“辅助生殖导致孕妇血清中妊娠相关血浆蛋白-A水平降低并导致唐氏综合征妊娠早期筛查中假阳率升高”点评

相玉倩
(复旦大学生物医学研究院发育生物学与出生缺陷研究所,上海 200032)

1 论文题目及原文摘要

Pregnancies conceived using assisted reproductive technologies (ART) have low levels of pregnancy-associated plasma protein-A (PAPP-A) leading to a high rate of false-positive results in first trimester screening for Down syndrome

Pregnancy screening for Down syndrome (DS) and other chromosome abnormalities has become part of routine antenatal care over the last 20 years. The measurement of second trimester biochemical markers in the blood of pregnant women to improve screening for DS based on maternal age alone was first described in 1988. Over the last 10 years, second trimester serum screening has been progressively replaced by first trimester combined screening. The first trimester combined screen measures maternal serum levels of free beta-human chorionic gonadotrophin (fβ-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 9—12 weeks gestation and measures nuchal translucency (NT) by ultrasound at 11—13 weeks gestation. These measurements are combined with maternal age, weight and gestational age to produce a risk estimate of the fetus having DS or trisomy 18 (T18). For pregnancies at increased risk, prenatal diagnostic testing, CVS or amniocentesis, can be offered. In the Victorian population, the sensitivity of the first trimester combined screen for DS is 91% (using a risk threshold of 1 in 300 at the time of ultrasound), with the proportion of unaffected pregnancies receiving an increased risk result (false positive rate, FPR) being 3.9%. Pregnancies conceived using assisted reproductive technologies (ART) now account for 3% of all live births in Australia. Previous studies of second trimester serum screening have shown that serum markers in ART pregnancies differ from natural conceptions, leading to an increased FPR. We hypothesized that in pregnancies conceived using ART, factors exist that are absent in natural conceptions, potentially influencing the marker levels, and consequently, risk results of the first trimester combined screen. The aims of this study were to investigate in a large population-based sample, the effect of ART on the individual markers of the first trimester combined screen (fβ-hCG, PAPP-A and NT) and on the FPR. We also aimed to investigate the effect of different ART modalities on these markers, and the impact of ART and screening results on the uptake of prenatal diagnostic testing (CVS and amniocentesis) following first trimester combined screening.

Learning Objectives: Through this article, the readers should be aware of the effects of ART on first trimester screening for Down syndrome and the factors exiting in the ART that cause the

effect.

2 论文核心内容及点评

本研究论文发表在 Human Reproduction, 2009,24(16):1330-1338 上。作者通过对大样本人群调查,研究辅助生殖技术(ART)对早期妊娠检测标志物(fβ-hCG、PAPP-A 和 NT)和假阳性率的影响,同时作者还研究了不同 ART 形式对上述结果影响的差别,以及 ART 和筛查结果对后续产前诊断(如绒毛膜取样和羊膜腔穿刺)的影响。该论文的核心内容如下:

唐氏综合征妊娠早期筛查包括检测母亲血浆中游离 β-绒毛膜促性腺激素(fβ-hCG)和妊娠相关血浆蛋白-A(PAPP-A)及超声探测胎儿颈部透明层厚度(NT),并结合母亲年龄、体重及孕龄,对胎儿患唐氏综合征的风险进行评估。

本研究以 2000～2004 年间澳大利亚的维多利亚州的 1 739 例 ART 单胎妊娠孕妇和 50 253 例自然受孕单胎妊娠孕妇为调查对象,比较了 ART 孕妇和自然受孕孕妇血清标记物(包括游离 β-hCG 和 PAPP-A)的水平及对应患儿检出的假阳性率。在 ART 孕妇中 PAPP-A 浓度为 0.83 MoM,而在非-ART 孕妇中为 1.00 MoM,与自然受孕孕妇相比,ART 孕妇的 PAPP-A 水平显著降低($P<0.001$),同时 ART 孕妇孕期并发症和产科并发症的发病率明显升高,且并发症孕妇中 PAPP-A 水平更低,排除妊娠综合征病例后,这种显著性差异仍然存在。与非 ART 孕妇相比,ART 孕妇早期筛查中假阳性率升高(OR 2.71,95% CI 2.19～3.35;$P<0.001$),从而导致需要进行绒毛膜取样或者羊膜腔穿刺的 ART 孕妇的数目增多(OR 2.10,95% CI 1.76～2.50;$P<0.001$)。作者同时分析了不同的 ART 对早期妊娠检测标志物(fβ-hCG、PAPP-A 和 NT)和假阳性率的影响。作者研究表明,与冰冻胚胎移植相比,新鲜胚胎移植更容易导致 PAPP-A 水平的降低,此外激素等因素也会引起 PAPP-A 水平的降低,从而增加了患儿检出的假阳性率。

综上所述,辅助生殖技术的应用显著降低了唐氏综合征产前筛查血清标志物 PAPP-A 水平,增加了患儿检出的假阳性率,这使得需要进行绒毛膜取样或者羊膜腔穿刺的 ART 孕妇增多。绒毛膜取样和羊膜腔穿刺对孕妇和胎儿都存在一定的危害性。作者最后指出,ART 孕妇,尤其是接受激素处理的 ART 孕妇,在筛查中存在假阳性率高的因素,如何准确评估所引起的风险改变,有待进一步的研究。

点评:辅助生殖技术(assisted reproductive technology,ART)是指所有涉及体外操作人的卵子和精子或胚胎,以达到妊娠目的的方法。近年来,随着辅助生殖技术的开展,越来越多的不孕不育患者借助各种 ART 技术怀孕。ART 包括体外受精、卵胞浆内精子注射技术和体外受精-胚胎移植技术等,ART 的应用使得高龄产妇和双胎(或多胎)孕妇增加,与自然受孕孕妇相比,ART 孕妇接触的各种影响因素更多,这很可能影响了妊娠早期筛查中的分子标志物的水平及假阳性率,并最终影响筛查结果的准确性。

读者 · 作者 · 编者

本刊对文稿撰写的要求

文稿应具科学性、实用性,论点明确,资料可靠,数据准确,层次清楚,文字精练,用字规范,文稿附图量不限,提倡多附图片和视频(音频)内容。论著性文章 4000 字左右,综述、讲座 5000 字左右,论著摘要、经验交流、病例报告等一般不超过 2000 字,欢迎以图像为主的来稿,并贯穿文字说明和评析,专家视频讲座为 30～40 分钟(分成 3～4 段)。当报告是以人为研究对象的试验时,作者应该说明其遵循的程序是否符合负责人体试验的委员会(单位性的、地区性的或国家性的)所制定的伦理学标准并得到该委员会的批准,是否取得受试对象的知情同意。文题力求简明,且能反映出文章的主题。中文文题一般不超过 20 个汉字。

中国产前诊断杂志(电子版)编辑部