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IMMUNOLOGICAL CHANGES ASSOCIATED WITH CHRONIC HEPATITIS B DURING PREGNANCY AND THEIR IMPACT ON PERINATAL RISK

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ABSTRACTS: Pregnancy induces a state of unique immunological tolerance to prevent fetal rejection, characterized by a shift from Th1 to Th2 immune responses. In women with Chronic Hepatitis B (CHB), this physiological immunosuppression may synergize with virus-induced T-cell exhaustion, leading to increased viral replication and altered perinatal outcomes. Objective: To investigate the dynamics of immunological markers (cytokines, T-cell subsets) and viral load during pregnancy in women with CHB, and to evaluate their association with perinatal risks such as preterm birth, fetal distress, and postpartum hepatic flares. Methods: A prospective cohort study was conducted at Andijan State Medical Institute involving 120 pregnant women: 60 with HBsAg-positive Chronic Hepatitis B (Main Group) and 60 HBsAg-negative healthy controls (Control Group). Serum levels of HBV DNA, ALT, and cytokines (IFN-γ, IL-10, IL-4) were measured at the 1st, 2nd, and 3rd trimesters and 3 months postpartum. Perinatal outcomes were recorded. Results: Pregnant women with CHB exhibited a profound Th2-shift, evidenced by significantly higher IL-10 and lower IFN-γ levels compared to healthy pregnant controls ($p<0.01$). This immune tolerance correlated with a significant rise in HBV DNA levels peaking in the 3rd trimester. Postpartum, 28% of CHB women experienced an ALT flare ("immune reconstitution"). High maternal viral load (>10^6 IU/mL) was independently associated with an increased risk of threatened preterm labor (OR=2.4) and lower neonatal Apgar scores. Conclusion: The synergistic immunotolerance of pregnancy and CHB leads to high viral replication in the third trimester. While this protects the liver from inflammation during pregnancy, it increases the risk of perinatal transmission and postpartum flares. Immunological monitoring is essential for timely antiviral prophylaxis.
Keywords: Chronic Hepatitis B, pregnancy, immunology, Th1/Th2 balance, postpartum flare, perinatal risk, Andijan State Medical Institute.

XOMILADORLIK DAVRIDA SURUNKALI GEPATIT B BILAN BOG‘LIQ IMMUNOLOGIK O‘ZGARISHLAR VA ULARNING PERINATAL XAVFGA TA’SIRI

ANNOTATSIYA: Kirish: Xomiladorlik homilani rad etishning oldini olish uchun Th1 dan Th2 immun javobiga o‘tish bilan tavsiflangan o‘ziga xos immun tolerantlik holatini keltirib chiqaradi. Surunkali gepatit B (SGB) bilan og‘rigan ayollarda ushbu fiziologik immunosupressiya virus chaqirgan T-hujayra toliqishi (exhaustion) bilan qo‘shilib, virus replikatsiyasining kuchayishiga va perinatal oqibatlarning o‘zgarishiga olib kelishi mumkin. Maqsad: SGB bilan og‘rigan xomilador ayollarda immunologik markerlar (sitokinlar, T-hujayra subpopulyatsiyalari) va virus yuklamasi dinamikasini o‘rganish hamda ularning muddatidan oldin tug‘ruq, homila distressi va tug‘ruqdan keyingi jigar xurujlari kabi perinatal xavflar bilan bog‘liqligini baholash. Usullar: Andijon davlat tibbiyot institutida 120 nafar xomilador ayol ishtirokida prospektiv kogorta tadqiqoti o‘tkazildi: 60 nafar HBsAg-musbat SGB bilan (Asosiy guruh) va 60 nafar HBsAg-

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manfiy sog‘lom ayol (Nazorat guruhi). HBV DNK, ALT va sitokinlar (IFN-γ, IL-10, IL-4) darajasi 1, 2 va 3-trimestrlarda hamda tug‘ruqdan keyingi 3-oyda o‘lchandi. Natijalar: SGB bilan og‘rigan xomiladorlarda kuchli Th2-siljish kuzatildi, bu sog‘lom xomiladorlarga nisbatan IL-10 ning yuqori va IFN-γ ning past darajasi bilan isbotlandi ($p<0.01$). Ushbu immun tolerantlik 3-trimestrda HBV DNK darajasining sezilarli oshishi bilan bog‘liq bo‘ldi. Tug‘ruqdan so‘ng SGB ayollarning 28 foizida ALT xuruji ("immun rekonstitutsiya") kuzatildi. Onadagi yuqori virus yuklamasi (>10^6 IU/mL) muddatidan oldin tug‘ruq xavfi (OR=2,4) va chaqaloqning past Apgar shkalasi bilan mustaqil bog‘liq ekanligi aniqlandi. Xulosa: Xomiladorlik va SGBning o‘zaro immun tolerantligi uchinchi trimestrda yuqori virus replikatsiyasiga olib keladi. Bu xomiladorlik paytida jigarni yallig‘lanishdan himoya qilsa-da, perinatal yuqtirish va tug‘ruqdan keyingi xurujlar xavfini oshiradi. O‘z vaqtida virusga qarshi profilaktika uchun immunologik monitoring zarur.

Kalit so‘zlar: Surunkali gepatit B, xomiladorlik, immunologiya, Th1/Th2 balansi, tug‘ruqdan keyingi xuruj, perinatal xavf, ADTI.

ИММУНОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ, СВЯЗАННЫЕ С ХРОНИЧЕСКИМ ГЕПАТИТОМ В ВО ВРЕМЯ БЕРЕМЕННОСТИ, И ИХ ВЛИЯНИЕ НА ПЕРИНАТАЛЬНЫЙ РИСК.

АННОТАЦИЯ: Введение: Беременность вызывает состояние уникальной иммунной толерантности для предотвращения отторжения плода, характеризующееся сдвигом иммунного ответа от Th1 к Th2. У женщин с хроническим гепатитом В (ХГВ) эта физиологическая иммуносупрессия может синергировать с вызванным вирусом истощением Т-клеток, что приводит к усилению репликации вируса и изменению перинатальных исходов. Цель: Изучить динамику иммунологических маркеров (цитокинов, субпопуляций Т-клеток) и вирусной нагрузки во время беременности у женщин с ХГВ, а также оценить их связь с перинатальными рисками, такими как преждевременные роды, дистресс плода и послеродовые обострения гепатита. Методы: В Андижанском государственном медицинском институте было проведено проспективное когортное исследование с участием 120 беременных женщин: 60 с HBsAg-позитивным ХГВ (основная группа) и 60 HBsAg-негативных здоровых женщин (контрольная группа). Уровни ДНК ВГВ, АЛТ и цитокинов (IFN-γ, IL-10, IL-4) измерялись в 1-м, 2-м и 3-м триместрах и через 3 месяца после родов. Результаты: У беременных с ХГВ наблюдался выраженный сдвиг в сторону Th2, что подтверждалось значительно более высоким уровнем IL-10 и более низким уровнем IFN-γ по сравнению со здоровыми беременными ($p<0.01$). Эта иммунная толерантность коррелировала со значительным повышением уровня ДНК ВГВ, достигающим пика в 3-м триместре. После родов у 28% женщин с ХГВ наблюдалось обострение АЛТ («восстановление иммунитета»). Высокая вирусная нагрузка у матери (>10^6 МЕ/мл) была независимо связана с повышенным риском угрозы преждевременных родов (ОШ=2,4) и более низкими оценками по шкале Апгар у новорожденных. Заключение: Синергетическая иммунотолерантность беременности и ХГВ приводит к высокой репликации вируса в третьем триместре. Хотя это защищает печень от воспаления во время беременности, это увеличивает риск перинатальной передачи и послеродовых обострений. Иммунологический мониторинг необходим для своевременной противовирусной профилактики.

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Ключевые слова: Хронический гепатит В, беременность, иммунология, баланс Th1/Th2, послеродовое обострение, перинатальный риск, АГМИ.

INTRODUCTION

Chronic Hepatitis B (CHB) remains a significant public health challenge in Uzbekistan, particularly among women of childbearing age. The prevalence of HBsAg positivity in pregnant women in the Fergana Valley region is estimated to be around 2-4%, necessitating a deeper understanding of the disease's behavior during gestation. Managing CHB during pregnancy presents a unique clinical dilemma due to the complex and dynamic interplay between the virus and the host's immune system.

Immunological landscape of pregnancy - Normal pregnancy is characterized by a physiological modulation of the immune system to tolerate the semi-allogeneic fetus. This involves a systemic shift from cell-mediated immunity (Th1 cytokines: IFN-γ, IL-2) towards humoral immunity (Th2 cytokines: IL-4, IL-10) and regulatory T-cell (Treg) upregulation. This environment, while essential for fetal survival, is theoretically favorable for the persistence and replication of intracellular pathogens like HBV.

Interaction with hepatitis B virus - In non-pregnant individuals, successful control of HBV requires a robust Th1 response (Cytotoxic T-Lymphocytes). In CHB patients, T-cells are often in a state of "exhaustion" due to persistent antigen exposure. During pregnancy, the physiological Th2 shift superimposes on this exhaustion, potentially leading to a "double hit" of immunosuppression. This creates two major clinical phases: 1) Pregnancy (Immune tolerance) - Reduced liver inflammation (normal ALT) but increased viral replication (High HBV DNA). 2) postpartum (Immune reconstitution) - Rapid withdrawal of cortisol and placental cytokines restores Th1 activity, potentially triggering a cytotoxic attack on infected hepatocytes, known as a hepatic flare.

Perinatal risks Beyond the well-established risk of Mother-to-Child Transmission (MTCT), the impact of maternal viremia and immune dysregulation on the fetus—such as preterm birth, low birth weight, and intrauterine distress—remains a subject of debate. This study aims to clarify these immunological mechanisms and their clinical consequences in the specific population of the Fergana Valley.

MATERIALS AND METHODS

Study design A prospective, comparative cohort study was conducted at the Department of Infectious Diseases and the Perinatal Center of Andijan State Medical Institute (2022–2024).

Main Group - 60 pregnant women with confirmed Chronic Hepatitis B (HBsAg+, HBeAg+/-) who did not receive antiviral therapy at the time of conception.

Control Group - 60 healthy pregnant women matched for age and gestational week (HBsAg-, anti-HCV-, HIV-).

Exclusion Criteria: Co-infection (HCV, HIV, HDV), decompensated cirrhosis, pre-eclampsia, gestational diabetes, or other autoimmune diseases. Laboratory Analysis Peripheral blood samples were collected at four time points: gestational weeks 12 (T1), 24 (T2), 36 (T3), and 12 weeks postpartum (PP). Virology: Quantitative HBV DNA (Real-time PCR). Biochemistry: ALT, AST (to assess hepatic inflammation). Immunology: Serum cytokine levels (IFN-γ, IL-4, IL-10) were measured by ELISA to determine Th1/Th2 balance.

Perinatal Outcomes: Gestational age at delivery, Apgar score (1 min/5 min), birth weight, and incidence of fetal distress/asphyxia.

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Statistical analysis - Data were analyzed using SPSS v.26. Continuous variables were presented as Mean ± SD. Differences between groups were assessed using ANOVA and Chi-square tests. Correlations were determined using Pearson's coefficient. A p-value < 0.05 was considered statistically significant.

RESULTS

Immunological profile - The enhanced Th2 Shift Both groups showed a physiological decrease in IFN-γ and an increase in IL-10 as pregnancy progressed. However, the magnitude of this shift was significantly more pronounced in the CHB group, indicating a deeper state of immune tolerance (Table 1).

Table 1. Cytokine dynamics during pregnancy (Mean ± SD)

Cytokine	Group	1st Trimester	2nd Trimester	3rd Trimester	Postpartum (12 wks)
IFN-γ (pg/mL)	Control	18.4 ± 3.2	14.1 ± 2.5	12.5 ± 2.1	19.1 ± 3.5
(Th1 marker)	CHB (Main)	12.2 ± 2.8*	9.5 ± 1.9*	7.8 ± 1.6*	22.4 ± 4.1^
IL-10 (pg/mL)	Control	8.5 ± 2.1	12.4 ± 3.0	15.6 ± 3.5	9.2 ± 2.2
(Th2/Treg marker)	CHB (Main)	14.2 ± 3.4*	21.5 ± 4.1*	28.4 ± 5.2*	11.5 ± 2.8

** p < 0.05 compared to Control; ^ p < 0.05 compared to 3rd Trimester (indicating Reconstitution)*

Interpretation - The CHB group exhibited profound suppression of Th1 immunity (low IFN-γ) and elevated anti-inflammatory IL-10, peaking in the 3rd trimester. Postpartum, IFN-γ levels surged in the CHB group, surpassing baseline levels, which signals immune reconstitution.

Viral load and liver enzymes In the CHB group, HBV DNA levels increased significantly from T1 to T3, inversely correlating with IFN-γ levels (r = -0.65). 3rd Trimester - Mean HBV DNA rose by 1.5 log IU/mL compared to baseline. ALT levels remained largely normal (<40 U/L) in 92% of women during pregnancy, reflecting the "immune tolerance" phase. Postpartum - At 12 weeks postpartum, a Hepatic Flare (ALT > 2x ULN) occurred in 17 women (28.3%). This flare coincided with the rapid rebound of IFN-γ levels shown in Table 1.

Perinatal outcomes - To assess the impact of the virus on the fetus, we stratified the Main Group into "High Viral Load" (>10^6 IU/mL) and "Low Viral Load" subgroups.

Table 2. Perinatal complications by viral load status

Outcome	Low viral load (n=32)	High viral load (n=28)	Control group (n=60)	P-value
Preterm birth (<37 wks)	6.2%	17.8%	5.0%	< 0.05
Threatened miscarriage	12.5%	28.5%	10.0%	< 0.05
Fetal distress	3.1%	14.2%	3.3%	< 0.05
Low birth weight (<2500g)	3.1%	10.7%	3.3%	> 0.05
Neonatal apgar < 7	3.1%	10.7%	1.6%	< 0.05

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Key finding: High maternal viremia was associated with a higher incidence of preterm birth and fetal distress, likely due to placental inflammation triggered by high antigen loads, despite systemic tolerance.

DISCUSSION

The results obtained at Andijan State Medical Institute highlight the "dual-edged sword" of immune tolerance in pregnant women with Hepatitis B.

Mechanism of viral replication The significant rise in IL-10 and decline in IFN-γ during the 3rd trimester creates a permissive environment for HBV replication. The virus exploits the maternal tolerance mechanism intended to protect the fetus. This explains why many women progress to a "high replicative state" (HBeAg-like phenotype) just before delivery, maximizing the risk of vertical transmission.

Postpartum immune reconstitution syndrome The sudden drop in IL-10 and cortisol after delivery releases the "brake" on the immune system. T-cells (Th1) recover function and recognize hepatocytes laden with viral antigens (accumulated during pregnancy). This results in cytolysis (ALT elevation). While this can clear the virus, severe flares can lead to hepatic decompensation. Our study found a 28% flare rate, emphasizing the need for continued postpartum monitoring for at least 6 months.

Impact on the fetus - Contrary to the belief that CHB is benign for the pregnancy itself, our data suggests that uncontrolled high viral load poses risks beyond transmission. The correlation between high HBV DNA and preterm birth suggests that viral antigens may trigger localized inflammation in the placenta (deciduitis) or induce oxidative stress, compromising fetal well-being.

CONCLUSION

Immunological dynamics - Pregnancy exacerbates the Th2/Treg dominance in CHB patients, leading to a peak in viral replication in the 3rd trimester.

Postpartum risk - The rapid restoration of Th1 immunity (IFN-γ rebound) postpartum triggers hepatic flares in approximately one-third of patients, representing a critical window for maternal health.

Perinatal risk - High maternal viral load (>200,000 IU/mL) is an independent risk factor for preterm birth and fetal distress, necessitating proactive management.

RECOMMENDATIONS

Screening - Universal HBsAg screening is mandatory.

Monitoring - HBV DNA and ALT levels must be monitored at 24-28 weeks to identify high-risk mothers.

Prophylaxis - Antiviral therapy (e.g., Tenofovir Disoproxil Fumarate) should be initiated in the 3rd trimester (week 28-32) for women with high viral load to protect the fetus from both transmission and adverse pregnancy outcomes.

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