J]. Eur J Radiol, 2019, 116: 152-159

[19] Xu L, Han F. Neurosyphilis complicated with pial arteriovenous fistula: A rare case report [J]. Medicine (Baltimore), 2019, 98 (45): e17770

[20] Snyder-Keller A, Kramer LD, Zink S, et al. Mouse Strain and Sex-Dependent Differences in Long-term Behavioral Abnormalities and Neuropathologies after Developmental Zika Infection [J]. J Neurosci, 2019, 39(27): 5393-5403

[21] Tamai K, Tada K, Takeuchi A, et al. Fetal ultrasonographic findings including cerebral hyperechogenicity in a patient with non-lethal form of Raine syndrome[J]. Am J Med Genet A, 2018, 176(3): 682-686

[22] Vawter-Lee MM, Wasserman H, Thomas CW, et al. Outcome of Isolated Absent Septum Pellucidum Diagnosed by Fetal Magnetic Resonance Imaging (MRI) Scan[J]. J Child Neurol, 2018, 33(11): 693-699

[23] Falk Delgado A, Van Westen D, Nilsson M, et al. Diagnostic value of alternative techniques to gadolinium-based contrast agents in MR neuroimaging-a comprehensive overview [J]. Insights Imaging, 2019, 10(1): e84

[24] Karaaslan B, Dogan E, Abayli SY, et al. Hyperbaric oxygen therapy in the treatment of malign edema complication after arteriovenous malformation radiosurgery [J]. Undersea Hyperb Med, 2019, 46 (5): 713-717

[25] Park A, Chute C, Rajpurkar P, et al. Deep Learning-Assisted Diagnosis of Cerebral Aneurysms Using the HeadXNet Model [J]. JAMA Netw Open, 2019, 2(6): e195600

[26] Rayes A, Munerato MS, Costa BE, et al. Atypical Intracranial Compound Simil Odontoma[J]. J Craniofac Surg, 2019, 30(4): e300-e301

[27] Shen S, Liu X, Chen J, et al. A cerebral arteriovenous malformation mistakenly diagnosed as dry eye and glaucoma: a case report[J]. BMC Ophthalmol, 2019, 19(1): e148

[28] Tanaka M, Takasugi J, Hatate J, et al. Anterior Cerebral Artery Dissection in a Patient With Autosomal Dominant Polycystic Kidney Disease[J]. J Stroke Cerebrovasc Dis, 2019, 28(9): e129-e131

[29] Gabor M, Papcun P, Krizko JM, et al. A novel fetal sequence patogenesis resulting in oral meningoencephalocele [J]. Bratisl Lek Listy, 2018, 119(5): 272-274

[30] Cairo SB, Arbuthnot M, Boomer LA, et al. Controversies in extracorporeal membrane oxygenation (ECMO) utilization and congenital diaphragmatic hernia (CDH) repair using a Delphi approach: from the American Pediatric Surgical Association Critical Care Committee (APSA-CCC)[J]. Ediatr Surg Int, 2018, 34(11): 1163-1169