OBSERVATIONS

Mutations in the Hereditary Hemochromatosis Gene Are Not Associated With the Increased Body Iron Stores Observed in Overweight and Obese Women With Polycystic Ovary Syndrome

We recently reported (1) that serum ferritin levels are increased in overweight and obese women with polycystic ovary syndrome (PCOS) independently of inflammation. This finding suggested increased body iron stores in these women, raising the possibility that genes related to iron metabolism are altered in PCOS.

Classic hereditary hemochromatosis is an autosomal recessive disorder caused by mutations in the *HFE* gene, resulting in increased intestinal iron absorption and iron accumulation in several organs. In the study by Sanchez et al. (2), >80% of the Spanish patients with hereditary hemochromatosis were homozygous for the *HFE* C282Y mutation or compound heterozygotes for the *HFE* C282Y and H63D mutations.

Although hereditary hemochromatosis has low penetrance in young women, we studied the *HFE* genotypes of 78 PCOS patients and 43 control subjects characterized in our previous report of increased body iron stores in PCOS (1). Genotyping was conducted by PCR/restriction fragment–length polymorphism methods using the *Pml*I and *Bcl*I restriction enzymes for the C282Y and H63D mutations, respectively. The ethics committee of the Hospital Ramón y Cajal approved the study, and informed consent was obtained from all participants.

We did not find homozygosity for the C282Y substitution in *HFE* in any PCOS patient or control subject. Three patients with PCOS but no control subjects were compound heterozygotes for the C282Y and H63D mutations ($\chi^2 = 1.696$, $P = 0.552$), but their serum ferritin levels were 14, 82, and 113 pmol/l (normal range 11–325), ruling out a condition of iron overload.

Forty-eight of the patients (61.5%) and 24 of the control subjects (55.8%) had one or more mutated alleles of the C282Y and H63D genotype alleles, whereas all other women were homozygous for wild-type alleles of both *HFE* mutations ($\chi^2 = 0.377$, $P = 0.539$). The *HFE* mutations studied here did not influence serum ferritin levels when considering PCOS patients and control subjects as a whole (C282C [$n = 110$] 109 ± 94 pmol/l vs. C282Y [$n = 11$]110 ± 115 pmol/l [$F = 0.122$, $P = 0.728$]; H63H [$n = 57$] 108 ± 98 pmol/l vs. H63D and D63D [$n = 64$] 110 ± 94 pmol/l [$F = 0.499$, $P = 0.481$]; and interaction between both genotypes [$F = 0.834$, $P = 0.363$]) or separately (data not shown).

Finally, a multivariate stepwise linear regression analysis model retained BMI ($\beta = 0.263$, $P = 0.003$) and PCOS status ($\beta = 0.238$, $P = 0.007$) as predictive variables of serum ferritin levels ($R^2 = 0.127$, $F = 8.557$, $P < 0.001$), whereas carrier status for C282Y and/or H63D mutations, as well as having oligo/amenorrhea compared with having regular cycles, were excluded as predictors.

In summary, PCOS is not associated with the C282Y and H63D mutations in *HFE*, and these mutations did not influence serum ferritin levels in our series. As discussed earlier (1), other mechanisms are possibly related to the increase in body iron stores observed in overweight and obese PCOS patients.

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DOI: 10.2337/dc-06-1655

Acknowledgments— This study was supported by grants FIS PI050341, PI050551, and RGDM G03/212 from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spain.

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On the Weighted-Average Relationship Between Plasma Glucose and HbA_{1c}

HbA_{1c} (A1C) is widely used to assess glycemic control in clinical and research settings, but the precise relationship between A1C and preceding self-monitored plasma glucose measurements is recognized to be complex. It has been reported that measuring plasma glucose levels in the 120 days before an A1C measurement has a nonuniform effect on the result depending on the time that has elapsed between the glucose level and subsequent A1C measurement (1). Tahara and Shima (2) attempted to model this weighted-average relationship between plasma glucose and A1C by measuring decreases in glucose and corresponding decreases in A1C in patients admitted to the hospital. Their model gives maximum weighting to glucose measurements immediately before the A1C measurement, with the weighting linearly decreasing for glucose measurements further back in time, reaching zero weighting for plasma glucose >120 days before the A1C.

Treviño (3) reported that this weighted-average relationship leads to an anomalous relationship between the exponential decay rates of glucose (G_t) and A1C. We have reviewed this result and believe that no such anomaly exists. Treviño subtracted A1C calculated from the Tahara model (H_t) from "the mean of patient-admission A1C values" (H_{start}), obtaining the counterintuitive result that a faster decay in blood glucose results in a slower

decay in ($H_{start} - H_t$). However, this "inverted" decay is likely to be due to subtracting H_t from a constant value. His expression for H_t is an absolute A1C value, not a change in A1C. An initial value, G_s, has been specified for G_t, and hence an initial value is implicit in his calculations. Subtracting H_t from a constant would not be expected to give a valid A1C estimate.

To verify this conclusion, we simulated a patient with a constant glucose level followed by an exponential decay upon admission to the hospital. During the preadmission time period, the simulated A1C reached a steady state under the constant glucose conditions, which avoided any ambiguity over the initial value (H_{start}) of A1C. In this simulation, the decay rates of H_t then varied in the same way as those for the glucose data, as would be intuitively expected. The use of two initial values by Treviño, one for *H* and one for *G*, appears to have led to the anomalous result previously reported, rather than any inherent defect in the weighted-average relationship proposed by Tahara and Shima.

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DOI: 10.2337/dc-06-1646

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Is Pregnancy Outcome Worse in Type 2 Than in Type 1 Diabetic Women?

Most research on pregestational diabetes has focused on type 1 diabetes, and surprisingly little knowledge exists concerning outcomes of pregnancies of women with type 2 diabetes. A dearth of published data suggest outcomes similar to those of type 1 diabetic women (1,2), although recent studies report poorer outcomes in women with type 2 diabetes (3–7).

We retrospectively compared maternal and perinatal outcomes of 93 consecutive singleton pregnancies in women with type 2 diabetes and 532 consecutive singleton pregnancies in women with type 1 diabetes referred to the Diabetes and Pregnancy Unit at University Hospital La Paz from 1984 to 2004.

Women with type 2 diabetes were significantly older ([means ± SD] 31.8 ± 5.5 vs. 29.4 ± 4.7 years, $P < 0.001$), were more frequently obese (45.2 vs. 9%, $P < 0.001$), and had a shorter duration of diabetes (5.7 ± 6 vs. 11.8 ± 7.1 years, $P < 0.001$). The rate of preconceptional care (16.1 vs. 22.6%, $P = 0.175$) and gestational age at first visit (12.1 ± 6.8 vs. 11.5 ± 6.9 weeks' gestation, $P = 0.529$) did not differ between type 2 and type 1 diabetic women. Maternal and perinatal outcomes are shown in Table 1. Insulin requirements and HbA_{1c} (A1C) were lower during all three trimesters of preg-

Table 1—*Maternal and perinatal outcomes*

	Type 2 diabetes	Type 1 diabetes	*P*
*n**	93	532	
Prepregnancy BMI (kg/m^2)	28.9 ± 6.5	23.3 ± 3.1	<0.001
Maternal weight gain during pregnancy (kg)	11.7 ± 5.0	13.7 ± 4.2	<0.001
Glycemic control during pregnancy			
A1C at admission (%)	6.4 ± 1.19	7.2 ± 1.19	<0.001†
A1C second trimester (%)	5.8 ± 0.84	6.3 ± 0.9	<0.001†
A1C third trimester (%)	5.8 ± 0.76	6.2 ± 0.8	0.001†
Insulin requirements			
First trimester (units/kg)	0.38 ± 0.19	0.68 ± 0.18	<0.001†
Second trimester (units/kg)	0.48 ± 0.23	0.76 ± 0.21	<0.001†
Third trimester (units/kg)	0.62 ± 0.31	0.93 ± 0.26	<0.001†
Pregnancy-induced hypertension	18 (19.4)	82 (15.4)	0.358
Preeclampsia	6 (6.5)	17 (3.2)	0.134
Caesarean delivery	41 (44.1)	298 (56)	0.032
Gestational age (weeks of gestation)	37.1 ± 1.6	36.7 ± 1.7	0.018
Preterm delivery	28 (30.4)	186 (35.4)	0.406
Birth weight (g)	3,182 ± 623	3,243 ± 606	0.375
Birth weight ratio	1.09 ± 0.2	1.13 ± 0.18	0.019
Large for gestational age	22 (23.9)	187 (35.6)	0.032
Small for gestational age	3 (3.3)	5 (1)	0.100
Perinatal mortality	1 (1.1)	9 (1.7)	1.000
Major congenital malformations	6 (6.5)	25 (4.7)	0.442
Neonatal hypoglycemia	24 (26.1)	172 (32.8)	0.226
Neonatal hyperbilirrubinemia	34 (37)	223 (42.5)	0.359
Neonatal hypocalcemia	4 (4.3)	30 (5.7)	0.805
Birth trauma	7 (7.6)	29 (5.5)	0.467
Neonatal sepsis	9 (9.8)	55 (10.5)	1.000
Neonatal polycythemia	14 (15.2)	71 (13.5)	0.626
Neonatal respiratory distress syndrome	7 (7.6)	95 (18.1)	0.010

Data are means ± SD or *n* (%) unless otherwise indicated. *In the case of stillbirths (one in type 2 and seven in type 1 diabetes), no perinatal data other than the presence of major congenital malformations was analyzed; †adjusted for multiplicity.