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## 血清 FABP4、OPG、CysC、Ang II 用于诊断妊娠期糖尿病合并妊娠期高血压的临床价值分析\*

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**摘要 目的:**探讨血清脂肪酸结合蛋白 4(FABP4)、护骨素(OPG)、胱抑素 C(CysC)、血管紧张素(Ang II)用于诊断妊娠期糖尿病合并妊娠期高血压疾病患者的临床价值。**方法:**选择 2016 年 4 月~2018 年 4 月于华北理工大学附属医院产科门诊建档并定期规律产检的妊娠期糖尿病 300 例,其中 104 例并发妊娠期高血压疾病患者设为观察组,196 例设为对照组。分析妊娠期糖尿病合并妊娠期高血压疾病患者血清 FABP4、OPG、CysC、Ang II 的表达及其与空腹血糖的相关性,并分析以上指标对妊娠期糖尿病合并妊娠期高血压的诊断价值。**结果:**观察组患者血清 FABP4、OPG、CysC、Ang II、空腹血糖水平均显著高于对照组( $P<0.05$ )。妊娠期糖尿病合并妊娠期高血压患者血清 FABP4、OPG、CysC、Ang II、空腹血糖水平显著低于轻度子痫前期、重度子痫前期患者;轻度子痫前期患者以上指标水平显著低于重度子痫前期患者( $P<0.05$ )。血清 FABP4、OPG、CysC、Ang II 和空腹血糖之间均呈显著正相关( $P<0.05$ )。FABP4、OPG、CysC、Ang II 诊断妊娠期糖尿病合并妊娠期高血压疾病的 AUC 分别为 0.648、0.654、0.898、0.913,95%CI 分别为 0.576~0.719、0.586~0.722、0.854~0.943、0.886~0.941,以上指标联合检测诊断妊娠期糖尿病合并妊娠期高血压疾病的 AUC 为 0.996,95%CI 为 0.992~1.000,单独检测分别和联合检测曲线下面积比较均具有显著差异( $Z=9.569, 9.669, 4.115, 6.310, P<0.05$ );联合检测诊断妊娠期糖尿病合并妊娠期高血压疾病的特异度、准确度分别为 94.17%、94.28%。**结论:**妊娠期糖尿病合并妊娠期高血压疾病患者血清 FABP4、OPG、CysC、Ang II 的表达均与空腹血糖存在显著正相关,以上四者联合检测诊断妊娠期糖尿病合并妊娠期高血压疾病时具有较高的临床价值。

**关键词:**妊娠期糖尿病;妊娠期高血压疾病;脂肪酸结合蛋白 4;护骨素;胱抑素 C;血管紧张素

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## Analysis of the Clinical Value of Serum FABP4, OPG, CysC, Ang II in the Diagnosis of Gestational Diabetes Merged the Function of Patients with Gestational Hypertension Disease\*

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**ABSTRACT Objective:** To study Analysis of the Serum Fatty acid binding protein 4 (FABP4) and bone, urinary inhibition (OPG), C (CysC), angiotensin (Ang II) in gestational diabetes merged the function of patients with gestational hypertension disease. **Methods:** 300 patients with gestational diabetes who were registered in the obstetrical outpatient department of the affiliated hospital of north China university of science and technology from April 2016 to April 2018 and underwent regular labor and examination were selected. Among them, 104 patients with gestational hypertension were set as the observation group and 196 patients were set as the control group. Analysis of gestational diabetes combined gestational hypertension disease patient serum FABP4, OPG, CysC, Ang II expression and its correlation with fasting glucose, and analyze the above indicators for gestational diabetes combined gestational hypertension diagnosis value. **Results:** Observation group of patients serum FABP4, OPG, CysC, Ang II, fasting blood glucose levels were significantly higher than that of control group ( $P<0.05$ ). Gestational diabetes with gestational hypertension patients serum FABP4, OPG, CysC, Ang II, fasting blood sugar level was significantly lower than in patients with mild preeclampsia, severe preeclampsia; The above level of indicators in patients with mild preeclampsia was significantly lower than that in patients with severe preeclampsia ( $P<0.05$ ). FABP4, OPG, serum CysC, Ang II and are significantly positive correlation between fasting glucose ( $P<0.05$ ). FABP4, OPG, CysC, Ang II diagnosis gestational diabetes with gestational hypertension disease AUC were 0.648, 0.654, 0.898, 0.913, 95% CI 0.576~0.719, 0.586~0.722, 0.854~0.943, 0.886~0.941, the above indexes combined detection in the diagnosis of gestational diabetes with gestational hypertension diseases of AUC is 0.996, 95% CI 0.992~1.000, There were significant differences between the area under the curve of separate detection and that under the curve of combined detection ( $Z=9.569, 9.669, 4.115, 6.310, P<0.05$ ). The specificity and accuracy of combined detection and diagnosis of gestational diabetes mellitus with gestational hypertension were 94.17% and 94.28%, respectively. **Conclusion:** Gestational

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diabetes with gestational hypertension disease patients serum FABP4, OPG, CysC, Ang II expression with significant positive correlation between fasting glucose, the above four joint detection in the diagnosis of gestational diabetes merger gestational hypertension disease has high clinical value.

**Key words:** Gestational diabetes mellitus; Hypertensive disorders of pregnancy; Fatty acid binding protein 4; Protection of bone; Cystatin C; Angiotensin

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## 前言

妊娠期糖尿病是指妊娠期发生的或者妊娠期首次发现的不同程度的糖耐量异常,包括了妊娠前已存在但被漏诊的孕前糖尿病患者,发病率较高。据调查显示,我国妊娠期糖尿病的发生率 1%~5%<sup>[1,2]</sup>。该病对母婴危害较多,可导致巨大儿、流产、产后出血、妊娠期高血压、羊水过多、感染等并发症的发生,其中妊娠期高血压是妊娠期常见并发症,而妊娠期糖尿病并发妊娠期高血压高达 25%~31%,较正常妊娠妇女高,对母婴结局有更严重的影响<sup>[3,4]</sup>。因此,对妊娠期糖尿病合并妊娠期高血压早期预测并及时有效治疗对母婴具有重要意义。

FABP4 参与全身的脂肪代谢,在细胞分化、糖代谢等调节方面起枢纽作用,有研究显示,FABP4 与高血压及先兆子痫的发病存在一定关系<sup>[5,6]</sup>。OPG 是一种可溶性的分泌型糖蛋白,广泛分布在成纤维细胞、血管内皮细胞、动脉平滑肌细胞中,在血管病变中发挥重要作用;CysC 是一种半胱氨酸蛋白酶抑制剂,可以反映肾小球滤过功能的指标;Ang II 是肾素-血管紧张素系统中最重要生物活性物质,影响滋养层细胞浸润能力,进而影响胎盘发育,与妊娠期高血压等母儿并发症有关<sup>[7,9]</sup>。血清 FABP4、OPG、CysC、Ang II 与妊娠期糖尿病合并妊娠期高血压的发生有密切联系,但其具体意义还需进一步研究。因此,本研究主要探讨了妊娠期糖尿病合并妊娠期高血压患者血清 FABP4、OPG、CysC、Ang II 的变化及其诊断价值,以期对早期临床判断提供参考,现报道如下:

## 1 资料与方法

### 1.1 一般资料

选择 2016 年 4 月~2018 年 4 月于华北理工大学附属医院产科门诊建档并定期规律产检,孕 36~40 周确诊的妊娠期糖尿病 300 例,其中 104 例并发高血压疾病患者设为观察组,孕周平均(38.42±0.26)周,孕龄平均年龄(29.18±4.31)岁,其中妊娠期高血压 40 例,轻度子痫前期 24 例,重度子痫前期 40

例。196 例设为对照组,孕周 36~39 周,平均(38.35±0.21)周,孕龄平均年龄(29.11±4.29)岁。两组基线资料无明显差异,具有可比性。

**诊断标准:**参照《妊娠合并糖尿病诊治指南》<sup>[10]</sup>:75 g 葡萄糖糖耐量试验(OGTT)空腹及服糖后 1、2 小时的血糖值分别为 5.1 mmol/L、10.0 mmol/L、8.5 mmol/L。3 项中≥1 项异常即可诊断。妊娠期高血压参照《妊娠期高血压疾病诊治指南》<sup>[11]</sup>诊治。**纳入标准:**(1)符合上述诊断标准;(2)临床数据完整;(3)入院前未进行相关治疗者;(4)签署知情同意书。**排除标准:**(1)孕前有糖耐量异常、慢性高血压或正在使用类固醇皮质激素治疗者;(2)患有意识障碍、精神障碍者;(3)采血前患急性慢性感染性疾病;(4)血液疾病患者;(5)药物、酒精滥用史;(6)多胎妊娠;(7)依从性较差者。

### 1.2 方法

采集空腹静脉血 5 mL,以 3000 r·min<sup>-1</sup> 的速度进行离心,时间 10 min,提取上层血清后,置于零下 20℃ 的冷冻箱内存储以备检测,使用酶联免疫吸附法对 FABP4、OPG、CysC、Ang II 进行检测,试剂盒由德国 Her-renberg 公司生产,检测仪器为西班牙生产的全自动酶免分析仪;采用葡萄糖氧化酶法测定空腹血糖,应用贝格曼 LX-20 全自动生化仪进行分析。

### 1.3 统计学分析

以 spss19.0 软件包处理,计量资料用均数±标准差( $\bar{x} \pm s$ )表示,多组比较采用方差分析,两组间比较采用 t 检验,相关性分析使用 Spearman 相关系数,并使用受试者工作特征曲线(ROC)分析血清 FABP4、OPG、CysC、Ang II 的诊断效能, $P < 0.05$  表示差异具有统计学意义。

## 2 结果

### 2.1 两组血清 FABP4、OPG、CysC、Ang II、空腹血糖水平比较

观察组患者血清 FABP4、OPG、CysC、Ang II、空腹血糖水平平均显著高于对照组,差异显著( $P < 0.05$ )见表 1。

表 1 两组血清 FABP4、OPG、CysC、Ang II、空腹血糖水平的比较( $\bar{x} \pm s$ )

Table 1 Comparison of the serum FABP4 in table 1, OPG, CysC, Ang II, fasting blood glucose levels between two groups( $\bar{x} \pm s$ )

| Groups            | n   | FABP4(ng/mL) | OPG(pmol/L) | CysC(mg/L) | Ang II (pg/ml) | Fasting plasma glucose(mmol/L) |
|-------------------|-----|--------------|-------------|------------|----------------|--------------------------------|
| Observation group | 104 | 17.69± 8.67  | 9.24± 3.45  | 1.58± 0.41 | 131.75± 20.35  | 11.93± 2.51                    |
| Control group     | 196 | 13.21± 5.21  | 7.05± 2.35  | 0.86± 0.28 | 70.18± 16.24   | 4.06± 0.52                     |
| t value           |     | 5.583        | 6.494       | 17.943     | 28.563         | 42.278                         |
| P value           |     | 0.000        | 0.000       | 0.000      | 0.000          | 0.000                          |

2.2 不同疾病严重程度血清 FABP4、OPG、CysC、Ang II、空腹血糖水平比较

妊娠期糖尿病合并妊娠期高血压患者血清 FABP4、OPG、CysC、Ang II、空腹血糖水平显著低于轻度子痫前期、重度子痫前期患者;轻度子痫前期患者血清 FABP4、OPG、CysC、Ang II、空腹血糖水平显著低于重度子痫前期患者,差异显著( $P<0.05$ ),见表 2。

妊娠期糖尿病合并妊娠期高血压患者血清 FABP4、OPG、CysC、Ang II、空腹血糖水平显著低于轻度子痫前期、重度子痫前期患者;轻度子痫前期患者血清 FABP4、OPG、CysC、Ang II、空腹血糖水平显著低于重度子痫前期患者,差异显著( $P<0.05$ ),见表 2。

表 2 不同疾病严重程度血清 FABP4、OPG、CysC、Ang II、空腹血糖水平比较( $\bar{x} \pm s$ )

Table 2 Comparison of the FABP4, OPG, serum CysC, Ang II, fasting blood glucose levels between patients with different disease severity( $\bar{x} \pm s$ )

| Groups                   | n  | FABP4(ng/mL) | OPG(pmol/L) | CysC(mg/L) | Ang II (pg/mL) | Fasting plasma glucose(mmol/L) |
|--------------------------|----|--------------|-------------|------------|----------------|--------------------------------|
| Gestational hypertension | 40 | 15.26± 8.14  | 8.08± 3.04  | 1.26± 0.37 | 105.36± 19.89  | 9.89± 2.13                     |
| Mild preeclampsia        | 24 | 17.08± 8.69  | 9.09± 3.52  | 1.49± 0.40 | 128.56± 21.46  | 11.59± 2.49                    |
| Severe preeclampsia      | 40 | 20.49± 8.83  | 10.49± 3.49 | 1.95± 0.46 | 160.05± 21.89  | 14.17± 2.56                    |
| F value                  |    | 3.833        | 5.267       | 28.555     | 67.927         | 32.483                         |
| P value                  |    | 0.025        | 0.007       | 0.000      | 0.000          | 0.000                          |

2.3 血清 FABP4、OPG、CysC、Ang II 和空腹血糖的相关性分析

将空腹血糖作为因变量,将血清 FABP4、OPG、CysC、Ang II 分别作为自变量,相关性分析结果显示血清 FABP4、OPG、CysC、Ang II 和空腹血糖之间均呈正相关( $P<0.05$ ),见表 3。

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表 3 血清 FABP4、OPG、CysC、Ang II 和空腹血糖的相关性分析

Table 3 FABP4, OPG, serum CysC, Ang II and correlation analysis of fasting plasma glucose

| Project | Fasting plasma glucose |         |
|---------|------------------------|---------|
|         | r value                | P value |
| FABP4   | 0.288                  | 0.000   |
| OPG     | 0.316                  | 0.000   |
| CysC    | 0.651                  | 0.000   |
| Ang II  | 0.801                  | 0.000   |

2.4 血清 FABP4、OPG、CysC、Ang II 在妊娠期糖尿病合并高血压疾病中的诊断价值分析

FABP4 诊断妊娠期糖尿病合并妊娠期高血压疾病的 AUC 为 0.648,95%CI 为 0.576~0.719,OPG 诊断妊娠期糖尿病合并妊娠期高血压疾病的 AUC 为 0.654,95%CI 为 0.586~0.722,CysC 诊断妊娠期糖尿病合并妊娠期高血压疾病的 AUC 为 0.898,95%CI 为 0.854~0.943,Ang II 诊断妊娠期糖尿病合并妊娠期高血压疾病的 AUC 为 0.913,95%CI 为 0.886~0.941,联合检测诊断妊娠期糖尿病合并妊娠期高血压疾病的 AUC 为 0.996,95%CI 为 0.992~1.000,单独检测分别和联合检测曲线下面积比较均具有显著差异 ( $Z=9.569,9.669,4.115,6.310,P<0.05$ );联合检测的特异度、准确度分别为 94.17%、94.28%,具体见图 1、表 4~5。

病的预测,目前国内研究及报道较少<sup>[14,15]</sup>。有研究显示早期通过血糖监测早期发现妊娠期糖尿病高危孕妇,对降低不良妊娠结局有重要意义<sup>[16]</sup>。本研究结果显示妊娠期糖尿病合并妊娠期高血压患者空腹血糖水平显著高于妊娠期高血压患者,且可随着疾病的严重程度而升高。

### 3 讨论

妊娠期糖尿病对孕产妇有严重危害,容易引发妊娠期高血压,研究表明妊娠期糖尿病并发妊娠期高血压的发生率逐年提高<sup>[12,13]</sup>。妊娠期糖尿病和妊娠期高血压疾病均是妊娠期常见合并症,二者并发可进一步增加孕产妇出现器官功能损害、胎盘早剥、新生儿窒息等不良妊娠结局的风险。因此,早期预测妊娠期糖尿病和妊娠期高血压疾病的发生,已经成为临床工作中迫切需要解决的问题,而作为妊娠期糖尿病合并妊娠期高血压疾

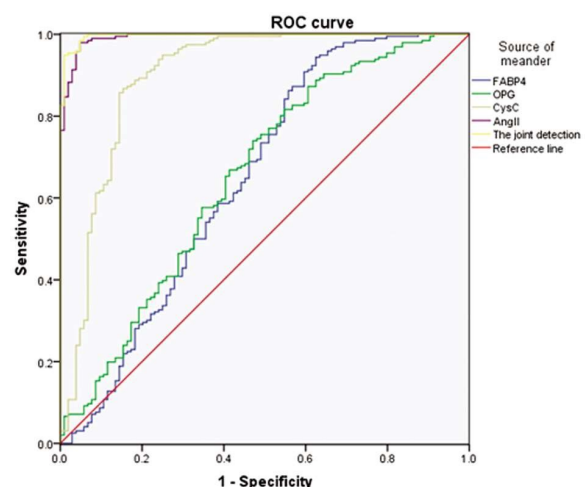


图 1 血清 FABP4、OPG、CysC、Ang II 单独检测和联合检测妊娠期糖尿病合并妊娠期高血压疾病的 ROC 曲线

Fig.1 FABP4, OPG, serum CysC, Ang II separate gestational diabetes hypertension disease detection and united detection of ROC curve

表 4 血清 FABP4、OPG、CysC、Ang II 单独检测和联合检测妊娠期糖尿病合并妊娠期高血压疾病的 ROC 曲线下面积(AUC)

Table 4 FABP4, OPG, serum CysC, Ang II separate inspection and joint gestational diabetes hypertension disease area under the ROC curve (AUC)

| Test variables      | AUC   | Standard error <sup>a</sup> | P     | 95%CI       |
|---------------------|-------|-----------------------------|-------|-------------|
| FABP4               | 0.648 | 0.036                       | 0.000 | 0.576~0.719 |
| OPG                 | 0.654 | 0.035                       | 0.000 | 0.586~0.722 |
| CysC                | 0.898 | 0.023                       | 0.000 | 0.854~0.943 |
| Ang II              | 0.913 | 0.013                       | 0.000 | 0.886~0.941 |
| The joint detection | 0.996 | 0.002                       | 0.000 | 0.992~1.000 |

表 5 血清 FABP4、OPG、CysC、Ang II 单独检测和联合检测妊娠期糖尿病合并妊娠期高血压疾病的诊断效能

Table 5 FABP4, OPG, serum CysC, Ang II separate inspection and joint gestational diabetes hypertension disease diagnosis efficiency

| Test variables      | Sensitivity | Specific degrees | The accuracy of | About an index |
|---------------------|-------------|------------------|-----------------|----------------|
| FABP4               | 81.31       | 77.27            | 84.31           | 0.57           |
| OPG                 | 80.58       | 76.82            | 85.93           | 0.53           |
| CysC                | 83.56       | 74.93            | 84.71           | 0.41           |
| Ang II              | 84.71       | 83.59            | 88.91           | 0.55           |
| The joint detection | 87.69       | 94.17            | 94.28           | 0.52           |

FABP4 是一种近年来被发现的细胞因子,是胞内脂质结合蛋白超家族成员,广泛分布在各种正常组织和细胞中,具有脂质调节作用和炎症反应调节作用,被证实了其在糖类的代谢中也起到重要的作用<sup>[17,18]</sup>。有研究显示 FABP4 也是细胞内重要的脂肪酸载体蛋白,参与脂肪酸的吸收和代谢过程<sup>[19]</sup>。Wang J<sup>[20]</sup>等发现 FABP4 在妊娠期糖尿病中较高,能促进胰岛素抵抗的发生及发展,参与了机体出现胰岛素抵抗的过程。本研究结果显示妊娠期糖尿病合并妊娠期高血压患者 FABP4 水平显著高于妊娠期高血压患者,妊娠期糖尿病合并妊娠期高血压患者血清 FABP4 水平显著低于轻度子痫前期、重度子痫前期患者;轻度子痫前期患者血清 FABP4 水平显著低于重度子痫前期患者,且血清 FABP4 和空腹血糖之间呈正相关。以上结果提示 FABP4 在妊娠期糖尿病合并妊娠期高血压患者中表达较高,随着疾病的严重程度而升高,且随着空腹血糖的升高而升高。

国外研究表明 OPG 能抑制破骨细胞的形成、分化,在 2 型糖尿病合并骨质疏松中表达异常,起到抗骨质疏松作用。本研究结果显示妊娠期糖尿病合并妊娠期高血压患者 OPG 水平显著高于妊娠期高血压患者,妊娠期糖尿病合并妊娠期高血压患者血清 OPG 水平显著低于轻度子痫前期、重度子痫前期患者;轻度子痫前期患者血清 OPG 水平显著低于重度子痫前期患者,且血清 OPG 和空腹血糖之间呈正相关。

肾脏是高血压损害的靶器官,是由高血压引起的慢性肾病可进展为终末期肾病,而终末期肾病是高血压患者死亡的重要因素。CysC 是一种存在于机体各组织细胞的碱性非糖化蛋白质,机体内所有有核细胞均可产生,能通过肾小球滤过膜后在近曲小管完全被重吸收并很快被分解。Dunn A B 等研究显示妊娠期糖尿病患者血清 CysC 水平高于正常妊娠患者,且随着病情的发展不断增高,与早期肾损害程度关系密切<sup>[21-24]</sup>。本研究结果显示妊娠期糖尿病合并妊娠期高血压患者血清 CysC 水平显著高于妊娠期糖尿病患者,随着疾病的严重程度而升高,且和空腹血糖之间呈正相关。Ang II 是肾素血管紧张素醛固酮系

统中的主要效应物质,能使小动脉的平滑肌收缩,刺激肾上腺皮质球状带分泌醛固,从而增加肾上腺素分泌,从而使血压升高。国外研究显示 Ang II 在高血压患者中表达较高,参与了高血压的发生。本研究结果显示妊娠期糖尿病合并妊娠期高血压患者血清 Ang II 水平显著高于妊娠期糖尿病患者,随着疾病的严重程度而升高,且和空腹血糖之间呈正相关<sup>[25,26]</sup>。以上结果提示 Ang II 在妊娠期糖尿病合并妊娠期高血压疾病中表达较高,可作为预测疾病的标志物,分析其原因可能是因为 Ang II 的高水平可使孕妇胎盘中血管收缩及痉挛,导致胎盘功能低下,参与了妊娠期高血压疾病的发生。此外,联合检测诊断妊娠期糖尿病合并高血压疾病的 0.996,95%CI 为 0.992~1.000,与各指标单独诊断妊娠期糖尿病合并高血压的 AUC 比较均具有显著差异<sup>[27]</sup>,且联合检测的特异度、准确度分别为 94.17%、94.28%,明显高于各指标单独检测,显示出联合检测在诊断妊娠期糖尿病合并妊娠期高血压疾病表达上具有更高的价值。但是本研究未观察治疗前后各指标变化,临床上对于妊娠期糖尿病合并妊娠期高血压疾病的诊断效能以及 FABP4、OPG、CysC、Ang II 与其预后关系还需进一步研究。

综上所述,妊娠期糖尿病合并妊娠期高血压疾病患者血清 FABP4、OPG、CysC、Ang II 的表达均与空腹血糖存在显著正相关,以上四者联合检测诊断妊娠期糖尿病合并妊娠期高血压疾病时具有较高的临床价值。

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