CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2641186

Available online at: http://www.iajps.com *Research Article*

A PROSPECTIVE COHORT TO EXPLORE BASELINE CHARACTERISTICS AND PREGNANCY OUTCOMES AMONG PREGNANT HBV CARRIERS AND NON-HBV CONTROLS

[1]Dr. Qandeel Hayat, [2]Dr Muhammad Moazam, [3]Sarah Razzaq

[1]Sandeman Provincial Hospital Quetta, [2]BHU Karianwala, [3]Sir Ganga Ram Hospital, Lahore.

Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:

Background: *Infection during Hepatitis-B (HBV) among expecting women is a threat to neonatal and maternal life.*

Objective: *The objective of this research was to explore the association between maternal HBV carriers' and outcomes of pregnancy.*

Methods: *This prospective cohort research was carried out at Jinnah Hospital, Lahore from March 2017 to October 2018 on a total of 21004 pregnant women which included asymptomatic HBV carriers (513) and non-HBV controls (20491). Major interesting pregnancy outcomes were stillbirth, miscarriage, preterm birth (PTB), intrahepatic cholestasis of pregnancy (ICP), gestational diabetes (GDM), low birth weight (LBW), preterm premature rupture of the membrane (PPROM), Apgar Score and small for gestational age (SGA). The comparison of adverse pregnancy outcomes between non-HBV controls and asymptomatic HBV carriers was carried out through logistic regression and chi-square test. Statistically significant two-sided P-Value was (< 0.05).*

Results: *The occurrence of stillbirth, GDM, PTB, PPROM, ICP, SGA and LBW were almost the same between both groups. Miscarriage proportion was reported 9.36% in HBV carrier and 5.7% in non-HBV groups (P-Value < 0.001). After employing multivariate modelling in order to adjust for the obstetric complications and socio-demographical variables the HBV carriers were more prone to miscarriage (Adjusted Odds Ratio 1.71, CI 95%, 1.23 – 2.38). Moreover, other neonatal and maternal outcomes of both groups were also the same.*

Conclusion: *Maternal Hepatitis-B (HBV) carrier status may represent miscarriage. Rather it is a risk factor for miscarriage among pregnant women; therefore, careful monitoring is suggested with grave concerns for the neonatal and maternal health.*

Keywords: *Hepatitis-B, HBV, Pregnancy, Infection, Virus, Miscarriage, Neonatal, Maternal, GDM, PTB, PPROM, ICP, SGA, LBW and Carriers.*

Corresponding author:

Dr. Qandeel Hayat,

Sandeman Provincial Hospital Quetta.

QR code

Please cite this article in press Qandeel Hayat et al., ***A Prospective Cohort to Explore Baseline Characteristics and Pregnancy Outcomes among Pregnant Hbv Carriers and Non-Hbv Controls.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

The onset of Hepatitis-B (HBV) has been reported all over the world repeatedly. Its prevalence among pregnant women may vary from 2% to 8% and in some other regions about 0.4% [1 – 3]. Majority of the pregnant women are chronic carriers of HBV which is identified through the positive status of the HBsAg. HBsAg is also reported in placental capillary endothelium or ovarian follicle cells [4]. HBV vertical transmission and intrauterine infection are basic reasons for the chronic HBV carriers. The overall estimated immune-prophylaxis failure rate among infants having positive HBsAg were (4.87%) and mothers positive for HBeAg were (9.66%) [5].

The status of HBV is common in pregnant women particularly in the case of highly endemic regions. Adverse pregnancy outcomes due to HBV is a less studied subject and literary evidence are scarcely available. Conflicting outcomes are available due to scarce literary references [6 – 15]. In the non-availability of related research material, we carried out this research to explore the association between maternal HBV carriers' and outcomes of pregnancy.

METHODS:

This prospective cohort research was carried out at Jinnah Hospital, Lahore from March 2017 to October 2018 on a total of 21004 pregnant women which included asymptomatic HBV carriers (513) and non-HBV controls (20491). Major interesting pregnancy outcomes were a stillbirth, miscarriage, PTB, ICP, GDM, LBW, PPROM, SGA and Apgar. We used WHO criteria for BMI classification to categorize patients into various BMI categories [16]. Every woman was screened for HBsAg, HBeAg, IgG antibodies against HIV and HCV, syphilis tests with TP-PA, specific IgM antibodies against Toxoplasma, RPR, CMV, rubella virus and HSV – 1/2.

Patients were enrolled in the research after fulfilling the set criteria which included normal ALT, the absence of HCV & HIV, active syphilis infection, IgM absence against TOX, rubella virus, cytomegalovirus, herpes simplex virus, ALD & NAFLDs exclusion, AILDs, preexistence of diabetes mellitus, heart diseases and hypertension. HBV carriers refer to positive HBsAg for more than six months and normal persistent ALT levels. We did not include those HBV carriers who were treated with antiviral therapy in last year. Majority of the patients received three health assessments and a follow-up for miscarriage or delivery.

Research commenced after institutional ethical approval and informed consent of the patients. Pregnancy outcomes were miscarriage, stillbirth and preterm. Maternal outcomes were preeclampsia, GDM, placental abruption, placenta previa and PPROM. Singleton pregnancy neonatal outcomes included low birth weight, small gestational age, Apgar Score or macrosomia [17, 18]. Social influence affects the onset of caesarean delivery [19].

In assumed HBV carriers to Non-HBV proportion of (1:20); the baseline adverse pregnancy risk was five percent; the power of increased risk was 80% in the approximately minimum sample population of 4200 there were 200 HBV carriers. Continuous variables were compared through T-Test. Categorical outcomes were assessed by Fisher's exact test and Chi-square test. The miscarriage was a dependent variable; whereas, demographic, medical history, education and laboratory factors were independent variables. The comparison of adverse pregnancy outcomes between non-HBV controls and asymptomatic HBV carriers was carried out through logistic regression and chi-square test. Statistically significant two-sided P-Value was (< 0.05).

RESULTS:

The occurrence of stillbirth, GDM, PTB, PPROM, ICP, SGA and LBW were almost the same between both groups. Miscarriage proportion was reported 9.36% in HBV carrier and 5.7% in non-HBV groups (P-Value < 0.001). After employing multivariate modelling in order to adjust for the obstetric complications and socio-demographical variables the HBV carriers were more prone to miscarriage (Adjusted Odds Ratio 1.71, CI 95%, 1.23 – 2.38). Moreover, other neonatal and maternal outcomes of both groups were also the same. Detailed outcomes of baseline characteristics and study outcomes of both HBV carriers and Controls are as under:

Table – I: Baseline Characteristics (Mean ± SD)

Characteristic	HBV Carriers (513)		Controls (20491)		P-Value
	Mean	±SD	Mean	±SD	
Maternal age (Years)	27.59	4.02	27.03	4.19	0.003
Height (cm)	156.23	8.43	155.81	7.32	0.201
Pre-pregnancy BMI	22.34	5.86	22.02	5.69	0.209
ALT (U/L)	24.75	7.22	22.34	6.49	< 0.001
Completed weeks' gestation	35.79	8.29	36.95	6.76	< 0.001
Apgar at 5 min	9.9	0.53	9.87	0.69	0.336

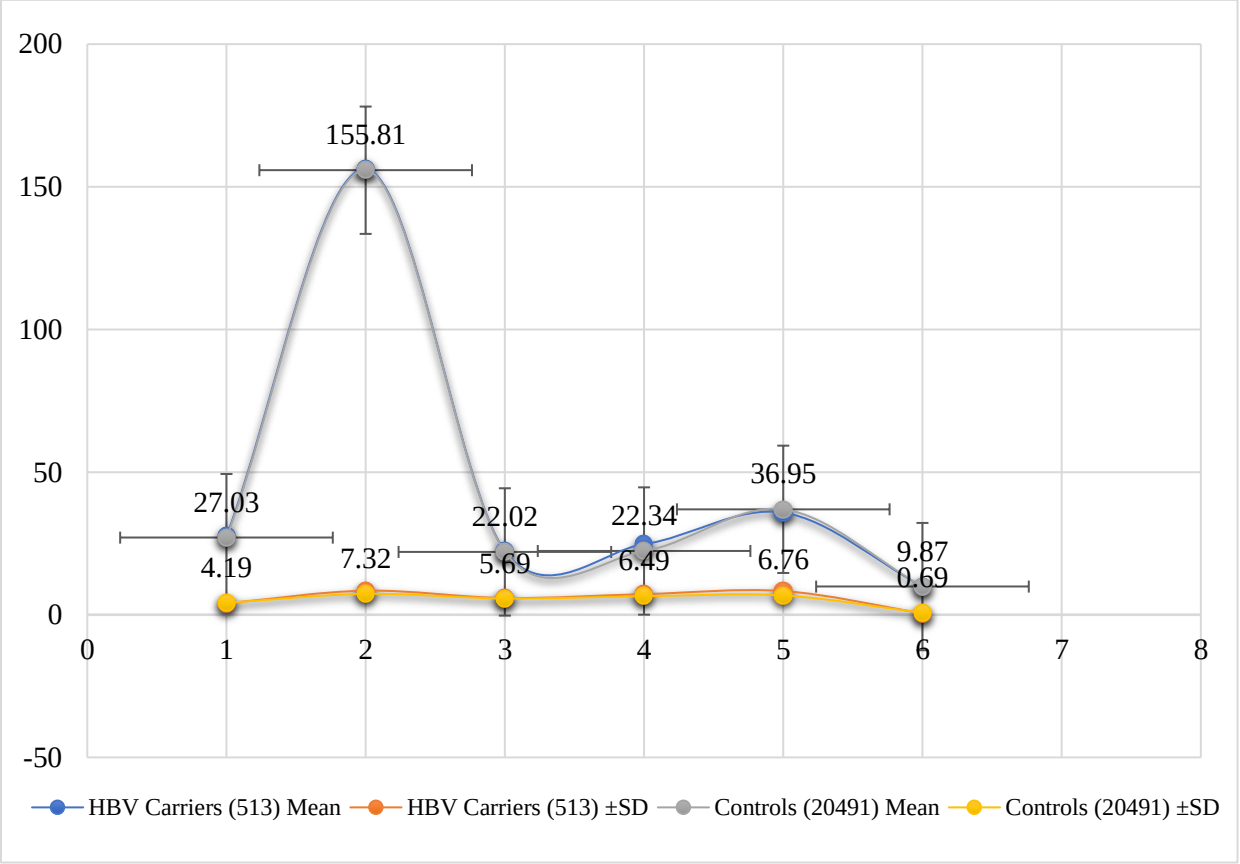


Table – II: Baseline Characteristics (HBV Carriers Versus Controls)

Characteristic		HBV Carriers (513)	Controls (20491)	P-Value
Maternal Age	≤ 19	2	239	0.234
	20 – 34	476	18,974	
	≥ 35	35	12,78	
Pre-pregnancy BMI	< 18.5	35	1,751	0.396
	18.5 – 24.9	408	16,137	
	25 – 29.9	67	2,536	
	≥ 30	3	67	
Educational Level	Primary / Middle	15	892	0.288
	Middle / High	171	6,785	
	College and Above	327	12,814	
Parity	0	373	15,524	0.258
	1	126	4,519	
	≥ 2	14	448	
Previous abortion	0	456	18,607	0.385
	1	42	1,329	
	≥ 2	15	555	
Previous preterm birth	0	504	20,168	0.907
	1	9	320	
	≥ 2	0	3	
Plurality	1	497	20,001	0.288
	≥ 2	16	490	
IVF	No	509	20,344	0.869
	Yes	4	147	

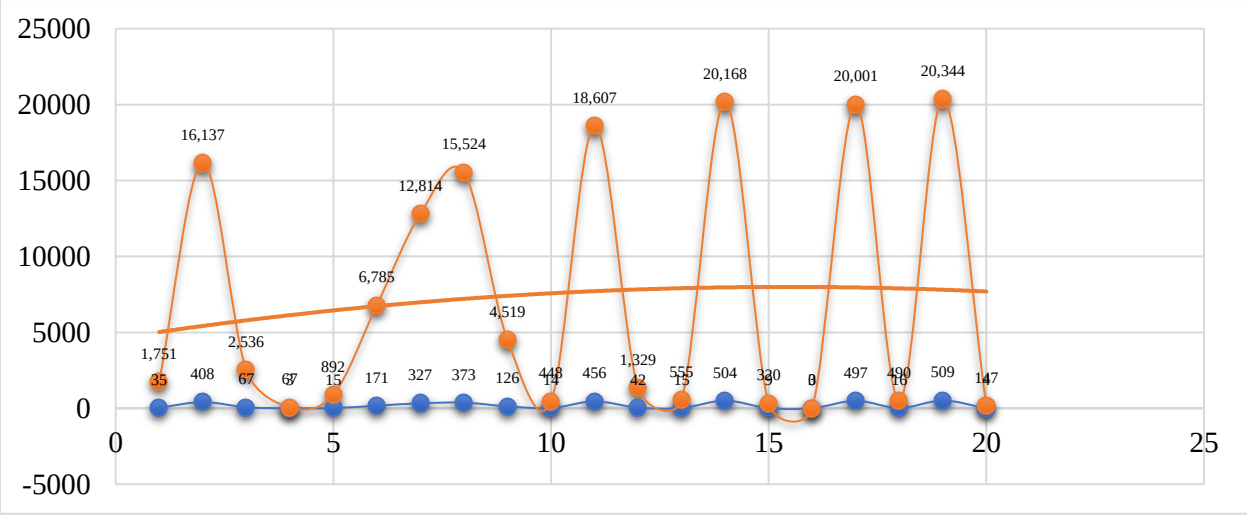
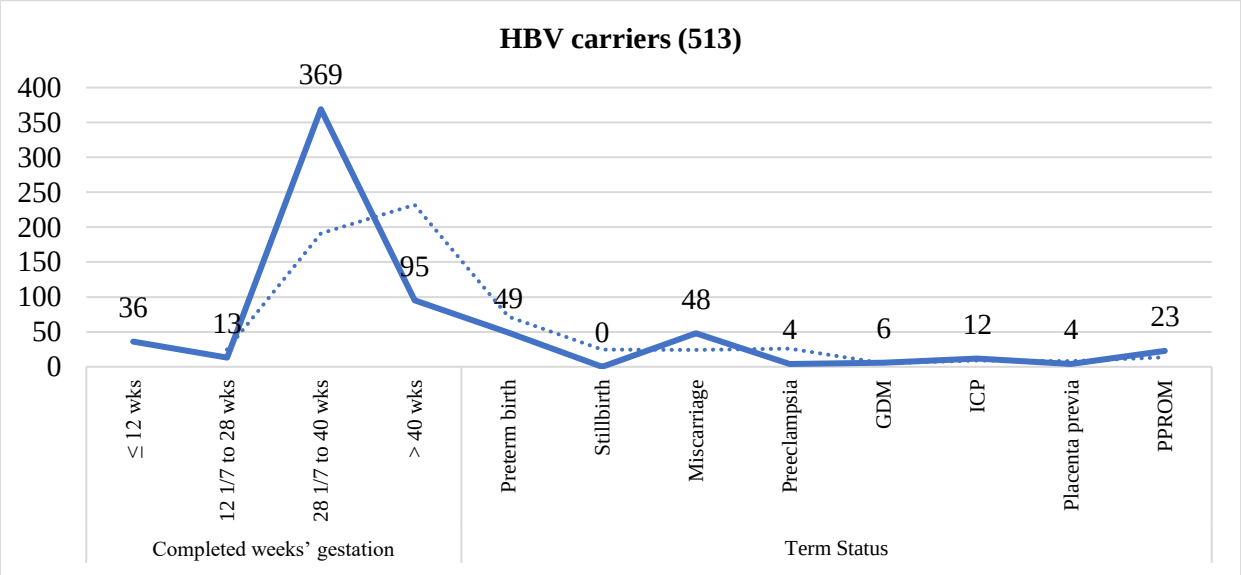


Table – III: Study Outcomes (HBV Carriers Versus Controls)

Outcome		HBV carriers (513)	Controls (20,491)	P-Value
Completed weeks' gestation	≤ 12	36	822	0.002
	12 1/7 to 28	13	390	
	28 1/7 to 40	369	14,755	
	> 40	95	4,524	
Term Status	Preterm birth	49	1718	0.347
	Stillbirth	0	18	0.502
	Miscarriage	48	1167	< 0.001
	Preeclampsia	4	216	0.6
	GDM	6	232	0.937
	ICP	12	331	0.201
	Placenta previa	4	216	0.547
	PPROM	23	845	0.686



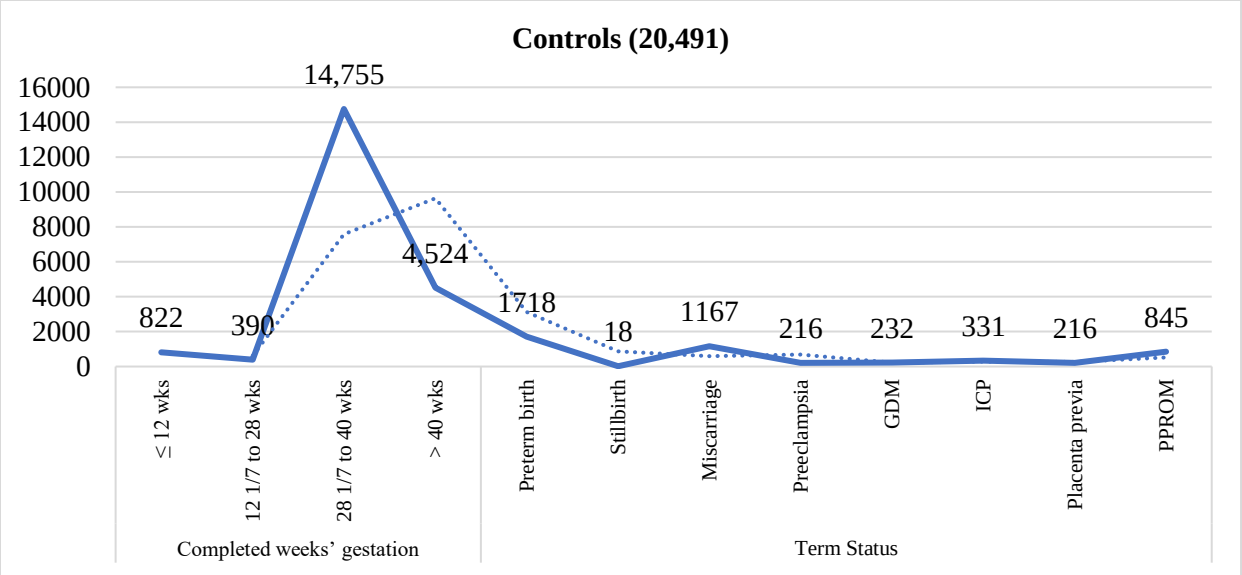


Table – IV: Study Outcomes (HBV Carriers Versus Controls)

Outcome		HBV carriers (497)	Controls (20,001)	P-Value
Term Status	Full-term birth	413	17364	0.016
	Preterm birth	36	1462	0.955
	Stillbirth	0	12	0.585
	Miscarriage	48	1163	<0.001
Weight of Neonates (grams)	Unknown	0	9	0.585
	< 1500	4	108	
	1500 – 2500	21	797	
	2500 – 3999	392	17,489	
	≥ 4000	32	1,598	
LBW	Unknown	0	9	0.594
	No	472	19,087	
	Yes	25	905	
SGA <10 centile	Unknown	0	9	0.461
	No	475	18,959	
Apgar	≥7	488	19,744	0.292
	<7	9	257	

Table – V: Baseline Features (Cases Versus Exposed)

Features		Cases	Exposed	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Age	< 35	1067	19691	1	1
	≥ 35	148	1313	2.22 (1.85–2.66)	1.17 (0.94–1.45)
Nulliparity	No	830	15897	1.48 (1.31–1.69)	1.80 (1.54–2.11)
	Yes	385	5107		
Education	High School	497	8063	0.83 (0.67–1.19)	
	College and Above	718	12941		
Pre-maternal BMI	< 25	1049	18331	1.09 (0.97–1.42)	
	≥ 25	166	2673		
Previous abortion	0	673	19063	7.95 (6.85–9.22)	9.33 (7.97–10.92)
	1	309	1371		
	≥ 2	233	570	18.89 (15.72–22.71)	23.36 (19.10–28.57)
HBV carrier	No	1167	20491	1.71 (1.26–2.31)	1.71 (1.23–2.38)
	Yes	48	513		
IVF	No	1196	20853	2.37 (1.46–3.84)	1.78 (1.03–3.05)
	Yes	19	151		

DISCUSSION:

Miscarriage among pregnant women is high among chronic HBV affected women than non-HBV controls. There is no change in the association of miscarriage with other maternal features such as abortion history, parity and age. Association between miscarriage and viral infection needs more investigative work for better understanding. Miscarriage is attributed to several viruses including CMV, human parvovirus B19, HSV-1/2, Coxsackie B virus and adenovirus [20, 21]. Other virus's association with miscarriage is still not established. First, the viral infection among pregnant cases is not always fatal due to the placental barrier. Secondly, there is a vertical transmission risk associated with placental viral infection not always disease or transmission of the fetus. Lastly, the intrauterine viral infection does not pose mortality and morbidity at an early gestational stage. For Instance, the miscarriage caused due to acute varicella do not exceeds the miscarriage rate among without chickenpox pregnant women [22].

The query of association of HBV infection and adverse pregnancy outcomes was first raised back in 1960; which has been a hot issue in the future literary perspective [23, 8 – 15]. Our outcomes reflect that chronic HBV carrier status may affect the function of the placenta in comparison to the preterm labour. Though the HBsAg prevalence was (2.5%) among pregnant cases which is lower than the outcomes reported by another author as (6.1%) with strong epidemiologic power. It is noteworthy that among HBV carriers the level of ALT serum was high than non-HBV controls which speak for the adverse long-term effects on the liver. Asymptomatic HBV carriers have immune tolerance clinical HBV phase and inactive carrier clinical HBV phase [24]. Immune Tolerance patients have normal values of ALT and positive serum HBeAg in last year. IT form patients form higher HBV-DNA loads (≥ 2 × 106) IU/mL with limited injury; whereas, among atypical form patients the HBV-DNA load is (< 2 × 106) IU/mL with an increased risk for the severe histological lesions. Inactive carriers show repeating normal values of ALT (< 40 IU/L) for a period of one-year positive HBeAb and negative HBeAg. Typical IC patients show reduced HBV-DNA load (< 2,000) IU/mL and reduced chances of histological lesions; whereas, the atypical form shows increased HBV-DNA load (≥ 2,000) IU/mL which is still problematic. Therefore, it difficult to segregate inactive HBsAg carriers from progressive liver injury in the absence of symptoms [25]. Our population maintained normal ALT levels in the course of pregnancy. The increase in ALT was in the range of (1 – 2 × ULN) which restored to normal in the time period of three months. Research reported that an abnormal ALT level was (0.57%) throughout the course of research which is low than abnormal liver function (3%) as reported in the past studies [26].

Previous pregnancy outcomes largely affect the onset of future pregnancies. This research reports that an

important predictive factor that affects miscarriage is a history of induced abortion or spontaneous abortion which is similar to other research studies [27, 28]. Whereas, aetiology of recurrent loss of a pregnancy is still unknown [29]. Whereas, induced abortion possibly increases mood disorder and preterm delivery; correlation of induced abortion to succeeding miscarriage is still under debate [30]. We did not include other potential contributing factors such as consumption of alcohol, cigarette and caffeine.

CONCLUSION:

This research reports that HBV carrier status confers with higher miscarriage risk. Maternal Hepatitis-B (HBV) carrier status may represent miscarriage. Rather it is a risk factor for miscarriage among pregnant women; therefore, careful monitoring is suggested with grave concerns for the neonatal and maternal health.

REFERENCES:

1. Siegel M, Fuerst HT, Peress NS. Comparative fetal mortality in maternal virus diseases. A prospective study on rubella, measles, mumps, chicken pox and hepatitis. N Engl J Med. 1966;274(14):768–71.
2. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatol. 2009;49(5 Suppl): S45–55.
3. Andreani T. HBV-carriers: When are monitoring and surveillance sufficient? (point of view). Clin Res Hepatol Gastroenterol. 2011;35(12):813–8.
4. Ch'ng CL, Morgan M, Hainsworth I, Kingham JG. A prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut. 2002;51(6):876–80.
5. Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on the risk of spontaneous abortion. BMJ. 1989;299(6698):541–5.
6. Bick RL, Madden J, Heller KB, Toofanian A. Recurrent miscarriage: causes, evaluation, and treatment. Medscape Women's Health. 1998;3(3):2.
7. Practice Committee of the American Society for Reproductive M. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103–11.
8. Thorp Jr JM, Hartmann KE, Shadigian E. Long-term physical and psychological health consequences of induced abortion: a review of the evidence. Obstet Gynecol Surv. 2003;58(1):67–79.
9. Pastorek 2nd JG, Miller Jr JM, Summers PR. The effect of hepatitis B antigenemia on pregnancy outcome. Am J Obstet Gynecol. 1988;158(3 Pt 1):486–9.
10. Yue YF, Zhang SL, Li GL. The effect of HBsAg antigenemia on pregnancy. J of Xi'an Med Univ. 1995;7(2):136–8.
11. Wong S, Chan LY, Yu V, Ho L. Hepatitis B carrier and perinatal outcome in a singleton pregnancy. Am J Perinatol. 1999;16(9):485–8.
12. Tse KY, Ho LF, Lao T. The impact of maternal HBsAg carrier status on pregnancy outcomes: a case-control study. J Hepatol. 2005;43(5):771–5.
13. Saleh-Gargari S, Hantoushzadeh S, Zendehdel N, Jamal A, Aghdam H. The Association of Maternal HBsAg Carrier Status and Perinatal Outcome. Hepat Mon. 2009;9(3):180–4.
14. Safir A, Levy A, Sikuler E, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier status as an independent risk factor for adverse perinatal outcome. Liver Int. 2010;30(5):765–70.
15. Elefsiniotis I, Tsoumakas K, Vezali E, Glynou I, Drakoulis N, Saroglou G. Spontaneous preterm birth in women with chronic hepatitis B virus infection. Int J Gynecol Obstet. 2010;110(3):241–4.
16. Connell LE, Salihu HM, Salemi JL, August EM, Weldeselasse H, Mbah AK. Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. Liver Int. 2011;31(8):1163–70.
17. Reddick KL, Jhaveri R, Gandhi M, James AH, Swamy GK. Pregnancy outcomes associated with viral hepatitis. J Viral Hepat. 2011;18(7): e394–8.
18. Sirilert S, Traisrisilp K, Sirivatanapa P, Tongsong T. Pregnancy outcomes among chronic carriers of hepatitis B virus. Int J Gynecol Obstet. 2014;126(2):106–10.
19. Shen Y, Zhang J, Cai H, Shao JG, Zhang YY, Liu YM, Qin G, Qin Y. Identifying patients with chronic hepatitis B at high risk of type 2diabetes mellitus: a cross-sectional study with pair-matched controls. BMC Gastroenterol. 2015; 15:32.
20. Zhu L, Zhang R, Zhang S, Shi W, Yan W, Wang X, Lyu Q, Liu L, Zhou Q, Qiu Q et al. Chinese neonatal birth weight curve for different gestational age. Zhonghua er ke za zhi Chinese J Pediatr. 2015;53(2):97–103.
21. Xu B, Jarvelin MR, Xu X, Wang Z, Qin H, Rimpela A. Maternal menstrual history and small-for-gestational-age births in a population-based Chinese birth cohort. Early Hum Dev. 1997;49(3):183–92.
22. Hellerstein S, Feldman S, Duan T. 50 % caesarean delivery rate: is it too high? BJOG. 2015;122(2):160–4.

23. el-Sayed Zaki M, Goda H. Relevance of parvovirus B19, herpes simplex virus2, and cytomegalovirus virologic markers in maternal serum for diagnosis of unexplained recurrent abortions. Arch Pathol Lab Med. 2007;131(6):956–60.
24. Konstantinidou A, Anninos H, Spanakis N, Kotsiakis X, Syridou G, Tsakris A, et al. Transplacental infection of Coxsackievirus B3 pathological findings in the fetus. J Med Virol. 2007;79(6):754–7.
25. Sauerbrei A, Wutzler P. Varicella-Zoster Virus Infections During Pregnancy: Epidemiology, Clinical Symptoms, Diagnosis, Prevention and Therapy. Curr Pediatr Rev. 2005; 1:205–16.
26. Huang Y, Li L, Sun X, Lu M, Liu H, Tang G, Wang D, Hutin YJ. Screening of pregnant women for hepatitis B virus surface antigen (HBsAg) and subsequent management, Qiandongnan prefecture, Guizhou, 2010.Vaccin. 2013;31 Suppl 9: J62–5.
27. Lao TT, Sahota DS, Law LW, Cheng YK, Leung TY. Age-specific prevalence of hepatitis B virus infection in young pregnant women, Hong Kong Special Administrative Region. Bull World Health Organ. 2014;92(11):782–9.
28. Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, Kern ER, McHugh JA, Petersen GM, Rein MF et al. National Institutes of Health consensus development conference statement: management of hepatitis B. Hepatol. 2009;49(5 Suppl): S4–S12.
29. Yu M, Jiang Q, Gu X, Ju L, Ji Y, Wu K, Jiang H. Correlation between vertical transmission of hepatitis B virus and the expression of HBsAg in ovarian follicles and placenta. PLoS One. 2013;8(1): e54246.
30. Lin X, Guo Y, Zhou A, Zhang Y, Cao J, Yang M, Xiao F, Zhang B, Du Y. Immuno prophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis. Pediatr Infect Dis J. 2014;33(9):897–903.