doi: 10.13241/j.cnki.pmb.2020.01.018

尿酸及 NLRP3 炎症小体与妊娠期高血压的相关性分析 *

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摘要 目的：观察妊娠期高血压孕产妇尿酸与 Nod 样受体蛋白 3 (nucleotide-binding oligomerization domain- leucine-rich repeats containing pyrin domain 3,NLRP3)炎症小体表达,分析二者与疾病的相关性,为妊娠期高血压的诊断提供参考。**方法**:选择我院产科 2016 年 3 月至 2019 年 3 月常规产检并诊断为妊娠期高血压孕产妇 200 例为研究组,参照《妊娠期高血压诊治指南(2015)》中各妊娠期高血压分级标准将研究组 200 例孕产妇分为妊娠期高血压组(86 例)、轻度子痫前期组(57 例)、重度子痫前期组(57 例),另选择同期在我院接受常规产检的 200 例健康孕产妇作为对照组。检测并比较 4 组孕产妇血清尿酸、NLRP3 炎症小体 mRNA 及 NLRP3 蛋白表达,经双变量 Spearman 相关性分析检验各指标与疾病的相关性。**结果**:4 组孕产妇年龄、孕周、孕次、产次等一般资料比较差异无统计学意义($P>0.05$);重度子痫前期组血清尿酸水平、NLRP3 mRNA 及 NLRP3 蛋白表达最高,后由高至低依次为轻度子痫前期组、妊娠期高血压组、对照组,组间两两比较差异均有统计学意义($P<0.05$);经双变量 Spearman 相关性分析检验证实,血清尿酸、NLRP3 mRNA 表达和蛋白表达与妊娠期高血压发生发展均呈正相关(r=0.709、0.833、0.693,P 均<0.001)。**结论**:妊娠期高血压孕产妇血清尿酸与 NLRP3 炎症小体水平上调,且随着孕产妇病情的加重升高,可考虑将其作为妊娠期高血压疾病早期诊断及预后评估的血清学参考指标。

关键词:妊娠期高血压;尿酸;NLRP3 炎症小体;相关性

中图分类号:R714.252 **文献标识码**:A **文章编号**:1673-6273(2020)01-85-04

Analysis of the Correlation of Uric Acid and NLRP3 Inflammasome with Hypertensive Disorder Complicating Pregnancy*

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ABSTRACT Objective: To investigate the levels of uric acid and nucleotide-binding oligomerization domain- leucine-rich repeats containing pyrin domain 3 (NLRP3) inflammasome expression in pregnant women with hypertensive disorder complicating pregnancy (HDCP) and their correlation with HDCP. **Methods:** 200 pregnant women who received routine antenatal examination and were diagnosed with HDCP in the department of obstetrics from March 2016 to March 2019 were selected as research group. According to the grading standard referring to the Guidelines for the Diagnosis and Treatment of Hypertensive Disorder Complicating Pregnancy (2015), 200 pregnant women in research group were divided into the gestational hypertension group (86 cases), mild pre-eclampsia group (57 cases), and severe pre-eclampsia group (57 cases). 200 healthy pregnant women who received routine antenatal examination were selected as control group. The serum uric acid, NLRP3 inflammasome mRNA, NLRP3 protein expression were compared among the four groups. The correlation between the indicators and the disease was examined by bivariate Spearman correlation analysis. **Results:** There was no statistical difference in the maternal age, gestational weeks, gravidity, parity among the four groups ($P>0.05$); Among four groups, the serum uric acid level, NLRP3 mRNA expression, NLRP3 protein expression in severe pre-eclampsia group were the highest, followed by mild pre-eclampsia group, gestational hypertension group and control group, and the difference was statistically significant ($P<0.05$); Bivariate Spearman correlation analysis confirmed that the serum uric acid, NLRP3 mRNA expression, NLRP3 protein expression had positive correlation with the occurrence and development of HDCP (r=0.709, 0.833, 0.693, $P<0.001$). **Conclusion:** The levels of uric acid and NLRP3 inflammasome in pregnant women with HDCP increase. With the aggravation of maternal conditions, uric acid and NLRP3 inflammasome can be used as serological indicators for early diagnosis and prognostic evaluation of HDCP.

Key words: Hypertensive disorder complicating pregnancy; Uric acid; NLRP3 inflammasome; Correlation

Chinese Library Classification(CLC): R714.252 Document code: A

Article ID: 1673-6273(2020)01-85-04

* 基金项目:江苏省卫计委科研基金项目(F-201661

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(收稿日期:2019-06-15 接受日期:2019-07-11)

前言

妊娠期高血压是妊娠期特有疾病，我国妊娠期高血压的患病率为 9.4%~10.4%，国外为 7%~12%[1]。妊娠期高血压是多种致病因素共同作用诱发的全身多器官、多系统的病变及损伤，是一种临床综合征[2]。子痫前期是妊娠期高血压较严重阶段，该阶段孕产妇脏器损伤程度更为严重[3]。众多研究表明血清尿酸是高血压主要风险因素之一，但目前研究结果存在较大争议，不同研究纳入人群的差异，得出的结论也不一致[4,5]。因此，血清尿酸与妊娠期高血压的相关性仍需要进一步探索[6,7]。

新近研究显示 NLRP3 炎症小体所介导的炎症通路及其相关下游产物也与妊娠期高血压的发生、发展密切相关[8]，但其对妊娠期高血压的诊断价值尚不完全明确。本研究主要探讨了妊娠期高血压孕产妇血清尿酸及 NLRP3 炎症小体水平与妊娠期高血压的相关性，以期为未来妊娠期高血压的早期诊断提供参考。现将结果报道如下。

1 资料与方法

1.1 纳入对象

在获得我院医学伦理委员会批准同意后，选择我院产科 2017 年 2 月至 2019 年 3 月常规产检并诊断为妊娠期高血压孕产妇 200 例作为研究组，均符合如下入选标准：(1)纳入标准：① 符合《妊娠期高血压诊治指南(2015)》[8]中妊娠期高血压各阶段诊断标准；② 孕周＞29 周；③ 单活胎；④ 无其他妊娠期合并症，诸如妊娠期高血压、妊娠期糖尿病等；⑤ 孕产妇及其家属对本次研究实施的内容均知情，并签署知情同意书。(2)排除标准：① 合并心、肝、肾等其他重要脏器功能衰竭者；② 合并糖尿病、恶性肿瘤疾病、出血性疾病者；③ 意识不清、表达能力不佳或合并精神疾病、心理疾病等无法很好的配合研究者。选择同期在我院接受常规产检的 200 例健康孕产妇作为对照组，对照组孕产妇及其家属对本次研究实施的内容知情，也签署知情同意书，均为单活胎，无合并症，意识清晰可很好的配合研究。

1.2 分组

参照《妊娠期高血压诊治指南(2015)》中各妊娠期高血压诊断标准将研究组患者分为 3 组，包括妊娠期高血压组(86 例)、轻度子痫前期组(57 例)、重度子痫前期组(57 例)。

1.3 检测方法

全部入组孕产妇均接受血清尿酸及 NLRP3 炎症小体表达检测。

1.3.1 血清尿酸检测 待孕产妇晨起后在空腹状态下抽取其外周静脉血 5 mL 放入促凝管内，采血后在 60 min 内离心，离心转速为 3000 r/min，离心时间为 5 min，离心后取上清液，在室温下保存，2h 内统一经全自动生化分析仪检测患者血尿酸浓度，全自动生化分析仪由德国罗氏公司提供，型号为 Cobas 8000 型。使用比色法检测分血清样本血清尿酸表达，添加启动试剂，在过氧化物酶、N- 乙基 -N-3- 甲基苯胺及 4- 氨基比林存在的条件下启动过氧化反应，生成亚胺染料，生成的亚胺染料颜色强度同尿酸的浓度呈正比，后采用光度法进行检测。

1.3.2 NLRP3 炎症小体检 (1)主要试剂及设备：德国 QIAGEN 公司提供的 400× 25 μL reactions RT-PCR 试剂盒，美国 CST 公司提供的 NLRP3 兔单克隆抗体，美国 Invitrogen 公司提供的 BCIP/NBT 显色剂，美国 BIO-RAD 公司提供的 BIO-RAD CFX 荧光定量 PCR 扩增仪、图像分析系统，相关试剂盒均由美国 eBscience 公司提供。(2)实时定量 PCR 测定 NLRP3 mRNA 表达：由血清样本中提取出 RNA，检测其纯度与 RNA 浓度，取 2 μL 进行逆转录，参照物为β-actin。利用 SYBR Green RT-PCR Kit，25 μL 反应体系，反转录产物 4 μL 作为模板，实施 PCR 扩增，PCR 引物均由上海上海英骏生物技术有限公司合成提供，扩增条件：95℃5 min 后 95℃20s 后 56℃5′ 20″ 后 72℃ 20 s，循环为 35 个。β-actin 浓度主要用来对扩增结果进行校正，上述试验重复 3 次，分别计算 NLRP3 mRNA 相对表达，取平均值。(3)经蛋白质印迹法测定 NLRP3 蛋白表达，收集(2)中各样本细胞并提取蛋白，检测蛋白浓度，高温煮沸并变性，时间为 10 min，分别取细胞蛋白 60 μg 与组织样品 200 μg 实施电泳转膜，封闭 120 min，向内加入 1:2000NLRP3 兔抗人单克隆一抗，在 4℃环境下孵育，洗膜后向内加入 1:5000 兔抗人二抗，室温孵育 60 min 显色。测定各条带光度值，计算 NLRP3 蛋白表达，内参蛋白为 β-actin。

1.4 观察指标

对比 4 组入组孕产妇血清尿酸、NLRP3 炎症小体蛋白表达，经双变量 Spearman 相关性分析检验二者与妊娠期高血压的相关性。

1.5 统计学方法

应用 SPSS20.0 统计学软件处理数据，以 $\bar{x}\pm s$ 表示计量资料，4 组间比较采用单因素方差分析检验，组间两两比较采用 LSD-t 检验，以百分比表示计数资料，用 x^2 检验，相关性分析采用双变量 Spearman 相关性检验，$P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 四组孕产妇一般资料比较

4 组孕产妇年龄、孕周、孕次、产次等一般资料比较差异无统计学意义($P>0.05$)，见表 1。

2.2 四组孕产妇血清尿酸、NLRP3 mRNA 和蛋白表达的比较

重度子痫前期组孕产妇血清尿酸水平、NLRP3 mRNA 和蛋白表达最高，后由高至低依次为轻度子痫前期组、妊娠期高血压组、对照组，组间两两比较差异均有统计学意义($P<0.05$)，见表 2。

2.3 尿酸、NLRP3 炎症小体与妊娠期高血压的相关性分析

经双变量 Spearman 相关性分析检验证实，尿酸、NLRP3 mRNA 表达、NLRP3 蛋白表达与妊娠期高血压发生发展均呈正相关($r>0$，$P<0.05$)。见表 3。

3 讨论

妊娠期高血压是对母婴均有严重危害的妊娠期特有疾病，是目前导致围产期新生儿及孕产妇死亡的主要原因之一，分为妊娠期高血压、子痫前期、子痫、慢性高血压并子痫前期、慢性高血压合并妊娠 5 类[10,11]。妊娠期高血压的发生率随着孕周的增加，将损伤母体各个重要脏器，轻者出现视物模糊、头晕、头痛等症状，重者出现脑梗死、脑出血、心力衰竭、视网膜脱落、肺

表 1 4 组孕产妇一般资料比较($\bar{x}\pm s$)

Table 1 Comparison of the general data among four groups of pregnant women($\bar{x}\pm s$)

Groups	Cases	Age (Years old)	Gestational weeks (Weeks)	Gravidity (Times)	Parity (Times)
Control group	200	27.02± 3.29	34.11± 1.29	1.95± 0.61	1.61± 0.59
Gestational hypertension group	86	27.12± 3.21	33.41± 1.21	2.02± 0.74	1.56± 0.61
Mild pre-eclampsia group	57	26.96± 3.31	34.02± 1.04	1.97± 0.71	1.54± 0.51
Severe pre-eclampsia group	57	27.25± 3.11	33.96± 1.32	2.11± 0.81	1.62± 0.71
F	-	0.085	2.621	0.476	2.376
P	-	0.968	0.071	0.700	0.065

表 2 4 组孕产妇血清尿酸、NLRP3mRNA 和蛋白表达的比较($\bar{x}\pm s$)

Table 2 Comparison of the levels of serum uric acid, NLRP3 mRNA and protein expression among four groups of pregnant women($\bar{x}\pm s$)

Groups	Cases	Serum uric acid (μmol/L)	NLRP3 mRNA expression	NLRP3 protein expression
Control group	200	256.02± 70.51	0.14± 0.08	0.24± 0.12
Gestational hypertension group	86	320.11± 84.11	0.24± 0.07	0.36± 0.14
Mild pre-eclampsia group	57	356.47± 67.45	0.41± 0.09	0.51± 0.13
Severe pre-eclampsia group	57	432.24± 80.51	0.76± 0.10	0.84± 0.26
F	-	49.257	257.668	85.567
P	-	＜0.001	＜0.001	＜0.001
$P_{\text{control group/gestational hypertension group}}$	-	＜0.001	＜0.001	0.002
$P_{\text{control group/mild pre-eclampsia group}}$	-	＜0.001	＜0.001	＜0.001
$P_{\text{control group/severe pre-eclampsia group}}$	-	＜0.001	＜0.001	＜0.001
$P_{\text{gestational hypertension group/mild pre-eclampsia group}}$	-	0.006	＜0.001	＜0.001
$P_{\text{gestational hypertension group/severe pre-eclampsia group}}$	-	＜0.001	＜0.001	＜0.001
$P_{\text{mild pre-eclampsia group/severe pre-eclampsia group}}$	-	＜0.001	＜0.001	＜0.001

表 3 尿酸、NLRP3 炎症小体与妊娠期高血压相关性分析

Table 3 Analysis of the correlation of serum uric acid, NLRP3 inflammasome with hypertensive disorder complicating pregnancy

Indexes	r	*P*
Serum uric acid	0.648	＜0.001
NLRP3 mRNA	0.722	＜0.001
NLRP3 protein	0.661	＜0.001

水肿等，危及孕产妇生命安全[12,13]。在对新生儿的影响方面，随着母体血压的升高将导致胎儿生长受限、宫腔窘迫等情况发生，部分临床医师为避免母体各脏器损伤情况加重，常会提前为孕产妇进行分娩，这将大大增加医源性早产儿数量[14,15]。此外，有研究指出，妊娠期高血压与中晚期早产儿多动、注意力不集中等不良行为问题相关，并对其长期的认知发育有一定的负面影响[16]。因此，找到准确且值得信赖的早期预测诊断指标对妊娠期高血压早期干预、改善母婴结局的重要意义。

妊娠期高血压孕产妇肝肾功能均有不同程度损伤，但肾功能异常常较肝功能异常更为严重且敏感[17]。肾小球毛细血管缺氧痉挛是妊娠期高血压孕产妇肾脏主要病理改变，孕产妇内皮增生、内皮细胞肿胀、内皮下纤维素沉积，肾小球滤过率及肾灌注降低，肾小球基底膜在受到损伤后，其透通性大大增加，大量的血浆蛋白漏出，故增加蛋白尿风险，而严重的肾脏功能损伤将诱发少尿甚至肾功能衰竭[18-20]。因此，早期监测妊娠期高血压孕产妇肾功能损害具有重要意义。血尿酸是人类嘌呤代谢最终产物，机体内尿酸产生后主要经肾脏代谢出体外，血清尿酸表达可用于直接反映机体肾脏受损程度，将其用于监测妊娠期高血压肾功能，相较于肌酐及尿素氮更为可靠且敏感[21,22]。临床检测妊娠期高血压特别是子痫前期患者的血清尿酸水平，结果显示其常常会有不同程度的升高，且血清尿酸的表达与患者疾病严重程度显著相关。本研究结果显示对照组血清尿酸表达最低，其次为妊娠期高血压组、轻度子痫前期组、重度子痫前期组，很好的证实了上述论证。在分析血清尿酸表达与妊娠期高血压相关性后，发现二者之间呈正相关，提示随着妊娠期高血压程度的加重，孕产妇血清尿酸表达升高，该结果也从侧面提

示血清尿酸表达的早期检测可作为妊娠期高血压诊断参考指标。血清尿酸在妊娠期高血压中的变化可能与以下机制有关：(1)妊娠期高血压作为一种全身小动脉痉挛性疾病，特别是在子痫前期，孕产妇胎盘血管痉挛致使胎盘血流灌注减少，这将增强胎盘脱氧 - 氧化酶氧化作用，大量自由基产生后直接增加尿酸合成，故血清内尿酸表达升高；(2)妊娠期高血压特别是子痫前期孕产妇肾素 - 血管紧张素活性增加，导致肾脏血管收缩，增加肾血管阻力，大大减少肾供血，肾脏灌注减少将降低肾排泄功能，尿酸代谢排出减少后，导致血尿酸表达升高。(3)孕产妇全身小动脉痉挛，引起缺血缺氧，增加无氧糖酵解，血肿乳酸增加，乳尖经肾脏代谢期间竞争性抑制近曲小管，影响尿酸分泌，减少尿酸排出，故血中尿酸升高。(4)胎儿生成的尿酸需要经母体代谢，妊娠期高血压特别是子痫前期孕产妇尿酸排泄能力降低后，胎儿来源尿酸将蓄积于母体血液中，故血清尿酸表达升高[23-25]。

除血尿酸外，新近的研究显示 NLRP3 炎症小体也对高血压早期诊断有一定的参考价值[26]。炎症小体是有核结合寡聚化结构域样构体家族及 Caspase-1 组成的一种细胞内多聚体蛋白复合物，部分炎症小体还具备 CARD 结构域凋亡颗粒样蛋白特性。NLRP3 炎症小体是目前核结合寡聚化结构域样受体家族中被研究最多、最具特征性的炎症因子，主要由 Cardinal 蛋白、pro-Caspase-1、ASC 及 NLRP3 蛋白构成，在免疫细胞内，其活化能够将中游分子 Caspase-1 激活，继而对下游的白细胞介素 -1β 前体进行剪接与加工，从而加速白细胞介素 -1β 的成熟释放，对免疫应答及炎症反应产生调节之效[27,28]。此外，NLRP3 炎症小体相关信号通路还能被诸多内源性及外源性刺激激活，但其具体机制尚未完全明确，最新研究认为钾离子水平降低可能与 NLRP3 炎症小体激活有关，细胞膜表面的三磷酸腺苷配体门控离子通道相关受体后，由胞外 ATP 直接激活 ATP-P2X7R 阳离子通道，诱使缝隙连接半通道泛连接蛋白通道开放，钾离子外流后，钙离子内流，最后激活 NLRP3 炎症小体，NLRP3 炎症小体在激活后将释放大量成熟白细胞介素 -1β，并参加淋巴细胞分化迁移，同时激活其他淋巴细胞，活化后的淋巴细胞又将生成更多诸如白细胞介素 -7 等炎性因子，增加 AngⅡ的释放，上述炎性因子组成的炎症环境将推动钠离子潴留于血管与肾脏，导致血管重建与血管收缩，最终诱发高血压[29,30]。本研究结果显示对照组健康孕产妇 NLRP3 蛋白表达最低，随着妊娠期高血压病情加重，孕产妇 NLRP3 表达随之升高，二者间呈正相关，表明 NLRP3 炎症小体也可作为妊娠期高血压早期诊断的参考指标。

综上所述，妊娠期高血压孕产妇血清尿酸与 NLRP3 炎症小体水平上调，且随着孕产妇病情的加重呈升高趋势，可能作为早期妊娠期高血压诊断和预后预测的血清学参考指标。

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