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孕中期羊膜腔穿刺术的胎儿丢失率

SOGC

【摘要】 **目的** 确定孕中期羊膜腔穿刺术后的胎儿丢失率。**结局** 减少良性的活组织检查率。**利益** 为孕妇提供更好的关于孕中期诊断性羊膜腔穿刺术利弊的咨询,并确保孕妇在作出产前筛查的决定前能够得到充分的信息和建议。**总结** 基于不同的变量,羊膜腔穿刺术后的流产风险是有个体差异的。

1 孕中期羊膜腔穿刺术:术后流产率究竟是多少?

对于染色体异常和单基因遗传病的产前诊断,孕中期羊膜腔穿刺术是最常用的一种侵入性检查方法。传统而言,诊断性羊膜腔穿刺术的手术指征是高龄孕妇(≥35 岁)、有染色体异常的生育史(家族史)以及非侵入性产前筛查(超声和/或生化指标)的结果异常者。选择 35 周岁年龄为界,是因为此年龄段的孕妇怀有染色体异常胎儿的风险约相当于操作后流产的风险,大多数加拿大研究中心的风险值为 0.5%(1/200)[1]。由于非侵入性产前筛查技术的提高,现在这个手术指征已被淘汰。根据加拿大妇产科医师协会最近发布的指南[2],所有的孕妇都必须进行多重的标记物筛查,只有筛查结果超过截断值的孕妇才需要进行侵入性检查,不再仅仅根据孕妇的年龄来决定是否行羊膜腔穿刺术。此外,分娩年龄≥40 周岁的孕妇因具有极高的风险,需告知其选择产前筛查或者直接进行侵入性检查的必要性。

2 背景

文献中报道的流产有两种类型:① 羊膜腔穿刺后总流产率,包括孕龄相关的自然流产和穿刺相关的流产;② 穿刺相关的流产率。总流产率的数据来自进行过羊膜腔穿刺的孕妇人数,由进行过别项侵入性检查的孕妇作为对照组或者不设对照组。穿刺相关流产率的数据来自进行过此项操作的孕妇,由未行"任何操作"的孕妇作为对照组。

Eddleman 等[3]最近的研究表明穿刺相关的流产率有可能小于之前的文献报道,这进一步挑战了传统的根据"利弊比率"来决定是否进行侵入性检查的观点。即使委员会认为应及时对这篇文献进行重新评定,我们还是认为他的结论,即羊膜腔穿刺造成的流产率为 0.06%(1/1600)有误导作用,要谨慎的加以解释[3]。Eddleman 的研究是对"孕早、中期非整倍体染色体评估试验"(Firstand Second Trimester Evaluation of Risk for Aneuploidy, FASTER)的数据进行了两次分析,FASTER 原本的目的是比较孕早、中期的非侵入性产前基因筛查方法。在被调查的 35 003 名孕妇中,有 3 096 名孕妇进行了羊膜腔穿刺,作为试验组;另外 31 907 名孕妇未行羊膜腔穿刺作为对照组。在试验组中,孕 24 周之前自然流产率为 1%,而对照组为 0.96%,两者相比无明显差异,在两组中因羊膜腔穿刺而引起的流产率为 0.06%(1/1600),是有差异的。然而,在试验组中流产率没有包括染色体异常的妊娠终止,反之在对照组(未进行羊膜腔穿刺)包括了染色体异常造成的自然流产。由此推论,假设试验组中妊娠终止的许多人会发生自然流产,那么与对照

此项会议共识由加拿大妇产科医师协会(the Society of Obstetricians and Gynaecologists of Ganada, SOGC)达成。本刊中文译稿获得 SOGC 的认可,在此特表感谢!

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组相比较而言,排除了这些人就低估了试验组中流产比率。

有多名学者以书信的形式对FASTER的结论进行了评论[5-9]。Nadel[5]指出,穿刺组与未穿刺组在孕24周之前未调整的胎儿流产率无明显差异(P=0.74),两组之间的点估计值(0.06%)的95%可信区间(CI)为−0.26%～0.49%。他认为在整倍体胎儿中,因羊膜腔穿刺术所引起的流产率可能不超过0.5%(但具体数值不清楚)。

Smith[7]提出,以往统计方法包括或除外了妊娠终止的患者,这导致了一个悖论:那些筛查结果阳性而没有进行羊膜腔穿刺术的孕妇,以及年龄达到或超过35周岁的孕妇,她们的自然流产率的统计学结果出现了明显的增加。文献报道的诊断性羊膜腔穿刺术的最低流产风险约为1:300[8]。

3 建议

在向患者建议行羊膜腔穿刺术之前,必须告知患者妊娠本身有一定的流产比率,而行穿刺术会增加额外的流产风险。告知孕妇人群的背景流产风险和其个体的流产风险是很重要的,因为患者不能够判断她的流产是"自然的"还是"穿刺相关的"。遗传咨询时需向患者提供总的流产率,使之能充分理解她所做的决定可能带来的后果。另外,个体的穿刺风险也是必须和患者讨论的,因为不同的因素会影响人群及个体的背景风险。

3.1 母体因素

3.1.1 生育年龄/孕龄[10-14];

3.1.2 既往生育史[13];

3.1.3 母体并发症(糖尿病、高血压、不孕、自身免疫性疾病);

3.1.4 孕期/子宫因素(辅助生殖技术、阴道流血、子宫肌瘤、胎盘位置、羊水丢失、羊水过少、绒毛膜后血肿、单/多胎妊娠)[16-19];

3.1.5 产前筛查方法[20]

3.1.5.1 检查时间(孕早期、孕中期、孕早中期);

3.1.5.2 方法(超声、生化指标、生化指标结合超声、颈部透明带和(或)生化指标、单一或多重的标记物)。

3.2 技术因素

3.2.1 穿刺针的大小[21];

3.2.2 操作者的经验[22-24];

3.2.3 超声引导(徒手、穿刺针引导);

3.2.4 子宫/胎盘位置;

3.2.5 母体的体重指数。

3.3 操作后因素

3.3.1 休息24小时或正常活动(没有基于有效对比实验的证据)

3.3.2 并发症(胎膜早破、感染)

表1、表2总结了最近发表的论文(随机对照试验、有或无对照组的队列分析,对照组为未进行侵入性检查或进行了其他的侵入性检查),得出孕中期羊膜腔穿刺的流产率范围为0.75%～3.3%(9项研究,平均值1.41%,中值1.1%)。4项孕中期羊膜腔穿刺与没有操作的对照研究中,两组数据有一定的统计学差异,穿刺后的流产率较高,其范围为0.06%～1.0%(平均0.64%;各项研究的数据分别是1.0%、0.80%、0.70%、0.06%)。根据第二组的对照研究(减去FASTER的结果),羊膜腔穿刺相关流产率的可信区间范围为0.19%～1.53%[26-38]。由此,根据文献对羊膜腔穿刺进行统计学分析,得出结论:基于对照组的流产率(1.08%)与穿刺组的流产率(1.68%)不同,因此羊膜腔穿刺相关的流产率为0.6%(CI为0.31～0.9)[38]。

表1 羊膜腔穿刺后总的妊娠流产率

研究课题(年份)	类型	穿刺组(人数)	对照组(人数)	穿刺后流产率	显著性
Smidt-Jensen[26](1992)	RCT	1 042	CVS TC 1010 TA 1 027	1.16%	—
Lippman[27](1992)	RCT	1 200	CVS 1 191	0.9%(0.3<4周)	—
Johnson[28](1996)	RCT	339	EA 344	3.3%	NS
CEMAT[29](1998)	RCT	1 775	EA 1 916	1.0%	—
Collins[30](1998)	C	1 747	EA 1 207	1.1%	—
Reid[31](1999)	C	3 953	—	0.7%	—
Antsalis[32](2000)	C	3 910	Other amnio* 5324	2.1%/1.5%	p=0.01
Horger[33](2001)	C	4 600	—	0.95%	—
Caughey[34](2006)	C	30 893	CVS 9886	0.83%;0.46%(原始);(调整)	—

表 2 羊膜腔穿刺术相关的妊娠流产率

研究课题(年份)	类型	穿刺组人数	对照组人数	穿刺相关流产率(穿刺组;无操作组)	统计学意义
Tabor[35](1986)	RCT	2 302	2 304	1%(3.2%; 2.2%)	NS
Muller[36](2002)	C	3 472	47 004	0.7%(1.12%; 0.42%)	95% CI 0.39～1.13
Kong[37](2006)	C	3 468	1 125	0.86%(经自然流产率校正)	95% CI 0.19～1.53
FASTER[3](2006)	C	3 096	31 907	0.06%(1.0%; 0.94%)	95% CI—0.26～0.49
Seeds[38](2004)	Review	11 372	12 097	0.6%(1.68%; 1.08%)	95% CI 0.31～0.9

注：RCT:随机对照试验;C:病例对照队列分析;CVS:绒毛膜绒毛取样(TA:经腹;TC:经阴道);EA:孕早期羊膜腔穿刺;RR:相关系数;CI:可信区间;NS:无显著性差异。

* 研究组:20～34 周岁,有非整倍体妊娠高风险或母体感染可能行羊膜腔穿刺术;

对照组:20～34 周岁,无高风险因素行羊膜腔穿刺术。

在这些对照研究中,FASTER 的流产率(行羊膜腔穿刺术组、未行羊膜腔穿刺术组)显然是异常的,这反映了将穿刺组中终止妊娠者排除的分析方法低估了孕中期羊膜腔穿刺后穿刺相关的流产率,结果导致了穿刺组比对照组更低的妊娠流产率。

4 结论

在单胎妊娠中,没有一个单一的百分比(或比值比)可以被看成是孕中期羊膜腔穿刺术后流产的风险。此项会议共识认为,穿刺术后流产的风险是有个体差异的,而且是受多因素影响的。由羊膜穿刺术所造成的流产率,最适估计范围为 0.6%～1.0%(1/175～1/100),其可信区间为 0.19%～1.53%。最近发表的双胎妊娠最适的风险估计值为 1.6%(CI 为 0.3～3%)[16]。

参 考 文 献

[1] Wilson RD. Amended Canadian Guideline for prenatal diagnosis (2005) change to 2005—techniques for prenatal diagnosis. SOGC Clinical PracticeGuidelines, No. 168, November 2005[R]. J Obstet Gynaecol Can, 2005,27:1048-1054.

[2] Summers AM, Langlois S, Wyatt P, et al. Prenatal Screening for Fetal Aneuploidy. Joint SOGC-CCMG Clinical Practice Guideline[R]. J Obstet Gynaecol Can, 2007,29(2):146-161.

[3] Eddleman KA, Malone FD, Sullivan L, et al. Pregnancy loss rates after midtrimester amniocentesis[J]. Obstet Gynecol, 2006,108:1067-1072.

[4] Fergal D, Malone FD, Jacob A, et al. First-trimester or second-trimester screening, or both, for Down's syndrome [J]. N Engl J Med, 2005,353(19):2001-2011.

[5] Nadel A. Letter to Editor: Pregnancy loss rates after midtrimesteramniocentesis[J]. Obstet Gynecol, 2007,109:451.

[6] Wilson RD. Letter to Editor: Pregnancy loss rates after midtrimesteramniocentesis[J]. Obstet Gynecol, 2007,109:451-452.

[7] Smith L. Letter to Editor: Pregnancy loss rates after midtrimesteramniocentesis[J]. Obstet Gynecol, 2007,109:452.

[8] Wapner RJ, Evans MI, Platt LD. Letter to the Editor: Pregnancy loss ratesafter midtrimester amniocentesis[J]. Obstet Gynecol ,2007,109(3):780.

[9] Nicolaides K. Letter to the Editor: Pregnancy loss rates after midtrimesteramniocentesis[J]. Obstet Gynecol, 2007,109(3):780.

[10] Papantoniou NE, Daskalakis GJ, Tziotis JG, et al. Risk factors predisposing to fetal loss following a secondtrimester amniocentesis[J]. BJOG, 2001,108(10):1053-1056.

[11] Jacobson B, Ladfors L, Milson I. Advanced maternal age and adverseperinatal outcome[J]. Obstet Gynecol, 2004,104(4):727-733.

[12] Bianco K, Caughey AB, Shaffer BL, et al. History ofmiscarriage and increased incidence of fetal aneuploidy in subsequentpregnancy[J]. Obstet Gynecol, 2006,107(5):1098-1102.

[13] Kleinhaus K, Perrin M, Friedlander Y, et al. Paternal age and spontaneous abortion[J]. Obstet Gynecol,2006,108(2):369-377.

[14] Savva GM, Morris JK, Mutton DE, et al. Maternal age-

specific fetalloss rates in Down syndrome pregnancies[J]. Prenat Diagn, 2006,26:499-504.

[15] Mattison DR. Characterizing the effect of environmental and occupational exposures on reproduction anddevelopment. In: Evans MI, Johnson MP, Yaron Y, Drugan A, eds. Prenatal Diagnosis[M]. New York: McGraw-Hill, 2006. 137-148.

[16] Wapner RL, Johnson A, Davis G, et al. Prenataldiagnosis in twin gestations: a comparison between second-trimesteramniocentesis and first-trimester chorionic villus sampling[J]. Obstet Gynecol,1993,82(1):49-56.

[17] Allen VM, Wilson RD. Pregnancy outcomes after assisted reproductivetechnology. Joint SOGC-CFAS Guideline, No. 173, March 2006[R]. J ObstetGynaecol Can, 2006,28:220-233.

[18] Millaire M, Bujold E, Morency AM, et al. Mid-trimester geneticamniocentesis in twin pregnancy and the risk of fetal loss[J]. J ObstetGynaecol Can, 2006,28(6):512-518.

[19] Srinivas SK, Ma Y, Sammel MD, et al. Placental inflammation and viral infection are implicated in second trimesterpregnancy loss[J]. Am J Obstet Gynecol, 2006, 195:797-802.

[20] Huang T, Owolabi T, Summers A, et al. The identification ofrisk of spontaneous fetal loss through second-trimester maternal serumscreening[J]. Am J Obstet Gynecol, 2005, 193:395-403.

[21] Gratacós E, Devlieger R, Decaluwé, et al. Is theangle of needle insertion influencing the created defect in human fetalmembranes? Evaluation of the agreement between specialists' opinions andex vivo observations[J]. Am J Obstet Gynecol, 2000,182(3):646-649.

[22] Johnson JM, Wilson RD, Singer J, et al. Technical factors in early amniocentesis predict adverse outcome. Results ofthe Canadian early (EA) versus mid-trimester (MA) amniocentesis trial[J]. Prenat Diagn, 1999,19:732-738.

[23] Blessed WB, Lacoste H, Welch RA. Obstetrician-gynecologists performinggenetic amniocentesis may be misleading themselves and their patients[J]. AmJ Obstet Gynecol, 2001,184:1340-1344.

[24] Welch RA, Salem-Elgharib S, Wiktor A, et al. Operator experience and sample quality in genetic amniocentesis[J]. Am JObstet Gynecol, 2006,194:189-191.

[25] Borgida AF, Mills AA, Feldman DM, et al. Outcome of pregnancies complicated by ruptured membranes after geneticamniocentesis[J]. Am J Obstet Gynecol, 2000,183: 937-939.

[26] Smidt-Jensen S, Permin M, Phillip J, et al. Randomised comparison of amniocentesis and transabdominal andtranscervical chorionic villus sampling[J]. Lancet, 1992, 340(8830):1237-1244.

[27] Lippman A, Tomkins D, Shime J, et al. Canadian multicentrerandomized clinical trial of chorion villus sampling and amniocentesis[J]. Prenat Diagn, 1992,12:385-476.

[28] Johnson JM, Wilson RD, Winsor EJ, et al. The early amniocentesis study: a randomized clinical trial of earlyamniocentesis versus midtrimester amniocentesis[J]. Fetal Diagn Ther,1996,11(2):85-93.

[29] The Canadian Early and Mid-trimester Amniocentesis Trial (CEMAT)Group. Randomised trial to assess safety and fetal outcome of early andmidtrimester amniocentesis[J]. Lancet, 1998,351:242-247.

[30] Collins VR, Webley C, Sheffield LJ, et al. Fetal outcome and maternalmorbidity after early amniocentesis[J]. Prenat Diagn, 1998,18:767-772.

[31] Reid KP, Gurrin LC, Dickinson JE, et al. Pregnancyloss rates following second trimester genetic amniocentesis[J]. Aust NZ J Obstet Gynaecol, 1999,39:281-285.

[32] Antsaklis A, Papantoniou N, Xygakis A, et al. Genetic amniocentesis in women 20-34 years old: associated risks[J]. Prenat Diagn 2000,20:247-250.

[33] Horger EO, Finch H, Vincent VA. A single physician's experience with fourthousand six hundred genetic amniocentesis[J]. Am J Obstet Gynecol,2001,185:279-288.

[34] Caughey AB, Hopkins LM, Norton ME. Chorionic villus samplingcompared with amniocentesis and the difference in the rate of pregnancyloss[J]. Obstet Gynecol, 2006,108(3): 612-616.

[35] Tabor A, Philip J, Madsen M, et al. Norgaard-Pedersen B. Randomized controlled trial of genetic amniocentesis in 4606 low-riskwomen[J]. Lancet, 1986,1:1287-1293.

[36] Muller F, Thibaud D, Poloce F, et al. Riskof amniocentesis in women screened with positive for Down syndromewith second trimester maternal serum markers[J]. Prenat Diagn, 2002,22:1036-1039.

[37] Kong CW, Leung TN, Leung TY, et al. Risk factors for procedure-related fetal losses after mid-trimester geneticamniocentesis[J]. Prenat Diagn, 2006,26:925-930.

[38] Seeds JW. Diagnostic mid trimester amniocentesis: how safe [J]? Am J Obstet Gynecol,2004,191:608-616.

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