HBsAg Carrier Status and the Association Between Gestational Diabetes With Increased Serum Ferritin Concentration in Chinese Women

TERENCE T. LAO, MD[1]
KA-YU TSE, MBBS[1]
LOUIS Y. CHAN, MBBS[1]
KAR-FAI TAM, MBBS[1]
LAI-FONG HO, BSC[1,2]

OBJECTIVE — To determine whether the high prevalence of hepatitis B surface antigen (HBsAg) carriage in our population can explain the previous observation of an association between increased maternal serum ferritin concentration and gestational diabetes in Hong Kong Chinese women.

RESEARCH DESIGN AND METHODS — A retrospective study was performed on 767 nonanemic women with singleton pregnancy who had iron status assessed at 28–30 weeks. The result of the routine antenatal HBsAg screening was retrieved from patient records. The HBsAg-positive and -negative groups were compared for maternal characteristics, prevalence of gestational diabetes in the third trimester, prevalence of high serum ferritin and iron concentrations, and transferrin saturation, which is defined as a value in the highest quartile established by the measurements obtained from the HBsAg-negative group.

RESULTS — The incidences of oral glucose tolerance test and gestational diabetes were significantly increased in the HBsAg-positive group. The HBsAg-positive women with gestational diabetes had significantly increased prevalence of high serum ferritin compared with the HBsAg-negative women, irrespective of the latter's gestational diabetes status. Multiple logistic regression analysis confirmed the independent association between HBsAg carrier status with gestational diabetes (relative risk 3.51, 95% CI 1.83–6.73) but excluded high ferritin as an independent factor.

CONCLUSIONS — Our results indicate that maternal HBsAg carriage could explain in part the association between increased serum ferritin concentration with gestational diabetes in Hong Kong Chinese women, and that HBsAg carrier status is an independent risk factor for gestational diabetes.

Diabetes Care 26:3011–3016, 2003

Increased serum ferritin concentration, which is associated with insulin resistance and diabetes in the general population (1,2), has also been recently reported in gestational diabetes (3,4). This was at variance with evidence of depletion of maternal/fetal iron stores in earlier studies (5–8), and the explanation remains unclear. Increased serum ferritin in gestational diabetes could represent an acute phase response, as in the case of preterm birth and infection (9–11) and preeclampsia (12,13). Another possibility is iron overload, as in transfusion-treated homozygous β-thalassemia (14) and hereditary hemochromatosis (15), which induces liver damage and diabetes. However, the latter conditions were absent and could not have accounted for the observation in the aforementioned studies (3,4).

In nonpregnant subjects, chronic hepatitis C virus (HCV) infection is associated with iron overload (16,17) and increased risk of type 2 diabetes (18–24). In Hong Kong, chronic HCV infection is of minor epidemiological significance (25), and HCV coinfection was found in only 0.7% of subjects with chronic hepatitis B virus (HBV) infection (26). However, 10% of our obstetric population are asymptomatic carriers of the hepatitis B surface antigen (HBsAg) (27), most of whom had contracted the infection vertically (28). Unlike chronic HCV infection, the influence of HBsAg carrier status on glucose tolerance is unclear, especially in the pregnant population. To determine whether maternal HBsAg carrier status could account for the increased iron parameters in gestational diabetes in our population, a retrospective cohort study was performed.

RESEARCH DESIGN AND METHODS

— Our hospital is a government-funded regional hospital with 5,000 deliveries per annum and caters to the residents of Hong Kong, of whom >90% are ethnic Chinese. A multivitamin preparation containing 29 mg of elemental iron was offered to all patients, but patient compliance was not monitored. At the booking antenatal visit, routine screening of HBsAg status (enzyme-linked immunosorbent assay) and hemoglobin concentration and mean corpuscular volume for carrier status of the thalassemia traits were performed. Hemo-

From the [1]Department of Obstetrics and Gynaecology, the University of Hong Kong, Hong Kong, China; and [2]Queen Mary Hospital, Hong Kong, China.

Address correspondence and reprint requests to Dr. Terence Lao, Department of Obstetrics and Gynaecology, Queen Mary Hospital, 102 Pokfulam Rd., Hong Kong, China. E-mail: laotth@hkucc.hku.hk.

Received for publication 18 February 2003 and accepted in revised form 13 August 2003.

L.Y.C. is currently affiliated with the Department of Obstetrics and Gynaecology, Prince of Wales Hospital, Shatin, Hong Kong, People's Republic of China.

Abbreviations: HBsAg, hepatitis B surface antigen, HBV, hepatitis B virus; HCV, hepatitis C virus; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Comparison of maternal characteristics between HBsAg-positive and negative groups*

	HBsAg positive	HBsAg negative	*P*
n	70	697	
Age (years)	31.2 ± 5.1	29.5 ± 4.9	0.006
≥35 years (%)	30.0	16.1	0.003
Weight (kg)	53.4 ± 7.9	52.5 ± 8.1	NS
Height (cm)	155.4 ± 5.7	155.5 ± 5.5	NS
BMI (kg/m^2)	21.9 ± 3.1	21.7 ± 2.8	NS
>25 kg/m^2 (%)	20.0	12.8	NS
Multiparas (%)	50.0	46.6	NS
OGTT performed	47 (67.1)	368 (52.8)	<0.001
Fasting value (mmol/l)	4.4 ± 0.4	4.3 ± 0.5	NS
2-h value (mmol/l)	7.6 ± 1.7	6.8 ± 1.5	<0.001
Abnormal result—whole group	23/70 (32.9)	77/697 (11.0)	<0.0001
Abnormal result—OGTT group	23/47 (48.9)	77/368 (20.9)	<0.0001
Diabetes:impaired glucose tolerance	1:22	2:75	NS
High serum ferritin (%)	38.6	24.3	0.009
High serum iron (%)	20.0	23.9	NS
High transferrin saturation (%)	24.3	24.3	NS

Data are means ± SD (compared with *t* test) or *n* (%) (compared with χ^2 test) unless otherwise indicated.

globin measurement was repeated at 28–30 weeks. Anemia (hemoglobin level <10 g/dl) was investigated and treated accordingly.

Women at high risk for gestational diabetes, including those of advanced age (≥35 years), relevant obstetric and family history, prepregnant weight ≥75 kg, and recurrent/significant glycosuria, underwent a 75-g oral glucose tolerance test (OGTT) interpreted by World Health Organization criteria. Gestational diabetes was diagnosed if the 2-h OGTT glucose value was ≥8.0 mmol/l (29). Low-risk women had random blood glucose testing at 28–30 weeks. Those with glucose levels >5.8 mmol/l if <2 h postprandial, and >5.0 mmol/l if >2 h postprandial, also underwent the 75-g OGTT. The diagnosis and management of gestational diabetes have been previously described (30).

In an earlier prospective study, the relationship between maternal first trimester hemoglobin and development of gestational diabetes in the third trimester has been examined after excluding women with late antenatal booking, preexisting anemia or hemoglobinopathies, gestational diabetes diagnosed before 28 weeks gestation, and multifetal pregnancy (30). Maternal iron status was examined at 28–30 weeks with the repeat hemoglobin estimation. The serum was aliquoted and stored for the batch assay of serum ferritin (microparticle enzyme immunoassay, IMx system; Abbott Laboratories, Abbott Park, IL) and serum iron and transferrin (measured as the total iron binding capacity with the calorimetric method) (Sigma, St. Louis, MO). Transferrin saturation was calculated as serum iron divided by the total iron binding capacity. Those who delivered elsewhere were excluded from the analysis.

For the present study, the same cohort, including women delivered in other hospitals, were reviewed to determine the maternal HBsAg status. Maternal demographics, including the incidence of advanced age (≥35 years) and increased BMI (>25 kg/m^2), the prevalence of OGTT and gestational diabetes, and parameters of maternal iron status, were compared between the HBsAg-positive and -negative groups. The nondiabetic HBsAg-negative group was used as the reference group to generate the 25th, 50th, and 75th percentile values for serum ferritin and iron concentrations and transferrin saturation. A high value in any of these parameters is defined as a value in the highest quartile, and the prevalence of high values for each of these parameters was compared between the HBsAg-positive and -negative groups and in relation to gestational diabetes status.

Statistical analysis was performed using a commercial computer package (SPSS for Windows; SPSS, Chicago, IL). Categorical variables were compared with the χ^2 test, and odds ratios (ORs) with 95% CIs were generated. Continuous variables were expressed as means ± SD and tested by the *t* test for initial comparison between the HBsAg-positive and -negative groups. Further analysis with respect to gestational diabetes and HBsAg status was performed with one-way ANOVA, with Duncan's test for post hoc analysis set at the 5% level, using the nondiabetic HBsAg-negative group as the reference group. Multiple logistic regression analysis was used to determine the role of HBsAg status compared with high serum ferritin in the development of gestational diabetes using both forward and backward stepwise logistic regression analysis after adjusting for age ≥35 years, BMI >25 kg/m^2, poor socioeconomic status (monthly income <HK$10,000), multiparity status, and the presence of significant obstetric, family, and past history.

RESULTS — The cohort consisted of 767 women, including 37 women who delivered elsewhere. The HBsAg-positive women were significantly older and had a higher prevalence of advanced maternal age, but the differences in anthropometric parameters did not reach statistical significance (Table 1). They had more OGTTs performed, and the 2-h glucose value was significantly higher due to a higher prevalence (48.9 vs. 20.9%, $P < 0.0001$) of abnormal results. On multiple logistic regression analysis, the only significant factors for gestational diabetes were maternal

Table 2—*Maternal and infant characteristics with respect to HBsAg carrier and gestational diabetes status*

	Diabetic women HBsAg status		Nondiabetic women HBsAg status	
	Positive	Negative	Positive	Negative
n	23	77	47	620
Maternal				
Age (years)*	34.4 ± 4.9†	32.0 ± 4.9‡	29.7 ± 4.6	29.2 ± 4.8
% ≥35 years§	52.2	35.1	19.1	13.5
Weight (kg)	52.7 ± 6.9	54.5 ± 8.7	53.7 ± 8.4	52.3 ± 7.9
Height (cm)	153.4 ± 5.1	154.8 ± 6.0	156.3 ± 5.8	155.5 ± 5.4
BMI (kg/m^2)‖	22.5 ± 3.0	22.7 ± 3.3	21.9 ± 3.0	21.6 ± 3.1
% >25 kg/m^2¶	17.4	22.1	21.3	11.6
Multiparas (%)	65.2	48.1	42.6	46.4
Infant				
Gestation (weeks)#	38.3 ± 2.1‡	38.7 ± 1.4	39.2 ± 1.5	39.1 ± 1.5
Birth weight (g)	3,042 ± 539	3,129 ± 505	3,235 ± 463	3,185 ± 413

Data are means ± SD (one-way ANOVA) or % (χ^2 test). *$P < 0.0001$; †$P < 0.05$ compared with the other three groups (Duncan's test); ‡$P < 0.05$ compared with nondiabetic groups (Duncan's test); §$P < 0.0001$; ‖$P = 0.024$; ¶$P = 0.023$; #$P = 0.041$.

age ≥35 years (OR 3.78, 95% CI 2.13–6.69) and HBsAg carrier status (3.32, 1.72–6.42). Most of the cases of gestational diabetes belonged to the World Health Organization category of impaired glucose tolerance, and there was no significant difference in the proportion of impaired glucose tolerance between the two groups. The mean 25th, 50th, and 75th percentile reference values for serum ferritin, serum iron, and transferrin saturation generated from the nondiabetic HBsAg-negative group were 37.4, 18.0, 28.0, and 45.0 pmol/l; 14.1, 9.1, 12.8, and 17.2 μmol/l; and 20.1, 12.2, 18.5, and 25.3%, respectively. The prevalences of high ferritin, iron, and transferrin saturation in the HBsAg-positive and -negative groups were 38.6 vs. 24.3% (P = 0.009, OR 1.95, 95% CI 1.17–3.26), 20.0 vs. 23.9% (P = NS), and 24.3 vs. 24.3% (P = NS), respectively, although there was no significant difference in the maternal serum concentrations of ferritin, iron, transferrin, or transferrin saturation (data not shown).

On further analysis with respect to gestational diabetes and HBsAg status combined, we found a significant difference in the mean age and prevalence of advanced age (≥35 years) among the four groups (Table 2). The gestational diabetes groups had significantly higher mean age, and there was an inverse correlation between prevalence of advanced age with prevalence of gestational diabetes (Spearman's correlation, $P < 0.0001$). Although there was no significant difference in the prevalence of multiparity, or mean weight or height, there was a significant difference in the mean BMI and prevalence of overweight (BMI >25 kg/m^2), but in no group was the BMI outstandingly high. Although there was a significant difference in gestational age, there was no difference in the mean birth weight. No significant difference was found among the four groups in the prevalence of poor socioeconomic status (45.5, 37.8, 45.2, and 33.2%, respectively), significant past obstetric history (22.7, 13.3, 18.6, and 15.2%, respectively), or significant family or medical history (21.1, 18.6, 22.9, and 22.2%, respectively).

While the 0- and 2-h values for the antenatal OGTT were significantly higher in the gestational diabetes groups, as expected, there was no difference in either the 0- or 2-h values of the postnatal OGTT (performed 6 weeks postpartum in women with gestational diabetes) between the HBsAg-positive and -negative groups (Table 3). Although the prevalence of abnormal postnatal OGTT values was higher in the HBsAg-negative women, this difference failed to reach statistical significance. The diabetic HBsAg-positive women had a significantly increased prevalence of high ferritin compared with diabetic HBsAg-negative women (OR 2.73, 95% CI 1.05–7.09) and with nondiabetic HBsAg-negative women (3.29, 1.48–7.32). Similarly, the diabetic HBsAg-positive women had a significantly increased prevalence of high transferrin saturation compared with the nondiabetic HBsAg-positive women (3.13, 1.02–9.71). The distribution of serum ferritin concentration in the four groups is shown in Fig. 1.

To determine the primacy of the association between maternal HBsAg carrier status and high ferritin status with the development of gestational diabetes, both forward and backward stepwise multiple logistic regression analysis were performed, taking into account multiparity, age ≥35 years, BMI >25 kg/m^2, past obstetric, medical, and family history, and poor socioeconomic status. In both analyses, only maternal age (relative risk 3.66, 95% CI 2.11–6.34 and 3.59, 2.08–6.21, respectively) and HBsAg carrier status (3.51, 1.83–6.73 and 3.46, 1.80–6.62, respectively) remained significant independent factors.

CONCLUSIONS — Hepatic damage secondary to chronic HCV infection leads to type 2 diabetes (18–24). Pregnancy also induces hepatic insulin resistance because significant changes in the early steps of insulin signal transduction in the liver occur without change in the insulin receptor concentration in pregnant rats at day 20 of gestation (31). Nevertheless, the combination of chronic hepatocellular damage with pregnancy on the risk of gestational diabetes has not yet been examined.

In this study, the prevalence of HBsAg carriage was 9.1%, which is similar to the 10% previously reported (27). We found a threefold higher prevalence (32.9%) of gestational diabetes among HBsAg carriers, whereas the 11.0% prevalence of gestational diabetes among the HBsAg-

Table 3—*Maternal glucose tolerance and prevalence of high iron status with respect to HBsAg carrier and gestational diabetes status*

	Diabetic women HBsAg status		Nondiabetic women HBsAg status	
	Positive	Negative	Positive	Negative
n	23	77	47	620
OGTT (mmol/l)				
Antenatal 0-h*	4.4 ± 0.4	4.5 ± 0.6†	4.4 ± 0.4 (*n* = 24)	4.3 ± 0.4 (*n* = 291)
Antenatal 2-h*	9.0 ± 0.9‡	8.9 ± 0.9‡	6.3 ± 1.1 (*n* = 24)	6.3 ± 1.0 (*n* = 291)
Postnatal 0-h	5.0 ± 0.3	5.0 ± 0.6	—	—
Postnatal 2-h	6.4 ± 1.6	7.1 ± 2.1	—	—
Abnormal (%)	1/8 (12.5)	15/51 (29.4)	—	—
Iron status (%)				
High ferritin	52.2§‖	28.6	31.9	23.9
High iron	30.4	23.4	14.9	24.0
High transferrin saturation	39.1¶	26.0	17.0	24.0

Data are means ± SD (one-way ANOVA) or % (χ^2 test). *$P < 0.0001$; †$P < 0.05$ compared with nondiabetic HBsAg-negative group (Duncan's test); ‡$P < 0.05$ compared with nondiabetic groups (Duncan's test); §$P = 0.036$ comparing diabetic HBsAg-negative group; ‖$P = 0.002$ comparing nondiabetic HBsAg-negative group; ¶$P = 0.043$ compared with nondiabetic HBsAg-positive group.

negative patients was similar to the 13.7% prevalence previously reported (32). As the prevalence of diabetes in the nonpregnant subjects with chronic HBV infection is between 2.5% to 12.0% (19–24), it is likely that the superimposed effect of pregnancy was responsible for the increased prevalence of gestational diabetes in the HBsAg-positive women.

Maternal HBsAg carrier status could explain the association between increased maternal ferritin concentration and gestational diabetes (3,4), as the prevalence of high ferritin concentration was increased in these women compared with the HBsAg-negative women, irrespective of the latter group's glucose tolerance status. This is similar to the finding of increased serum iron and ferritin in subjects with chronic HBV infection attributed to hepatocellular release secondary to tissue necrosis (16,17).

Serum ferritin concentration could also have reflected the activity of the chronic inflammatory state, which induces insulin resistance and endothelial dysfunction (33). The HBsAg-positive women with gestational diabetes also had significantly increased prevalence of high transferrin saturation. Excess iron can affect insulin synthesis and secretion and enhance oxidation of lipids, especially free fatty acids, the increased oxidation of which decreases glucose utilization in muscles and increases gluconeogenesis in liver, leading to liver-mediated insulin resistance (34). Iron accumulation in hepatocytes also impairs hepatic insulin extraction (35). However, the exclusion of increased serum ferritin as an independent factor for gestational diabetes in this study suggests that chronic HBV infection plays the primary role.

The HBsAg-positive group had a significantly higher prevalence of women aged ≥35 years, and the development of gestational diabetes was associated with

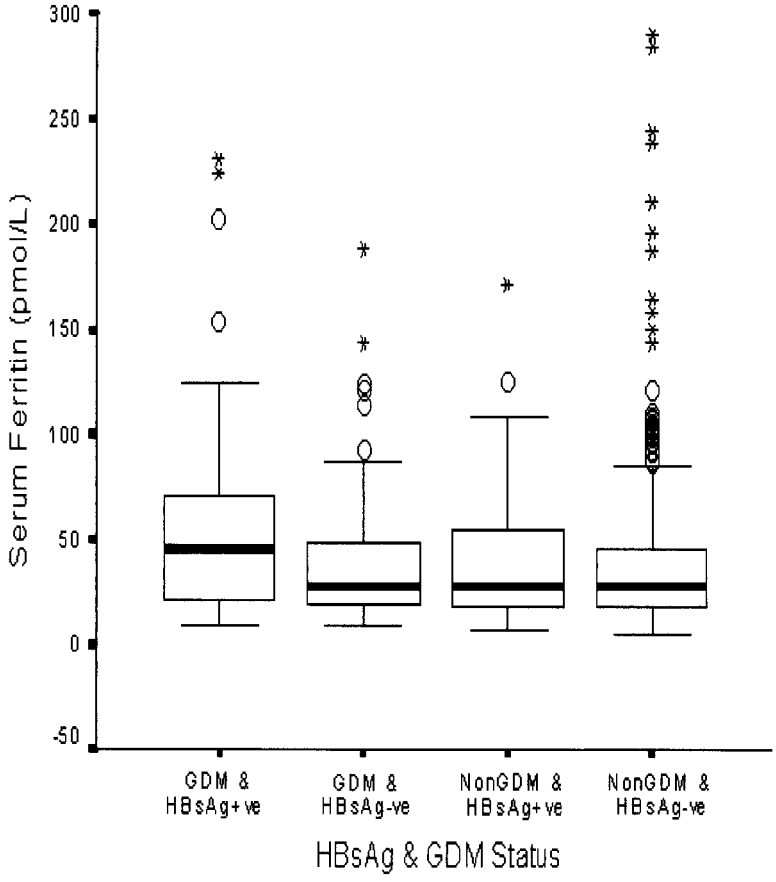

Figure 1—*Box plot of serum ferritin concentrations expressed in median value and interquartile range according to gestational diabetes and HBsAg status. Outlying values are circles. Extreme outlying values are asterisks. GDM, gestational diabetes; HBsAg+ve, HBsAg positive; HBsAg-ve, HBsAg negative.*

increased age and decreased height, which are known risk factors for gestational diabetes in the overall obstetric population, but there was no difference in these factors between the HBsAg-positive and -negative women with gestational diabetes. Aging increases hepatic insulin resistance, as is seen in 20-month-old rats, which demonstrated a significant decrease in insulin signal transduction in the liver in the absence of any difference in insulin receptor concentration when compared with 2-month-old rats (31,36). Our finding that advanced age is an independent factor for gestational diabetes was similar to the finding of age as a risk factor for type 2 diabetes in HCV-infected subjects (22–24) and suggests that aging aggravates the effect of chronic HBV infection in pregnancy.

As a retrospective study, we could not determine the presence or degree of hepatocellular damage in relation to the development of gestational diabetes. Nevertheless, our finding suggests that HBsAg carrier status aggravates pregnancy-induced hepatic insulin resistance leading to gestational diabetes in susceptible individuals because there was no increased prevalence of postnatal abnormal glucose tolerance, and it could account for the increased maternal serum ferritin concentration associated with gestational diabetes in our population (3,4). In populations with a low prevalence of HBV infection, this association may not be demonstrable. The role of HBsAg carrier status as a risk factor for gestational diabetes and diabetes should be explored further in the at-risk populations of the developing world.

References

1. Tuomainen T-P, Korpela H, Nyyssonon K, Lakka T, Salonen R, Kaplan GA, Tervahauta A, Salonen JT: Body iron stores are associated with serum insulin and blood glucose concentrations: population study in 1,013 eastern Finnish men. *Diabetes Care* 20:426–428, 1997
2. Fernandez-Real J-M, Casamitjana-Abella R, Ricart-Engel W, Cabrero D, Arroyo E, Fernández-Castañer, Soler J: Serum ferritin as a component of the insulin resistance syndrome. *Diabetes Care* 21:62–68, 1998
3. Lao TT, Tam KF: Maternal serum ferritin and gestational impaired glucose tolerance. *Diabetes Care* 20:1368–1369, 1997
4. Lao TT, Chan PL, Tam KF: Gestational diabetes mellitus in the last trimester: a feature of maternal iron excess? *Diabet Med* 18:218–223, 2001
5. Georgieff MK, Landon MB, Mills MM, Hedlund BE, Faassen AE, Schmidt RL, Ophoven JJ, Widness JA: Abnormal iron distribution in infants of diabetic mothers: spectrum and maternal antecedents. *J Pediatr* 117:455–461, 1990
6. Petry CD, Eaton MA, Wobken JD, Mills MM, Johnson DE, Georgieff MK: Iron deficiency of liver, heart and brain in newborn infants of diabetic mothers. *J Pediatr* 121:109–114, 1992
7. Petry CD, Wobken JD, McKay H, Eaton MA, Seybold VS, Johnson DE, Georgieff MK: Fetal transferrin receptor in diabetic pregnancies with increased fetal demand. *Am J Physiol* 207:E507–E514, 1994
8. Fujimoto S, Kawakami N, Ohara A: Nonenzymatic glycation of transferrin: decrease of iron-binding capacity and increase of oxygen radical production. *Biol Pharm Bull* 18:396–400, 1995
9. Goldenberg RL, Tamura T, DuBard M, Johnston KE, Copper RL, Neggers Y: Plasma ferritin and pregnancy outcome. *Am J Obstet Gynecol* 175:1356–1359, 1996
10. Tamura T, Goldenberg RL, Johnston KE, Cliver SP, Hickey CA: Serum ferritin: a predictor of early spontaneous preterm delivery. *Obstet Gynecol* 87:360–365, 1996
11. Scholl TO: High third-trimester ferritin concentration: associations with very preterm delivery, infection, and maternal nutritional status. *Obstet Gynecol* 92:161–166, 1998
12. Entman SS, Richardson LD, Killam AP: Elevated serum ferritin in the altered ferrokinetics of toxemia of pregnancy. *Am J Obstet Gynecol* 144:418–422, 1982
13. Raman L, Pawashe AB, Yasodhara P: Hyperferritinemia in pregnancy-induced hypertension and eclampsia. *J Postgrad Med* 38:65–67, 1992
14. Saudek CD, Hemm RM, Peterson CM: Abnormal glucose tolerance in β-thalassaemia. *Metabolism* 26:43–52, 1977
15. Adams PC, Kertesz AE, Valberg LS: Clinical presentation of hemochromatosis: a changing scene. *Am J Med* 90:445–449, 1991
16. Di Bisceglie AM, Axiotis CA, Hoofnagle JH, Bacon BR: Measurements of iron status in patients with chronic hepatitis. *Gastroenterol* 102:2108–2113, 1992
17. Haque S, Chandra B, Gerber MA, Lok ASF: Iron overload in patients with chronic hepatitis C: a clinicopathologic study. *Hum Pathol* 27:1277–1281, 1996
18. Gray H, Wreghitt T, Alexander GJM, Turner RC, O'Rahilly S: High prevalence of hepatitis C infection in Afro-Caribbean patients with type 2 diabetes and abnormal liver function tests. *Diabet Med* 12: 244–249, 1995
19. Grimbert S, Valensi P, Levy-Marchal C, Perret G, Richardet JP, Raffoux C, Trinchet JC, Beaugrand M: High prevalence of diabetes mellitus in patients with chronic hepatitis C: a case-control study. *Gastroenterol Clin Biol* 20:544–548, 1996
20. Fraser GM, Harman I, Meller N, Niv Y, Porath A: Diabetes mellitus is associated with chronic hepatitis C but not with chronic hepatitis B infection. *Isr J Med Sci* 32:526–530, 1996
21. Özylikan E, Arslan M: Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection (Letter). *Am J Gastroenterol* 91:1480–1481, 1997
22. Mason AL, Lau JYN, Hoang N, Qian K, Alexander GJM, Xu L, Guo L, Jacob S, Regenstein FG, Zimmerman R, Everhart JE, Wasserfall C, Maclaren NK, Perrillo RP: Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 29:328–333, 1999
23. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, O'Rahilly S, Shore S, Tom BDM, Alexander GJM: Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 30:1059–1063, 1999
24. Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A: Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc* 75:355–359, 2000
25. Leung NW, Tam JS, Lai JY, Leung TW, Lau WY, Shiu W, Li AK: Does hepatitis C virus infection contribute to hepatocellular carcinoma in Hong Kong? *Cancer* 70: 40–44, 1992
26. Lau GK, Wu PC, Lo CK, Lau V, Lam SK: Histological changes of concurrent hepatitis C virus infection in asymptomatic hepatitis B virus patients. *J Gastroenterol Hepatol* 13:52–56, 1998
27. Kwan LC, Ho YY, Lee SS: The declining HbsAg carriage rate in pregnant women in Hong Kong. *Epidemiol Infect* 119:281–283, 1997
28. Wong VC, Ip HM, Reesink HW, Lelie PN, Reerink-Brongers EE, Yeung CY, Ma HK: Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HbeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin: double-blind randomised placebo-controlled study. *Lancet* 1:921–926, 1984
29. World Health Organization: *WHO Expert Committee on Diabetes Mellitus. Second Report*. Geneva, World Health Org., 1980, p. 8–12 (Tech. Rep. Ser., no. 646)
30. Lao TT, Chan LY, Tam KF, Ho LF: Maternal hemoglobin and risk of gestational diabetes mellitus in Chinese women. *Obstet*

Gynecol 99:807–812, 2002
31. Saad MJA, Maeda L, Brenelli SL, Carvalho CRO, Paiva RS, Velloso LA: Defects in insulin signal transduction in liver and muscle of pregnant rats. *Diabetologia* 40:179–186, 1997
32. Lao TT, Tam KF: Gestational diabetes diagnosed in third trimester pregnancy and pregnancy outcome. *Acta Obstet Gynecol Scand* 80:1003–1008, 2001
33. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW: C-reactive protein in healthy subjects: association with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscl Thromb Vasc Biol* 19:972–978, 1999
34. DeFronzo RA: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–687, 1988
35. Niederau C, Berger M, Stremmel W, Starke A, Strohmeyer G, Ebert R, Siegel E, Creutzfeldt W: Hyperinsulinaemia in non-cirrhotic haemochromatosis: impaired hepatic insulin degradation? *Diabetologia* 26:441–444, 1984
36. Carvalho CRO, Brenelli SL, Silva AC, Nunes ALB, Velloso LA, Saad MJA: Effect of aging on insulin receptor, insulin receptor substrate-1, and phosphatidylinositol 3-kinase in liver and muscle of rats. *Endocrinology* 137:151–159, 1996