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慢性乙型肝炎病毒感染对妊娠期糖尿病及妊娠结局的影响*

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摘要 目的:探讨慢性乙型肝炎病毒(HBV)感染对妊娠期糖尿病(GDM)及妊娠结局的影响,为妊娠期产妇慢性 HBV 感染预防提供参考。**方法:**回顾性分析 2015 年 2 月-2017 年 2 月在我院住院分娩的 2615 例慢性 HBV 感染产妇的临床病历资料,根据《慢性乙型肝炎防治指南》(2015 年版)诊断标准,将所有产妇分为 4 组:慢性 HBV 携带者(A 组)1128 例、乙型肝炎 e 抗原(HBeAg)阳性慢性乙型肝炎(B 组)406 例、HBeAg 阴性慢性乙型肝炎(C 组)307 例、非活动性乙型肝炎表面抗原(HBsAg)携带者(D 组)774 例,并收集同期入院的 823 例 HBV 阴性产妇为对照组(E 组)。比较各组的 GDM 发生率及不良妊娠结局发生率。**结果:**2615 例慢性 HBV 感染产妇中,共发生 GDM 866 例,发生率为 33.12%。B 组与 C 组 GDM 发生率分别为 38.92%、37.46%,均大于 E 组的 30.74%($P<0.05$)。A 组、B 组、C 组的妊娠期高血压疾病(PIH)发生率分别为 7.98%、8.87%、9.77%,均高于 E 组的 3.52%($P<0.05$)。A 组、B 组、C 组及早产发生率分别为 3.10%、3.94%、4.56%,均高于 E 组的 0.49%($P<0.05$)。C 组的新生儿窒息发生率为 1.63%,高于 E 组的 0.36%($P<0.05$)。**结论:**产妇慢性 HBV 感染若合并肝功能受损或肝组织学病变,可能增加 GDM 的发生率,若 HBV 病毒复制活跃,可能导致 PIH 及早产发生风险增加。

关键词:慢性;乙型肝炎病毒;妊娠期糖尿病;妊娠结局;感染;产妇

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Influence of Chronic Hepatitis B Virus Infection on Gestational Diabetes Mellitus and Pregnancy Outcomes*

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ABSTRACT Objective: To investigate the influence of chronic hepatitis B virus (HBV) infection on gestational diabetes mellitus (GDM) and pregnancy outcome so as to provide reference for the prevention of chronic HBV infection in puerpera during pregnancy. **Methods:** The clinical data of 2615 puerpera with chronic HBV infection who were hospitalized delivery in our hospital from February 2015 to February 2017 were performed retrospective analysis. According to the diagnostic criteria in Guidelines for Prevention and Treatment of Chronic Hepatitis B (2015 Edition), the puerpera were divided into four groups: 1128 cases of chronic HBV carriers (group A), 406 cases of chronic hepatitis B with HBeAg-positive (group B), 307 cases of chronic hepatitis B with HBeAg-negative (group C), 774 cases of inactive hepatitis B with HBsAg carriers (group D), and 823 cases of puerpera with HBV-negative admitted to hospital in the same period were selected as the control group (group E). Then the incidence difference of GDM and pregnancy outcomes were compared between those five groups. **Results:** 866 cases of GDM occurred in 2615 puerpera with chronic HBV infection, the incidence rate was 33.12%. And the GDM incidence rates of group B and group C were 38.92%, 37.46% respectively, which were higher than 30.74% of group E ($P<0.05$). The incidence rate of pregnancy induced hypertension (PIH) of group A, group B and group C were 7.98%, 8.87%, 9.77% respectively, which were higher than 3.52% of group E ($P<0.05$). The incidence rate of premature delivery of group A, group B and group C were 3.10%, 3.94%, 4.56% respectively, which were higher than 0.49% of group E ($P<0.05$). The incidence of neonatal asphyxia of group C was 1.63%, which was higher than 0.36% of group E ($P<0.05$). **Conclusion:** Puerpera with chronic HBV infection have higher risk in the GDM incidence when complicated with liver dysfunction or liver histological lesions, and when their HPV replication is active, it could increased the risk of PIH and preterm birth.

Key words: Chronic; Hepatitis B virus; Gestational diabetes mellitus; Pregnancy outcomes; Infection; Puerpera

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前言

乙型肝炎病毒(hepatitis B virus, HBV)感染是危害人们健

康的感染性疾病,其在全球范围内的发病率及病死率均较高^[1]。根据世界卫生组织数据显示,全球 20 亿 HBV 感染者中 2.4 亿人为慢性 HBV 感染,并且我国是感染率较高的国家^[2,3]。而

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HBV 可通过影响肝脏功能对物质的代谢产生影响,从理论上分析可能导致妊娠期糖尿病 (gestational diabetes mellitus, GDM) 的发生, GDM 为妊娠期妇女容易发生的妊娠并发症,主要表现为妊娠期首次发生糖代谢异常,其发病率约为 1%至 14%,且呈上升趋势,是临床中不可忽视的重要疾病^[4,5]。但目前关于作用机制尚未统一说法,部分研究表明产妇产前 HBV 感染对 GDM 及妊娠结局均有不同程度的影响^[6-8],而也有少数研究显示,无症状 HBV 感染不会增加 GDM 的发生及不良妊娠结局^[9,10],且不同 HBV 感染状态的影响也尚未不明确。本研究通过对近几年到本院分娩的 2615 例发生慢性 HBV 感染的产妇临床病历资料进行回顾性分析,旨在探讨慢性 HBV 病毒感染对 GDM 及妊娠结局的影响。现做如下报道。

1 资料与方法

1.1 一般资料与分组

收集从 2015 年 2 月-2017 年 2 月在我院住院分娩且病历资料完整的 2615 例慢性 HBV 感染产妇,纳入标准:(1)均为单胎妊娠者;(2)均符合《慢性乙型肝炎防治指南》(2015)指南的相关诊断标准^[11];(3)非肝硬化产妇;(4)患者或家属知情同意并签署知情同意书者。排除标准:(1)合并巨细胞病毒、EB 病毒、梅毒和艾滋等其他病原学感染者;(2)有孕期肝炎活动史、抗病毒治疗史者;(3)其他基础性疾病如糖尿病、高血压等病史者。产妇年龄 22-36 岁,平均(28.63±3.27),体质指数 23-29 kg/m²,平均(26.17±1.95)kg/m²。根据生物化学试验、病毒学、血清学等相关临床辅助检查结果将患者分为慢性 HBV 携带者 1128 例(A 组)、乙型肝炎 e 抗原(hepatitis B e antigen, HBeAg)阳性慢性乙型肝炎 406 例(B 组)、HBeAg 阴性慢性乙型肝炎 307 例(C 组)、非活动性乙型肝炎表面抗原(hepatitis B surface antigen, HBsAg)携带 774 例(D 组)。收集同期入院的 823 例 HBV 阴性产妇为对照组(E 组),年龄 30-35 岁,平均(27.94±3.06),体质指数 21-28kg/m²,平均(26.59±2.07)kg/m²。慢性 HBV 感染产妇与对照组产妇一般资料比较差异无统计学意义($P>0.05$),提示组间具有可比性。研究经医院伦理委员会批准通过。

表 1 各组 GDM 发生率比较[n(%)]

Groups	n	Incidence rate
Group A	1128	350(31.03)
Group B	406	158(38.92)*
Group C	307	115(37.46)*
Group D	774	243(31.40)
Group E	823	253(30.74)

Note: Compared with Group E, * $P<0.05$.

1.2 诊断标准

慢性 HBV 感染^[11]:(1)慢性 HBV 携带:血清 HBeAg、HBV DNA、HBsAg 均为阳性,肝组织无病变或轻微病变,1 年内连续随访 2 次以上显示天门冬氨酸氨基转移酶(aspartate amino-

transferase, AST)、丙氨酸转氨酶(alanine aminotransferase, ALT)水平属于正常范围内。(2)HBeAg 阳性慢性乙型肝炎:血清 HBeAg、HBV DNA、HBsAg 均为阳性,有肝炎病变且 ALT 处于反复异常水平。(3)HBeAg 阴性慢性乙型肝炎:血清 HBeAg 为阴性,HBV DNA、HBsAg 为阳性,有肝炎病变且 ALT 处于反复异常水平。(4)非活动性 HBsAg 携带者:血清抗-HBe 阳性或阴性,HBsAg 阳性、HBeAg 阴性、HBV DNA 低于检测最小值,1 年内连续随访 3 次,每次间隔 3 个月以上,ALT 处于正常范围内。肝组织学检查显示:组织学活动指数(histology activity index, HAI)评分<4 或根据其他的半定量计分系统判定病变轻微。

GDM 诊断标准^[12]:①空腹血糖值 ≥ 5.1 mmol/L (92 mg/dl);② 1h 血糖值 ≥ 10.0 mmol/L (180 mg/dl);③ 2h 血糖值 ≥ 8.5 mmol/L (153 mg/dl),上述标准任何一项血糖值达要求则判定为 GDM。

1.3 观察指标

收集各组产前检查病历和住院病历,比较其 GDM 的发生率。比较各组不良妊娠结局发生率,其中母体不良妊娠结局包括妊娠期高血压疾病(pregnancy induced hypertension, PIH)、胎膜早破、产后出血、羊水过多、早产,新生儿不良妊娠结局包括巨大儿、新生儿窒息、新生儿畸形。

1.4 统计学方法

采用 SPSS 20.0 软件进行统计分析,GDM 发生率、不良妊娠结局发生率等计数资料采用[n(%)]进行统计描述,组间差异采用 χ^2 检验,所有 P 值来源于双侧检验,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 慢性 HBV 感染对 GDM 的影响

2615 例慢性 HBV 感染产妇中,共发生 GDM 866 例,发生率为 33.12%。B 组与 C 组 GDM 发生率分别为 38.92%、37.46%,均大于 E 组的 30.74%($P<0.05$);A 组、D 组与 E 组 GDM 发生率比较无统计学差异($P>0.05$)。见表 1。

2.2 慢性 HBV 感染对母体不良妊娠结局的影响

A 组、B 组、C 组的 PIH 发生率分别为 7.98%、8.87%、9.77%,均高于 E 组的 3.52%($P<0.05$);A 组、B 组、C 组早产发生率分别为 3.10%、3.94%、4.56%,均高于 E 组的 0.49%($P<0.05$);各组胎膜早破、产后出血、羊水过多发生率比较无统计学差异($P>0.05$)。见表 2。

2.3 慢性 HBV 感染对新生儿不良妊娠结局的影响

C 组的新生儿窒息发生率为 1.63%,高于 E 组的 0.36%($P<0.05$);各组巨大儿、新生儿畸形发生率比较无统计学差异($P>0.05$)。见表 3。

3 讨论

GDM 的发病机理与胰岛素分泌不足和妊娠期胰岛素抵抗增强两大因素有关,有研究显示,HBV 对胰腺具有很强的亲和性,在病毒复制活跃时可直接侵犯胰腺组织或通过自身免疫反应导致胰腺组织不同程度的损伤,进而引起胰岛素分泌下降,血糖升高^[13-15]。肝脏是合成、代谢葡萄糖的重要脏器,可维持机体血糖稳定,若肝细胞内的 HBV 复制活跃,则容易引起炎症细

表 2 各组不良妊娠结局(母体)发生率比较[n(%)]

Table 2 Comparison of incidence rate of pregnancy outcomes(maternal) among different groups[n(%)]

Groups	n	PIH	Premature rupture of fetal membranes	Postpartum hemorrhage	Amniotic fluid	Premature delivery
Group A	1128	90(7.98)*	89(7.89)	74(6.56)	71(6.29)	35(3.10)*
Group B	406	36(8.87)*	33(8.13)	28(6.90)	31(7.64)	16(3.94)*
Group C	307	30(9.77)*	24(7.82)	22(7.17)	19(6.19)	14(4.56)*
Group D	774	26(3.36)	60(7.75)	54(6.98)	45(5.81)	10(1.29)
Group E	823	29(3.52)	65(7.90)	55(6.68)	49(5.95)	4(0.49)

Note: Compared with Group E, * $P<0.05$.

表 3 各组妊娠结局(新生儿)发生率比较[n(%)]

Table 3 Comparison of incidence rate of pregnancy outcomes(newborns) among different groups[n(%)]

Groups	n	Macrosomia	Asphyxia neonatorum	Neonatal malformation
Group A	1128	74(6.56)	13(1.15)	16(1.42)
Group B	406	26(6.40)	5(1.23)	5(1.23)
Group C	307	18(5.86)	5(1.63)*	4(1.30)
Group D	774	41(5.30)	6(0.78)	6(0.78)
Group E	823	46(5.59)	3(0.36)	9(1.09)

Note: Compared with Group E, * $P<0.05$.

胞异常导致肝细胞坏死,从而损害肝功能^[16,17]。肝功能异常影响葡萄糖的摄取和利用,并且也是慢性 HBV 感染者的特征之一,肝功能异常者蛋白合成能力下降,排泄功能受到阻碍,最终导致 GDM^[18,19]。已有研究报道,HBV 感染会增加妊娠期并发症的发生率,导致妊娠期羊水过多、巨大胎儿、早产、新生儿反应性低血糖等,且增加产妇罹患 2 型糖尿病的风险,但不同的 HBV 感染状态是否导致产妇不同的妊娠结局目前尚不明确^[20-22]。

本研究 2615 例慢性 HBV 感染产妇中,共发生 GDM 866 例,发生率为 33.12%。相关研究发现,慢性肝病产妇的 GDM 发生率显著高于普通人群^[23]。B 组与 C 组 GDM 发生率分别为 38.92%、37.46%,均大于 E 组的 30.74%,A 组、D 组与 E 组 GDM 发生率比较无统计学差异,说明 HBeAg 阳性慢性乙型肝炎、HBeAg 阴性慢性乙型肝炎产妇的 GDM 发生率均高于 HBV 阴性产妇,而其余慢性乙型肝炎病毒感染类型(慢性 HBV 携带者,非活动性 HBsAg 携带者)的 GDM 发生率与对照组均无显著性差异。HBeAg 阳性慢性乙型肝炎与 HBeAg 阴性慢性乙型肝炎的共同特征为 ALT 持续或反复异常,肝组织有肝炎病变,根据本研究结果,推测 HBV 对 GDM 的发生主要是通过影响肝功能及肝组织病变产生作用,HBV 病毒本身抗原及复制能力大小对 GDM 的发生并无直接影响。本研究结果还显示,A 组、B 组、C 组的 PIH、早产的发生率高于 E 组,C 组的新生儿窒息发生率高于 E 组,慢性 HBV 携带、HBeAg 阳性慢性乙型肝炎、HBeAg 阴性慢性乙型肝炎产妇的共同特征为 HBV DNA 阳性,表征 HBV 复制活跃。结合本研究数据,推测 HPV 感染对 PIH 及早产的影响主要是由于 HBV 复制活跃引起。有研究报道,醛固酮的升高与高血压具有密切相关性,并且肝脏是消灭醛固酮的主要场所^[24,25],当 HBV 感染肝脏且 HBV 复制活跃时肝脏受到严重损害,致使肝脏抑制醛固酮能力显著

下降,最终诱发 PIH 的发生^[26]。此外 HBV 复制活跃时体内促炎性细胞因子的表达异常升高,如 IL-2、IL-6、IL-10、TNF- α 等^[27,28]。相关研究报道,小于 34 周的自发性早产孕妇与孕 15-20 周羊水中高浓度的 IL-6 具有紧密相关性^[29]。并且 HBV 再体内不断的复制可能激活母体补体系统,破坏母胎界面的免疫耐受性,从而出现母体对胎儿的免疫攻击,增加发生早产的风险。另一方面,HBV 可干扰孕期雌激素在肝脏中的代谢,当肝脏中的雌激素不断积累,增加了子宫肌对催产素的敏感性,容易出现子宫肌收缩,也是早产发生的重要原因之一^[30]。然而本研究样本来源均为本医院,研究人群具有一定的局限性,在以后的研究工作中,应开展多区域的临床研究,对慢性 HPV 感染产妇进行更细化的分组比较,深入探讨其对 GDM 及妊娠结局的作用机制。

综上所述,慢性 HPV 感染产妇 GDM 的发生率较高,尤其是乙型肝炎携带者,且慢性 HPV 感染产妇的母体及新生儿不良妊娠结局发生率增加,值得临床重视。

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