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胎儿侧脑室增宽的妊娠结局和预后的回顾性队列研究*

陈慧玲[1,2]，白 鹏[3]，李俊星[4]，李沁桐[2]，肖 雪[1,2△]

1. 四川大学华西第二医院 妇产科（成都 610041）；2. 出生缺陷与相关妇儿疾病教育部重点实验室（四川大学）（成都 610041）；
3. 四川大学华西基础医学与法医学院 法医物证教研室（成都 610041）；4. 四川省德阳市人民医院 妇产科（德阳 618099）

【摘要】 目的 评价胎儿侧脑室增宽（ventriculomegaly, VM）的妊娠结局和胎儿神经发育等预后。**方法** 采用回顾性队列研究纳入2011年3月–2020年9月四川大学华西第二医院住院收治的所有超声诊断的VM胎儿，采用随机数字表选取同时期的非VM胎儿作为对照组，比较两组间的妊娠结局及胎儿出生后的神经发育等预后情况。**结果** VM组的活产率77.63%（229/295），对照组活产率94.31%（265/281），VM组胎儿的活产率低于对照组（*P*<0.001），且VM组胎儿出生后转新生儿科监护观察的比例高于对照组〔20.96%（48/229）vs. 4.53%（12/265），*P*<0.001〕。随访中VM组胎儿出现神经发育异常率高于对照组〔11.79%（27/229）vs. 1.90%（5/265），*P*<0.001〕，且VM胎儿出生后的神经发育异常与侧脑室增宽的分度（*P*=0.010）、VM宫内进展（*P*=0.024）、出生后头颅超声是否提示VM（*P*=0.001）有关，且出生后头颅超声提示VM是神经发育异常的独立危险因素（*OR*=9.434, 95% *CI*：1.791～49.688，*P*=0.008）。**结论** VM降低了胎儿活产率，且可能增加胎儿出生后发生神经发育异常的风险。所有VM出生后均应严密随访神经发育等情况，尤其是重度VM、出现宫内进展、出生后头颅超声结果仍提示VM者。

【关键词】 侧脑室增宽 妊娠结局 神经发育 危险因素

Pregnancy Outcomes and Prognosis of Fetal Ventriculomegaly: A Retrospective Cohort Study

CHEN Hui-ling[1,2], *BAI Peng*[3], *LI Jun-xing*[4], *LI Qin-tong*[2], *XIAO Xue*[1,2△]. 1. *Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University*, Chengdu 610041, China; 2. *Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education, Sichuan University*, Chengdu 610041, China; 3. *Faculty of Forensic Medicine, West China School of Basic Medical Sciences and Forensic Medicine, Sichuan University*, Chengdu 610041, China; 4. *Department of Obstetrics and Gynecology, People's Hospital of Deyang City*, Deyang 618099, China

△ Corresponding author, E-mail: 19811454@qq.com

【Abstract】 Objective To evaluate the pregnancy outcomes and neurodevelopment prognosis of subjects prenatally diagnosed with fetal ventriculomegaly (VM). **Methods** All the subjects with VM diagnosed by ultrasound and were admitted and treated at West China Second Hospital, Sichuan University between March 2011 and September 2020 were retrospectively enrolled for a chohort study, while non-VM subjects of the same period were selected with a random number table to form the control group. Pregnancy outcomes of the two groups were compared, and the fetuses of both groups were followed up after birth for further assessment and comparison of their neurodevelopmental prognosis. **Results** The live birth rate of the VM group was lower than that of the control group (77.63% [229/295] vs. 94.31% [265/281], *P*<0.001). Furthermore, the proportion of subjects that were transferred to NICU for monitoring and observation after birth was higher in the VM group than that of the control group (20.96% [48/229] vs. 4.53% [12/265], *P*<0.001). During the follow-up, it was found that the rate of neurodevelopmental abnormalities of the VM group was significantly higher than that of the control group (11.79% [27/229] vs. 1.90% [5/265], *P*<0.001). Moreover, neurodevelopmental abnormalities of VM fetuses were correlated to the following factors, the degree of VM (*P*=0.010), intrauterine progression of VM (*P*=0.024), and whether the postnatal cranial ultrasound result was suggestive of VM (*P*=0.001). In addition, postnatal cranial ultrasound suggestive of VM was found to be an independent risk factor for neurodevelopmental abnormalities (*OR*=9.434, 95% *CI*: 1.791-49.688, *P*=0.008). **Conclusion** VM reduces the fetal live birth rate and may increase the risks of neurodevelopmental abnormalities after birth. All VM fetuses should be closely followed up for neurodevelopment status after birth, especially those with severe VM, intrauterine progression, and postnatal cranial ultrasound indicative of VM.

【Key words】 Ventriculomegaly Outcome of pregnancy Neurodevelopment Risk factor

胎儿侧脑室增宽（ventriculomegaly, VM）是一种孕期B超中最常见的胎儿神经系统异常[1-2]。根据既往研究建立的胎儿侧脑室正常宽度的参考范围，将VM定义为胎儿侧脑室宽度≥10 mm[3-4]。国际上产前检查中需常规监测脑室宽度，VM的发生率大致为0.3‰～10‰[5-8]。目前，普遍认为VM是一项非特异的超声软指标，并非一种独立的疾病，而是代表各种病理过程的一种共同表现，可能是胎儿颅脑结构的正常变异，也可能是其他颅脑结构异常的

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△ 通信作者，E-mail: 19811454@qq.com

继发表现或一些全身性疾病、染色体异常或病毒感染的颅内表现[6, 9-11]。

既往研究提示VM的预后具有较大的异质性,可能导致不同程度的神经精神发育异常,尤其在运动、认知、语言能力等方面[12-13]。由于目前VM预后的研究存在不同程度的差异,且大多数研究未纳入非VM作为对比。因此,本次回顾性队列研究旨在以非VM为参考标准,评估VM胎儿的妊娠结局及其出生后的神经精神发育等情况,以期为涉及VM的临床实践提供指导。

1 资料与方法

1.1 研究对象及资料收集

采用回顾性队列研究纳入2011年3月–2020年9月四川大学华西第二医院住院收治的所有超声诊断为VM的受试者,采用随机数字表选取同时期的非VM的受试者作为对照组,以尽可能保证医疗条件、诊治水平和随访时间一致性。VM组纳入标准:孕期超声检测提示胎儿侧脑室宽度≥10 mm;在我院规律产检并终止妊娠。对照组纳入标准:孕期超声未提示VM者;在我院规律产检并终止妊娠。排除标准(VM组和对照组):临床资料不全者。回顾所有参与者的影像学及临床资料,并在所有受试胎儿出生6个月后随访1次,随访时间为2021年3月–2021年5月。随访内容包括婴幼儿的神经系统发育情况,如运动、语言、认知等情况,以及神经精神系统相关疾病等。本研究经四川大学华西第二医院医学伦理委员会批准通过(2021年68号)。

1.2 分类及结局指标

VM分类按照孕期检测到最大的侧脑室宽度分为轻度(10 ~ 12 mm)、中度(12.1 ~ 15 mm)和重度(> 15 mm)VM。不伴有其他超声影像学上的颅内畸形及脏器畸形、染色体异常、或超声软指标的VM定义为孤立性VM,反之则称为非孤立性VM。按照孕期监测胎儿侧脑室宽度是否增加≥2.0 mm,分为VM进展和非进展(宽度增加< 2.0 mm或缩小)。

妊娠结局分为非活产以及活产,非活产包括流产、死胎、围产期死亡、要求终止妊娠。胎儿神经发育异常定义为:胎儿出生后出现任何神经发育异常的临床表现或诊断神经精神异常相关的疾病,如癫痫、多动症、自闭症、精神分裂症等,否则视为神经发育无异常。

1.3 统计学方法

定量资料用$\bar{x} \pm s$描述,分类资料用事件数和/或百分数描述。定量资料比较采用t检验,分类资料的比较采用χ^2检验或Fisher精确概率检验,双尾$P< 0.05$为差异有统计学意义。使用二元logistic回归分析VM神经发育异常的危险因素,使用Enter法筛选协变量,$P< 0.05$为差异有统计学意义。

2 结果

2.1 VM组与对照组一般资料比较

共纳入666例参与者,其中334例VM,332例非VM对照。除去失访后(VM组失访39例,对照组失访51例),295例VM与281例非VM的一般情况如表1所示。VM组与对照组在孕妇年龄、体质量指数、孕次、产次、妊娠合并症/并发症、是否多胎、随访时间方面差异均无统计学意义。VM组本次妊娠行体外受精与胚胎移植(*in vitro* fertilization and embryo transfer, IVF-ET)的比例高于对照组($\chi^2= 5.133$, $P= 0.023$),VM组男性胎儿比例多于对照组($\chi^2= 5.27$, $P= 0.022$)。VM组和对照组TORCH筛查IgM阳性率以及胎儿染色体异常率的差异均无统计学意义。

2.2 VM组与对照组妊娠结局比较

VM组的活产率77.63%(229/295),对照组活产率94.31%(265/281),VM组活产率低于对照组($\chi^2= 32.790$, $P< 0.001$)。VM组胎儿出生后转新生儿科监护观察的比例高于对照组($\chi^2= 31.086$, $P< 0.001$)。两组分娩孕周($\chi^2= 16.468$, $P< 0.001$)、胎儿身长($t= -2.526$, $P= 0.012$)、胎儿体质量($t= -2.432$, $P= 0.015$)差异均有统计学意义,新生儿Apgar(1 min-5 min-10 min)评分差异均无统计学意义。见表1。

2.3 活产VM胎儿的神经发育异常情况

2.3.1 VM神经发育异常的单因素分析 对比229例活产的VM(非活产66例)与265例对照组(非活产51例),VM组神经发育异常率(11.79%, 27/229)高于对照组(1.89%, 5/265)($\chi^2= 17.388$, $P< 0.001$)。随访的229例VM中,27例出现神经发育异常,运动能力异常17例,语言能力异常11例,认知能力异常4例,个人-社交能力异常4例,癫痫1例,多动症1例,自闭症2例。由表2可见,VM的分度(Fisher精确检验值= 10.412, $P= 0.010$)、VM宫内进展($\chi^2= 6.260$, $P= 0.024$)在有无神经发育异常组间的差异有统计学意义。共有104例VM出生后行头颅超声检查,神经发育异常组出生后超声提示VM的比例高于神经发育无异常组($\chi^2= 13.491$, $P= 0.001$)。胎儿性别、染色体异常率、分娩方式、初诊孕周是否大于28周、是否为非孤立VM、双侧VM与神经发育异常无关。

2.3.2 VM神经发育异常的多因素分析 将表2中与胎儿预后相关的3个因素(VM的分度、VM宫内进展情况、出生后超声是否提示VM),既往研究提示可能与VM预后相

表 1　VM组与对照组一般情况及妊娠结局

Table 1　Generalconditions and pregnancy outcome of the VM group and the control group

Category	VM group (*n*=295)	Control group (*n*=281)
Maternal age/yr.	30.89±4.36	31.30±4.06
Body mass index/(kg/m^2)	21.08±2.84	21.00±2.70
Gravidity	2.43±1.49	2.29±1.51
Parity	1.29±0.56	1.34±0.56
Pregnancy with complications/case (%)	158 (53.56)	142 (50.53)
IVF-ET/case (%)	35 (11.86)*	18 (6.41)
Multiple pregnancy/case (%)	40 (13.56)	28 (9.96)
Male fetus/case (%)[a]	174 (59.59)*	138 (50.00)
Follow-upperiod/month	33.17±26.01	37.56±28.60
IgM positive of TORCH/case (%)[b]	11 (14.67)	6 (13.04)
Abnormal chromosomal analysis of amniocentesis/case (%)[c]	11 (8.46)	3 (5.17)
Gestational week of delivery/case (%)#		
<28 weeks	26 (8.81)	13 (4.63)
28-36 weeks	81 (27.46)	46 (16.37)
⩾37 weeks	188 (63.73)	222 (79.00)
Body length of fetus/mm[d]	46.70±6.17*	47.93±5.35
Body mass of fetus/g[d]	2 836.56±955.58*	3 007.18±703.65
Apgar score at 1 minute[d]	9.72±0.75	9.83±0.66
Apgarscore at 5 minutes[d]	9.92±0.35	9.94±0.28
Apgarscore at 10 minutes[d]	9.96±0.24	9.97±0.18
Transfer to NICU/case (%)[d]	48 (20.96)*	12 (4.53)

a: 3 VM and 5 control had unclear gender; b: 75 VM subjects and 46 controls underwent the TORCH test; c: 130 VM subjects and 58 controls underwent amniocentesis for fetal karyotyping or chromosome microarray analysis; d: 229 VM subjects vs. 265 controls; *P<0.05, vs. control group; # P<0.05, gestational weeks of delivery between the two groups was statistically different.

表 2　有无神经发育异常的活产VM胎儿的临床资料比较

Table 2　Clinical data comparison of viable VM fetuses with or without neurodevelopmental abnormalities

Factor	VM with normal neurodevelopment/case (%), *n*=202	VM with abnormal neurodevelopment/case (%), *n*=27
Male fetus	124 (61.39)	13 (48.15)
Abnormal chromosomal analysis of amniocentesis[a]	9 (8.91)	1 (8.33)
Gestational week at delivery		
<28 weeks	1 (0.00)	0 (0.00)
28-36 weeks	42 (20.79)	5 (18.52)
⩾37 weeks	159 (78.71)	22 (81.48)
Cesarean delivery	137 (67.82)	19 (70.37)
Non-isolated VM	73 (36.14)	11 (40.74)
Postnatal cranial ultrasound suggestive of VM[b]	25 (26.88)	9 (81.82)*
Bilateral VM	56 (27.72)	9 (33.33)
Gestational age at initial diagnosis⩾28 weeks	97 (48.02)	17 (62.96)
Progression of VM	15 (7.43)	6 (22.22)*
Degrees of VM#		
Mild	159 (78.71)	15 (55.56)
Moderate	39 (19.31)	9 (33.33)
Severe	4 (1.98)	3 (11.11)

a: 101 cases with normal neurodevelopment and 12 cases with abnormal neurodevelopment underwent amniocentesis for fetal karyotyping or chromosome microarray analysis; b: Postnatal cranial ultrasonography was performed in 93 cases with normal neurodevelopment and 11 cases with abnormal neurodevelopment; *P<0.05, vs. VM with normal neurodevelopment; #P<0.05, degrees of VM of the two groups showed statistically significant difference.

关的因素(是否为非孤立VM、单/双侧VM)以及分娩的孕周共6个因素,定义为自变量$X(X_1, X_2, X_3\cdots\cdots X_6)$,将VM预后定义为因变量$Y$($Y=0$,神经发育无异常;$Y=1$,神经发育异常),进行VM神经发育异常的二元logistic回归分析。

回归分析结果如表3显示,出生后B超提示VM是出现神经发育异常的独立危险因素($OR=9.434$, 95%CI: 1.791 ~ 49.688, $P=0.008$)。其他因素,如VM的分度、VM宫内进展情况、是否为非孤立VM、单/双侧VM以及分娩的孕周,并非VM预后不良的独立危险因素。

表 3 VM神经发育预后的二元logistic回归分析结果

Table 3 Binary logistic regression analysis of neurodevelopmental prognosis of VM

Factor	Category	β	*SE*	Wald	*P*	*OR*	95% *CI*
Gestational week at delivery	⩾37 weeks					1	Ref
	28-36 weeks	−0.515	0.577	0.797	0.372	0.597	0.193-1.851
	<28 weeks	−21.338	40 192.970	<0.001	1.000	0.000	–
Isolated VM	Yes					1	Ref
	No	−0.120	0.472	0.065	0.799	0.887	0.352-2.237
Unilateral/bilateral VM	Unilateral					1	Ref
	Bilateral	−0.345	0.529	0.425	0.514	0.708	0.251-1.998
Degrees of VM	Mild					1	Ref
	Moderate	0.576	0.611	0.891	0.345	1.780	0.538-5.889
	Severe	2.038	1.042	3.828	0.050	7.672	0.996-59.083
Variation of width	Not-progressing					1	Ref
	Progressing	0.329	0.730	0.203	0.653	1.389	0.332-5.811
Postnatal cranial ultrasound	Without VM					1	Ref
	With VM	2.244	0.848	7.010	0.008	9.434	1.791-49.688
	Not done	1.601	0.780	4.219	0.040	4.959	1.076-22.851
Constant		−3.503	0.737	22.609	<0.001		

β: Partial regression coefficient; *SE*: Standard error; *OR*: Odds ratio; *CI*: Confidence interval.

3 讨论

胎儿VM是最常见的中枢神经系统异常,其对胎儿造成的影响尚无确切定论。本研究以非VM胎儿为参考标准,回顾性队列研究VM的妊娠结局及胎儿预后,可以更好地实现优生。

3.1 VM妊娠结局

本研究结果显示,VM组活产率低于对照组。非活产的VM共66例,其中64例系终止妊娠,且其中大部分为合并中枢神经系统结构畸形、染色体异常或双侧侧脑室增宽。对于这部分引产的VM继续妊娠能否活产,以及VM是否会降低自然活产率,研究尚存疑问。VM组胎儿出生后转新生儿科监护观察的比例高于对照组,临床中在一定程度上给予了VM胎儿更密切的监护。PISAPIA等[14]的研究建议,产后应密切监测VM患儿是否出现颅内压升高的迹象,包括活动减少、呕吐、囟门增宽、呼吸暂停等,必要时转新生儿科监护观察。

3.2 VM胎儿预后

VM可能导致胎儿出生后认知、语言和行为障碍,与自闭症、精神分裂症、癫痫、注意力缺陷/多动障碍等疾病有关[12, 15-16]。本研究显示VM胎儿的神经发育异常率高于对照组,且其预后与多种因素相关。

3.2.1 *出生后B超提示VM与VM胎儿神经发育异常的关系* 出生后B超提示VM的患儿出现神经发育预后异常的风险高于出生后无VM的患儿($OR=9.434$, 95%CI: 1.791 ~ 49.688, $P=0.008$)。因此,对于出生后的VM,应积极完善头颅B超等相关影像学检查,可更好预测患儿预后,及时干预。

3.2.2 *侧脑室增宽的严重程度与VM胎儿神经发育异常的关系* 侧脑室增宽的严重程度与VM胎儿神经发育异常有关。轻、中、重度VM胎儿神经发育无异常的比例分别为91.38%(159/174)、81.25%(39/48)及57.14%(4/7)。2018年美国母胎医学会指出,侧脑室宽度接近10 mm,尤其是孤立性VM,预后良好率大于90%,侧脑室宽度在

13 ~ 15 mm预后良好率为75% ~ 93%[17], 本研究的数据也在此范围内。重度VM提示胎儿预后不良, 但本研究中二元logistic回归分析并未得出重度VM是预后不良的危险因素。因本研究活产的重度VM仅7例, 故需扩大样本量进一步研究。2020年美国母胎学会更新共识, 认为轻度VM也可能出现严重神经发育异常[18]。本研究27例神经发育异常的胎儿中, 有12例均为轻度孤立性VM。一些轻度的神经发育异常在后期的康复训练中, 可以逐渐好转, 甚至恢复正常。因此即使对于轻度VM, 出生后也应长期密切随访神经发育相关情况, 及时干预, 但目前尚缺乏大样本的前瞻性研究评估干预的作用。

3.2.3 *非孤立性VM与VM胎儿神经发育异常的关系*　非孤立性VM可能预示预后不良, 且其预后与合并的结构畸形相关[11, 17, 19]。VM合并胼胝体发育不良出生后可能出现轻重不一的神经精神系统症状, VM合并脊柱裂出生后可能有下肢功能或排便控制障碍, Dandy-Walker综合征存活者常智力低下, 无叶全前脑为致死性畸形, 半叶全前脑存活者智力低下[20]。本研究中66例VM非活产中有64例均为医源性终止妊娠, 其中57例合并结构异常。本研究结果显示, 非孤立性VM与神经发育异常无关。由于大多数合并严重颅脑结构畸形的VM已经终止妊娠, 故未再纳入随访队列中分析, 这可能是与现有其他研究结果不一致的原因。且有部分VM未完善胎儿头颅MRI, 不除外合并其他颅脑结构异常, 因此尚不能排除非孤立性VM与神经发育异常的相关性。

3.2.4 *其他因素对VM胎儿预后的影响*　有研究表明, VM宫内进展率14%, 宫内进展的VM比宫内无进展者的神经发育情况更差[9, 19]。本研究中, VM的宫内进展率为9.17%(21/229), 宫内进展的VM胎儿出现神经发育异常的比率为28.57%(6/21), 且VM宫内进展与神经发育异常有关。二元logistic回归分析示VM宫内进展的预后不良风险是非进展的1.389倍, 但差异无统计学意义, 宫内进展对预后的影响尚需更多累积证据证实。

本研究发现, 初诊孕周、胎儿性别、分娩方式与预后无关。孕16周后胎儿神经系统结构及完整的脑室系统基本形成, VM通常在孕16周后被监测出。孕期无论任何时候发现VM, 均应告知孕妇及家属胎儿出生后可能出现神经发育异常等风险, 并严密动态监测。本研究VM中剖宫产率68.12%(156/229), 分娩方式与胎儿出生后神经发育异常无关, 且胎儿侧脑室并非剖宫产指征, VM终止妊娠的时机和方式应根据母胎其他情况, 遵循产科指征, 不因胎儿VM行剖宫产[17]。

本研究尚存不足之处: VM的不良预后可能会在出生后1年或直到学龄才表现出来[21], 由于部分胎儿的随访时间有限, 可能无法追踪到胎儿的一些临床症状; 并非所有孤立性VM的诊断均得到MRI检查的证实, 因此得出的结论可能存在偏倚; 活产的重度VM例数过少, 需扩大这部分样本以得出更可靠的结论。

综上, VM降低了胎儿活产率, 且可能增加胎儿出生后发生神经发育异常的风险。出生后头颅超声结果仍提示VM是神经发育异常的独立危险因素。孕期应综合评估VM, 尤其是重度VM、合并严重颅脑结构畸形等情况应考虑终止妊娠。轻度孤立性VM出生也可能出现严重神经发育异常, 所有VM出生后均应严密随访神经发育等情况, 尤其是重度VM、出现宫内进展、出生后头颅超声结果仍提示VM者。

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利益冲突　所有作者均声明不存在利益冲突

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