

正常与宫内生长受限胎儿神经系统发育产前超声监测

石莉¹, 符小艳¹, 王丽¹, 彭软²

(1. 海南省人民医院//海南医学院附属海南医院超声科, 海口 570311; 2. 中山大学附属第一医院超声医学科, 广东广州 510080)

摘要:【目的】应用产前三维超声分析正常胎儿大脑发育规律,并评估宫内生长受限胎儿其神经系统的发育状况。【方法】选取2017年6月1日至2018年12月31日在我院行产前超声检查的病例。所有病例按照胎儿估计体质量是否在正常范围分为两组:正常组和胎儿宫内生长受限(FGR)组(胎儿估计体质量低于同孕周第5百分位数),并按照不同孕周分析胎儿大脑外侧裂、顶枕沟及距状沟深度的变化规律。比较正常胎儿和FGR胎儿其大脑外侧裂、顶枕沟及距状沟深度在两组间的差异。【结果】研究期间,共纳入正常胎儿组386例,FGR胎儿组64例。正常组胎儿孕周中位数25(22~29)周;FGR组胎儿孕周中位数28(26~30)周。应用线性回归分析显示大脑外侧裂、顶枕沟及距状沟的深度与孕周呈正相关,且一次方程拟合度最高。与正常胎儿相比,FGR组胎儿其大脑外侧裂、顶枕沟及距状沟深度的差异均具有统计学意义。【结论】大脑外侧裂、顶枕沟及距状沟的深度随孕周变化而变化。FGR胎儿其大脑实质产前发育较正常胎儿迟缓,出生后需尽早进行干预及康复治疗。

关键词:宫内生长受限;产前超声;神经系统;距状沟;大脑外侧裂

中图分类号:R71 **文献标志码:**A **文章编号:**1672-3554(2020)05-0767-07

Prenatal Evaluation of the Development of Nervous System in Fetuses with Fetal Growth Restriction by Using Three-dimensional Ultrasound

SHI Li¹, FU Xiao-Yan¹, WANG Li¹, PENG Ruan²

(1. Department of Ultrasound, The People's Hospital of Hainan Province// Hainan Hospital Affiliated to Hainan Medical College, Haikou 570311, China; 2. Department of Ultrasound, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China)

Correspondence to: PENG Ruan; E-mail: pengruan1123@163.com

Abstract:【Objective】To evaluate the development of fetal nervous system by using three-dimensional ultrasound and to compare the difference between normal fetuses and fetuses with growth restriction. 【Methods】Fetuses that underwent prenatal ultrasound screening between June 1st 2017 and December 31st 2018 were included. All the cases were divided into two groups according to the estimated weight of the fetus: the normal group and the FGR group (the estimated weight less than 5 percent of the gestational week). The development of fetal sylvian fissure, parietooccipital sulcus and calcarine sulcus were analyzed according to gestational week. The depth of fetal sylvian fissure, parietooccipital sulcus and calcarine sulcus were compared between normal fetuses and the fetuses with growth restriction. 【Results】During the study period, 386 normal fetuses and 64 fetuses with growth restriction were included. The median gestational week in normal group was 25⁺² (22⁺⁵~29⁺¹) weeks and the median gestational week in FGR group was 28⁺² (26⁺²~30⁺⁵) weeks. The depth of fetal sylvian fissure, parietooccipital sulcus and calcarine sulcus had a linear positive correlation with gestational week. The depth of fetal sylvian fissure, parietooccipital sulcus and calcarine sulcus were significantly different between normal fetuses and fetuses with growth restriction. 【Conclusions】The depth of fetal sylvian fissure, parietooccipital sulcus

收稿日期:2020-04-27

基金项目:国家自然科学基金(81501491)

作者简介:石莉, 学士, 主治医师, E-mail: 475414475@qq.com; 彭软, 通信作者, 博士, 副主任医师, E-mail: pengruan1123@163.com

and calcarine sulcus varies according to gestational week. Fetal brain parenchyma may be mal-developed in FGR fetuses, so intervention and rehabilitation need to be carried out after birth.

Key words: fetal growth restriction; prenatal ultrasound; nervous system; calcarine sulcus; sylvian fissure

[J SUN Yat-sen Univ (Med Sci), 2020, 41 (5): 767-773]

胎儿生长受限(fetal growth restriction, FGR)其围生期死亡率和发病率较高,是引起新生儿死亡的最主要原因之一^[1]。FGR 胎儿即使出生后存活,亦会出现多种胎源性疾病,其中最严重的是神经系统功能障碍。对 FGR 病例进行神经系统功能障碍风险评估、定期监测其神经系统发育状况是改善预后的重要措施。目前评估 FGR 神经系统改变的主要方式是行三维磁共振成像(magnetic resonance imaging, MRI)和功能性 MRI 检查,费用昂贵且可重复性低。此外,这些方式主要集中于出生后进行评估,此时已错过干预最佳时机。目前已有研究^[2]报道应用经阴道三维超声显示大脑外侧裂的角度在妊娠 25 周时和参考线平行,顶枕沟和距状沟的深度与孕周呈正相关^[3]。本研究拟采用产前超声监测正常胎儿大脑表面沟回随孕周变化的规律且与 FGR 胎儿进行对比分析,以期对分析 FGR 神经系统改变提供精准的参考信息。

1 材料与方法

1.1 研究对象

选取 2017 年 6 月 1 日至 2018 年 12 月 31 日在我院行产前超声检查的病例。病例纳入孕周:20~32⁺6 周。病例纳入标准:单胎妊娠(正常及 FGR 胎儿)、签署知情同意书;FGR 的诊断标准是胎儿估计体质量低于同孕周的第 10 百分位数。胎儿体质量按照双顶径(biparietal diameter, BPD)、头围(head circumference, HC)、腹围(abdomen circumference, AC)和股骨长径(femur length, FL)的测量值并依据 Hadlock 算式(Hadlock-4)估算,其计算算式^[4]为: $\text{Log}_{10} \text{weight} = 1.359 6 - 0.0038 6 \text{ AC} \times \text{FL} + 0.006 4 \text{ HC} + 0.000 61 \text{ BPD} \times \text{AC} + 0.042 4 \text{ AC} + 0.174 \text{ FL}$ 。病例排除标准:合并胎儿畸形、孕妇合并症、病例失访。本研究获得本机构的伦理委员会审批,所有纳入研究者均签署知情同意书。

1.2 超声仪器及检查方法

1.2.1 超声仪器 Voluson E6、Voluson E8、Volu-

son E10 三维彩色多普勒超声诊断仪(GE, Kretztechnik, Austria);经腹三维超声容积探头(4~8 MHz);经阴道三维超声容积探头(7~10 MHz)。

1.2.2 检查方法 所有病例均经早孕期超声检查确定孕周,且在中孕期行结构筛查排除胎儿畸形,中孕期超声筛查依据国际妇产超声协会中孕期超声检查指南进行^[3]。首先进行二维超声扫查,观察胎儿形态结构、进行生物学测量、测量羊水最大深度并估计胎儿体质量。然后采用经腹部超声观察胎儿颅内结构,结合经阴道二维超声进行扫查,之后则获取经腹部或经阴道胎儿头颅的三维超声容积数据并存储以供离线分析。初始切面采用头颅横切面和冠状切面,且每例患者储存至少 2 个容积数据,采集角度 50°~70°,角度依据不同孕周而变化。

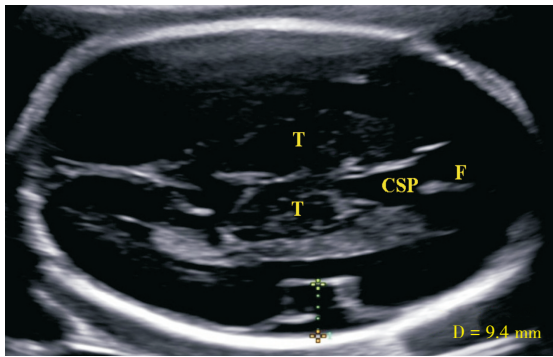
1.2.3 测量方法 本研究中颅内各超声指标的测量方法依据 Alonso 等^[4]提出的方法进行,详细描述如下。

大脑外侧裂的深度采用胎儿头颅经侧脑室切面进行测量,在此切面需显示透明隔腔及侧脑室体部及其内的脉络膜丛。测量大脑外侧裂中点与同侧颅骨内缘的距离,测量时注意将测量标尺置于大脑外侧裂外缘中点处和颅骨内缘处(图 1)。

大脑外侧裂测量完毕后,探头继续向胎儿头部移动,至可清晰显示顶枕沟为止。在此切面顶枕沟呈三角形且其顶端远离脑中线,然后测量顶枕沟顶端与脑中线的距离,测量时将测量标尺置于顶枕沟的顶端和同侧脑中线处,需注意测量线应垂直于脑中线(图 2)。

获取测量距状沟深度的切面时则首先获得测量小脑横径的切面,在此切面显示透明隔腔、侧脑室前角、丘脑、小脑和后颅窝池,然后将探头旋转 90°即可获得经小脑的冠状切面可清晰显示距状沟即可。测量距状沟顶端与小脑幕的距离,测量时将标尺置于距状沟顶端和同侧小脑幕处(图 3)。

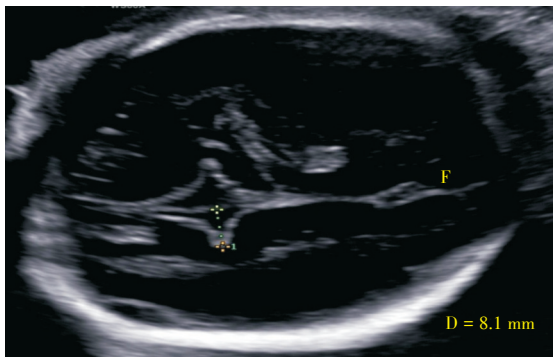
所有测量由同一检查者进行。测量时将图像放大至整个屏幕的 2/3,可清晰显示颅骨及颅内



The gestational week of this case was 25 weeks. T: thalamus; CSP: cavity of septum pellucidum; F: cerebral falx

图1 大脑外侧裂深度测量方法的图示

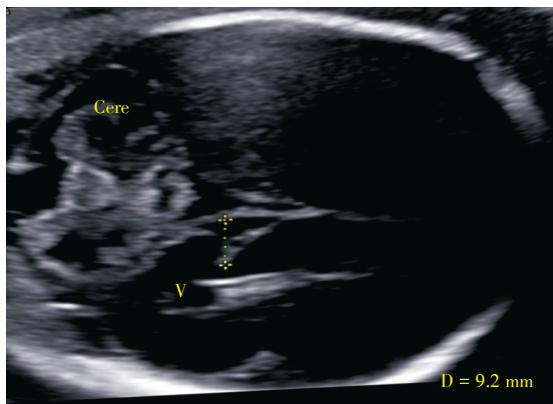
Fig.1 Diagram of measurement of the depth of sylvian fissure in fetus



The gestational week of this case was 28 weeks. F: cerebral falx

图2 顶枕沟深度测量方法的图示

Fig.2 Diagram of measurement of the depth of parietooccipital sulcus in fetus



The gestational week of this case was 28 weeks. Cere: cerebellum; V: ventricle

图3 距状沟深度测量方法的图示

Fig.3 Diagram of measurement of the depth of calcarine sulcus in fetus

结构。测量3次并取3次测量值的平均值进行记录。

1.3 病例追踪及随访

对所有入组病例进行追踪随访。新生儿随访内容:出生体质量、分娩方式、新生儿Apgar评分、住院时间等。随访婴幼儿一般发育及语言、行动状况,采用Bayley-III(Bayley Scales of Infant Development, version III)评估其神经系统发育情况^[5-6]。随访方式为电话随访,必要时请病例返院复查,随访者不知其产前具体情况。神经系统发育迟缓包括脑瘫、双眼失明、双侧耳聋或运动/认知/语言评分<70分。

1.4 统计方法

采用SPSS19.0统计分析软件进行分析。描述不同孕周大脑外侧裂、顶枕沟及距状沟深度的均数、第5百分位数及第95百分位数。非正态分布的计量资料采用中位数和四分位数描述,即 $M(P_{25} \sim P_{75})$ 。应用线性回归分析,选取拟合度较高的数学模型,计算残差,写出回归方程,分析拟合效果。正常组和FGR组间大脑外侧裂、顶枕沟及距状沟深度的比较采用两独立样本比较的Wilcoxon秩和检验。 $P < 0.05$ 认为差异具有统计学意义。

2 结果

2.1 一般资料

研究期间,正常胎儿组共纳入病例386例,FGR胎儿组64例。正常组孕妇年龄中位数31(28~35)岁;胎儿孕周中位数25(22~29)周。正常胎儿不同孕周病例数分布如下:31例(20~20⁺周),35例(21~21⁺周),40例(22~22⁺周),33例(23~23⁺周),27例(24~24⁺周),25例(25~25⁺周),28例(26~26⁺周),25例(27~27⁺周),33例(28~28⁺周),29例(29~29⁺周),30例(30~30⁺周),26例(31~31⁺周),24例(32~32⁺周)。

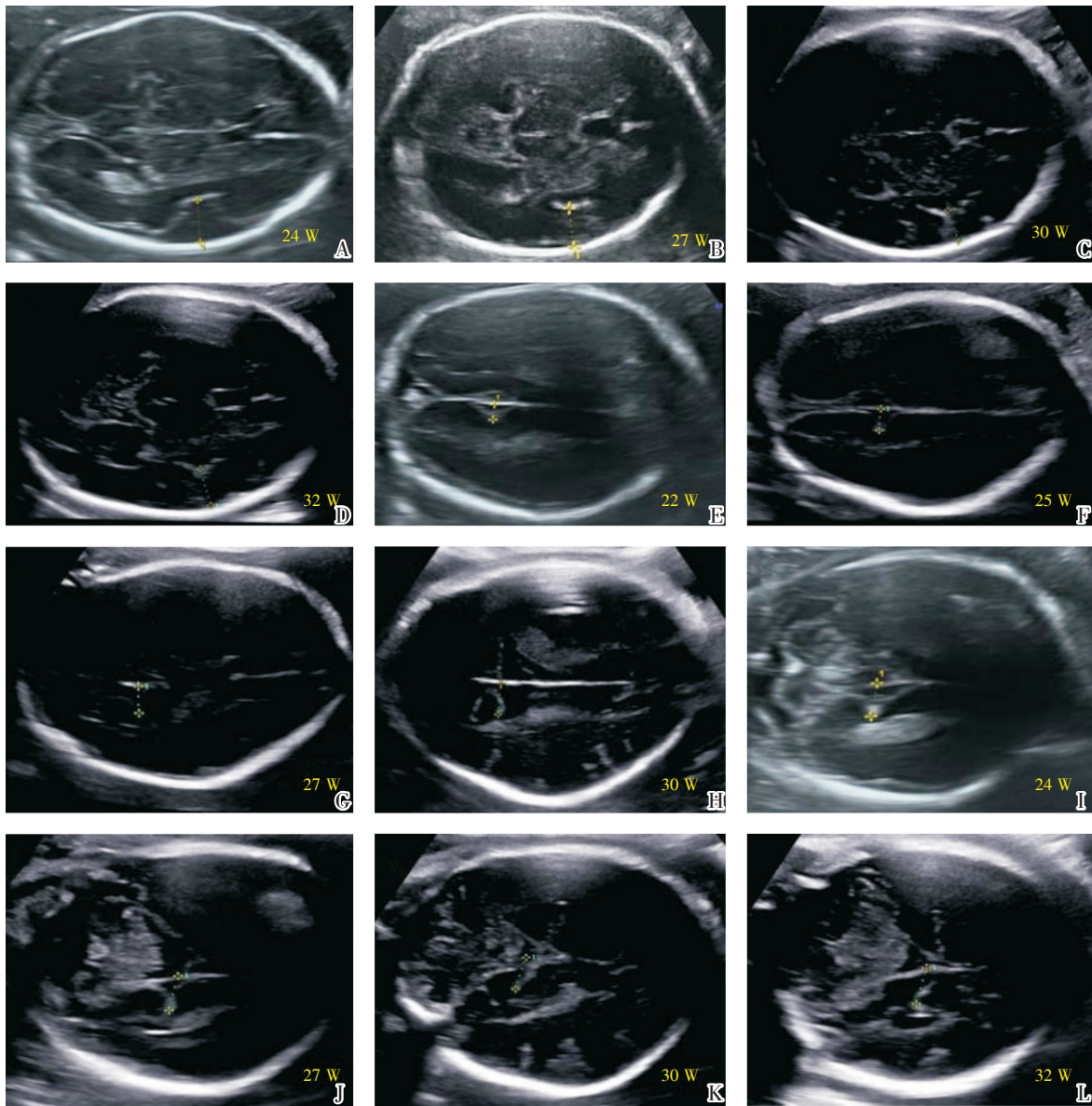
FGR组孕妇年龄中位数36(31~40)岁;胎儿孕周中位数28(26~30)周。FGR组不同孕周病例数分布如下:1例(21~21⁺周),2例(22~22⁺周),4例(23~23⁺周),5例(24~24⁺周),4例(25~25⁺周),5例(26~26⁺周),5例(27~27⁺周),7例(28~28⁺周),9例(29~29⁺周),7例(30~30⁺周),8例(31~31⁺周),7例(32~32⁺周)。

2.2 正常组胎儿颅内指标测量结果和出生结局分析

表1详细列出了不同孕周大脑外侧裂、顶枕沟及距状沟深度的均数、第5百分位数及第95百分位数。胎儿大脑外侧裂、顶枕沟及距状沟在不同孕周的超声特征详见图4。所测量的大脑外侧裂、顶枕沟及距状沟的深度与孕周呈正相关,且一次方程拟合度最高。大脑外侧裂、顶枕沟及距状沟的深度与孕周间关系的线性回归方程分别如下:大脑外侧裂的深度= $-3.506 + 0.493 \times \text{孕周}$ ($R^2 = 0.569, F = 187.2, P = 0.001$);顶枕沟的深

度= $-12.286 + 0.749 \times \text{孕周}$ ($R^2 = 0.764, F = 444.2, P < 0.001$);距状沟的深度= $-9.917 + 0.608 \times \text{孕周}$ ($R^2 = 0.730, F = 316.4, P < 0.001$)。

正常组胎儿出生体质量中位数3 320(2 560~4 410)g;剖宫产102例,阴道分娩284例;分娩孕周中位数38(35~40)周。新生儿Apgar评分情况:1 min < 7分11例,5 min < 7分4例,10 min < 7分4例。随访时间中位数17个月(9~15个月)。出生后对所有胎儿采用Bayley-III进行神经系统发育评估,1例出现神经系统发育迟缓(0.26%, 1/386)。



A-D: sylvian fissure; E-H: parietooccipital sulcus; I-L: calcarine sulcus

图4 胎儿大脑外侧裂、顶枕沟及距状沟在不同孕周的超声特征图像

Fig.4 The characteristics of sylvian fissure, parietooccipital sulcus and calcarine sulcus in different gestational weeks

表1 不同孕周大脑外侧裂、顶枕沟及距状沟深度的均数、第5百分位数及第95百分位数

Table 1 The mean, 5th percent and 95th percent of the depth of sylvian fissure, parietooccipital sulcus and calcarine sulcus in different gestational weeks

GA	Sylvian fissure			Parietooccipital sulcus			Calcarine sulcus		
	M	5 th	95 th	M	5 th	95 th	M	5 th	95 th
20~20 ⁺	6.84	6.35	7.34	3.78	2.30	5.26	3.76	2.22	5.30
21~21 ⁺	6.93	5.29	8.58	4.46	2.41	6.51	4.28	2.39	6.18
22~22 ⁺	7.75	5.93	9.58	4.72	2.53	6.91	4.56	2.61	6.51
23~23 ⁺	7.75	5.56	9.95	4.90	2.76	7.03	5.04	2.75	7.33
24~24 ⁺	8.31	6.83	9.78	5.13	3.12	7.14	5.11	2.93	7.29
25~25 ⁺	8.46	6.53	9.89	6.73	4.78	8.69	6.91	4.62	9.20
26~26 ⁺	8.73	6.36	11.10	7.55	5.73	9.37	8.18	4.95	11.41
27~27 ⁺	9.87	7.88	11.87	8.48	5.73	11.23	8.65	5.80	11.50
28~28 ⁺	10.61	7.85	13.37	9.29	6.11	12.47	9.37	6.11	12.63
29~29 ⁺	10.83	7.87	13.79	9.77	6.88	12.66	9.64	6.75	12.53
30~30 ⁺	11.83	7.69	15.98	10.02	6.73	13.31	10.46	6.97	13.95
31~31 ⁺	12.00	8.88	15.12	11.20	6.99	15.41	10.93	7.11	14.75
32~32 ⁺	11.71	7.52	15.91	11.39	7.29	15.49	11.48	7.33	15.63

GA: gestational age; M: mean

表2 FGR组和正常胎儿组大脑外侧裂、顶枕沟和距状沟深度的比较

Table 2 Comparisons of the depth of sylvian fissure, parietooccipital sulcus and calcarine sulcus between normal fetus group and FGR group $M(P_{25} \sim P_{75})$

	Sylvian fissure	Parietooccipital sulcus	Calcarine sulcus
Normal group	10.30(6.93~14.13)	8.82(3.91~12.06)	7.41(3.03~13.58)
FGR group	8.12(5.56~11.28)	6.65(2.47~9.86)	5.87(2.18~8.51)
Z	18.11	10.61	17.29
P	<0.001	0.002	<0.001

2.3 FGR组胎儿颅内指标测量结果及与正常胎儿组的比较

FGR组和正常组进行比较时,首先在正常组中随机选择与FGR组孕周匹配的病例,然后再进行比较。统计分析结果显示,与正常胎儿组相比,FGR组胎儿其大脑外侧裂、顶枕沟及距状沟的深度相比,其差异均具有统计学意义(P 值分别是 <0.001 , $=0.005$ 和 <0.001 ,表2)。

2.4 FGR组胎儿出生后的随访结果

FGR组共64例,其中63例新生儿出生后存活,1例新生儿出生后死亡。所有FGR胎儿出生

体质量中位数2 150 g,出生体质量范围1 610~2 480 g;剖宫产60例,阴道分娩4例;分娩孕周中位数35(33~37)周。新生儿Apgar评分情况:1 min <7 分11例,5 min <7 分9例,10 min <7 分9例。6例新生儿出生后住院时间 >15 d。随访时间中位数18(10~22)个月。出生后对所有FGR胎儿采用Bayley-III进行神经系统发育评估,神经系统发育迟缓病例占6.35%(4/63),与正常胎儿组相比,神经系统发育迟缓发生率差异具有统计学意义($P=0.002$,Fisher确切概率法)。

3 讨论

胎儿生长受限(FGR)又称宫内生长受限(intrauterine growth restriction)是指因胎盘功能损害以致胎儿生长和发育未达到其潜能^[7]。FGR整个儿童期(从出生至12岁)在不同领域内神经功能受损的风险均明显增加^[8],严重的、早期发生的或伴有脐动脉血流频谱异常的FGR胎儿出生后其新生儿期及婴幼儿期预后相对更差。FGR出生后不仅在婴幼儿期伴有认知、运动及语言迟缓,在学龄期仍会出现认知功能受损。FGR伴有大脑中动脉-脐动脉PI比值异常的儿童在其6~8岁时认知功能和学业成绩较正常组降低^[9]。FGR儿童在9岁时其IQ评分较低且神经心理障碍的发生率更高,神经心理障碍主要包括语言、创造力和执行力障碍^[10-11],提示可能伴有额叶功能和短期记忆异常。三维MRI的应用研究显示FGR婴幼儿其大脑半球容积缩小近10%且灰质比白质减少更明显^[12],更细致化地分析研究显示FGR婴幼儿丘脑和基底神经节体积缩小,但是小脑体积却并无明显改变^[13]。

三维超声可以利用快速采集数个三维容积来完成整个检查,故可以取代繁琐的二维超声图像采集过程,仅仅通过少数几个包含无数切面的三维容积重建来代替整个二维超声检查过程。经阴道神经学超声检查可避免孕妇腹壁脂肪的影响,

获得更清晰、质量更高的容积数据,故可提高后续分析的精准程度。应用经阴道三维超声显示大脑外侧裂的角度在妊娠25周时和参考线平行^[1];顶枕沟和距状沟与脑中线的距离与孕周呈正相关^[14]。本研究的结果显示大脑外侧裂与颅骨内缘的距离、顶枕沟及距状沟与脑中线距离与孕周呈正相关,提示在孕期大脑表面沟回处于动态发展中。产前超声观察大脑沟回需结合孕周进行评估,尤其是距状沟,在22周前其距离脑中线距离较小,需仔细观察。

应用MRI分析FGR大脑改变的研究显示FGR胎儿大脑发育与正常胎儿存在差异^[15]。Sanz-Cortes等^[16]研究显示晚期发生的FGR胎儿其胼胝体的各个部分,包括嘴部、膝部、体部、压部等较正常组有改变,而反映皮质发育的大脑外侧裂、距状沟、顶枕裂等并无明显改变。但是本研究的结果显示,与正常胎儿相比,FGR组胎儿其大脑外侧裂与颅骨内缘的距离、顶枕沟及距状沟与脑中线距离的差异均具有统计学意义。FGR出生后其婴幼儿神经系统发育迟缓的比例较正常组高,因此,建议FGR胎儿出生后可尽早开始康复干预。

综上所述,本研究显示大脑外侧裂与颅骨内缘的距离、顶枕沟及距状沟与脑中线的距离随孕周而发生变化。FGR胎儿其大脑实质产前发育较正常胎儿迟缓,因此出生后需尽早进行干预及康复治疗。

参考文献

- [1] 陈嫦娥. 单绒毛膜双胎胎儿生长受限合并脐带帆状附着一例[J]. 新医学, 2016, 47(8): 567-570. Chen CE. A case of single chorionic twins with fetal growth restriction and umbilical cord velum attachment[J]. J New Med, 2016, 47(8): 567-570.
- [2] Poon LC, Sahota D, Chaemsaitong P, et al. Transvaginal three-dimensional assessment of Sylvian fissures at 18-30 weeks' gestation [J]. Ultrasound Obstet Gynecol, 2019, 54(2): 190-198.
- [3] Salomon LJ, Alfrevic Z, Berghella V, et al. Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan [J]. Ultrasound Obstet Gynecol, 2011, 37(1): 116-126.
- [4] Alonso I, Borenstein M, Grant G, et al. Depth of brain fissures in normal fetuses by prenatal ultrasound between 19 and 30 weeks of gestation [J]. Ultrasound Obstet Gynecol, 2010, 36(6): 693-699.
- [5] Bayley, N. Bayley scales of infant and toddler development—Third edition: Administration manual [S]. 2006, San Antonio, TX: Harcourt Assessment.
- [6] Bayley, N. Bayley scales of infant and toddler development—Third edition: Technical manual [S]. 2006, San Antonio, TX: Harcourt Assessment.
- [7] 陈洁,潘石蕾,行李林,等. 单绒毛膜双胎选择性

- 胎儿生长受限产妇产胎盘血管铸型模型的建立及其形态学研究[J]. 广东医学, 2017, 38(7): 1014-1019.
- Chen J, Pan SL, Xing LL, et al. Establishment and morphological study of placental vascular casting model in parturients with single chorionic twins and selective fetal growth restriction [J]. Guangdong Med J, 2017, 38(7): 1014-1019.
- [8] Hadlock FP, Harrist RB, Sharman RS, et al. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study [J]. Am J Obstet Gynecol, 1985, 51: 333-337.
- [9] Murray E, Fernandes M, Fazel M, et al. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review [J]. BJOG, 2015, 122(8): 1062-1072.
- [10] Bellido-González M, Díaz-López MÁ, López-Criado S, et al. Cognitive functioning and academic achievement in children aged 6-8 years, born at term after intrauterine growth restriction and fetal cerebral redistribution[J]. J Pediatr Psychol, 2017, 42(3): 345-354.
- [11] Geva R, Eshel R, Leitner Y, et al. Verbal short-term memory span in children: long-term modality dependent effects of intrauterine growth restriction [J]. J Child Psychol Psychiatry, 2008, 49(12): 1321-1330.
- [12] Geva R, Eshel R, Leitner Y, et al. Memory functions of children born with asymmetric intrauterine growth restriction [J]. Brain Res, 2006, 1117(1): 186-194.
- [13] Padilla N, Falcon C, Sanz-Cortes M, et al. Differential effects of intrauterine growth restriction on brain structure and development in preterm infants: a magnetic resonance imaging study [J]. Brain Res, 2011, 1382(5): 98-108.
- [14] Bruno CJ, Bengani S, Gomes WA, et al. MRI differences associated with intrauterine growth restriction in preterm infants [J]. Neonatology, 2017, 111(4): 317-323.
- [15] Alonso I, Borenstein M, Grant G, et al. Depth of brain fissures in normal fetuses by prenatal ultrasound between 19 and 30 weeks of gestation [J]. Ultrasound Obstet Gynecol, 2010, 36(6): 693-699.
- [15] 高敏, 盛茂. 磁共振动脉自旋标记技术在小儿脑部疾病中的应用 [J]. 影像诊断与介入放射学, 2017, 26(3): 236-240.
- Gao M, Sheng M. Application of magnetic resonance arterial spin labeling in children with brain diseases [J]. J Diagn Imag Intervent Radiol, 2017, 26(3): 236-240.
- [16] Sanz-Cortes M, Egaña-Ugrinovic G, Simoes RV, et al. Association of brain metabolism with sulcation and corpus callosum development assessed by MRI in late-onset small fetuses [J]. Am J Obstet Gynecol, 2015, 212(6): 804.e1-8.

(编辑 余菁)