Diabetes-Related Autoantibodies and Gestational Diabetes

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Gestational diabetes mellitus (GDM) has long been recognized as a heterogeneous disorder (1,2), with autoimmunity against the β-cell contributing in a small subset of patients (3).

HETEROGENEITY OF AUTOIMMUNE DIABETES: AN OVERVIEW

— Autoimmune diabetes is caused by the destruction of β-cells of pancreatic islets by an immune-mediated process, promoted by the interaction of genetic and environmental factors (4). Autoantibodies (AAs) against pancreatic β-cell antigens precede the clinical onset of type 1 diabetes (4). Circulating islet cell antibodies, originally described by indirect immunofluorescence in 1974 (5), have been demonstrated in the great majority of individuals with type 1 diabetes, both at the preclinical state and at the onset of clinically overt diabetes, and they persist in the circulation for a long time. Islet cell AAs include autoantibodies to islet cell cytoplasm (islet cell autoantibodies [ICAs]), to native insulin (insulin autoantibodies [IAAs]), to GAD (GADA) (6–8), and to tyrosine phosphatases (insulinoma-associated antigens IA-2A and IA-2β) (9,10).

Age not only modifies the risk of autoimmune diabetes, but also the presence of AAs, the intensity of β-cell destruction, the rate of progression to overt diabetes, and the degree of residual insulin secretion. Approximately 30% of subjects with classic autoimmune diabetes (type 1A diabetes) present after age 35 years (11). Childhood autoimmune diabetes is associated with an increased prevalence of alleles DR3, DQB1*0201 and DR4, and DQB1*0302, with the proportion of heterozygotes declining with age at diagnosis (12). Children with the allele HLA DR2, DQB1*0602, almost never develop diabetes, whereas this allele confers a much lower protection for adult-onset autoimmune diabetes (13).

Since the discovery of AAs against islet cell antigens, it has been recognized that a fraction of adults considered to have type 2 diabetes probably have autoimmune diabetes and that the presence of GADAs indicates a strong possibility of requiring insulin treatment earlier. These patients with adult-onset autoimmune diabetes can be initially easily misclassified as having type 2 diabetes. Actually, assessment of diabetes-related autoantibodies (DRAs) might allow them to be classified as having latent autoimmune diabetes in adults (LADA). Characteristically, they display a lower rate of metabolic syndrome than patients with type 2 diabetes (14). The distinction between adult-onset type 1 diabetes and LADA is sometimes difficult, but, characteristically, patients with LADA evolve slowly toward insulin requirement (within 6 years) and older patients with LADA show even a slower progression (15,16).

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Abbreviations: AA, autoantibody; DRA, diabetes-related autoantibody; GADA, autoantibodies to GAD; IA, insulin antibody; IAA, insulin autoantibody; ICA, islet cell autoantibody; LADA, latent autoimmune diabetes in adults.

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

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DRAs AND DIABETIC PREGNANCY

Prevalence and titers

ICAs. The prevalence of cytoplasmic islet cell antibodies in GDM has been reported to range between 0.98 and 14.7% in Caucasians (1,2,3,17–37). Only some authors have studied a control group, with ICAs being reported to be higher in women with GDM (1,24,29,32,36,37), except in studies with low statistical power (26,28). Characteristically, ICA titers are low when compared with subjects with new-onset type 1A diabetes and their first-degree relatives (19,24,26,28,32,36) (Table 1).

Our group has compared ICA titers in 38 ICA^+ women with GDM and 66 women with new-onset type 1 diabetes and results are displayed in Fig. 1.

IAAs. The presence of IAAs in sera of subjects with type 1 diabetes before initiating insulin treatment was first reported in 1982 (38). Since then, IAAs have been shown in 20–50% of patients with type 1 diabetes of recent diagnosis (39,40). IAA positivity displays a strong negative association with age: IAAs are positive in 90% of children who develop type 1 diabetes before the age of 5 years, but in <40% after the age of 12 years (41). This result is in accordance with the low prevalence of IAAs in women with GDM (0–5.9%), even when addressed just by a low number of reports (3,26,27,28,37), with only one of them reporting a higher prevalence than in the control population (37). When positive, IAA titers are also lower than those of patients with type 1 diabetes and their first-degree relatives (28).

We have investigated the frequency of IAAs in women with GDM using a radiobinding assay. We observed that only 0.98% (2 of 203) of consecutive women at diagnosis of GDM displayed IAAs in their sera before initiation of treatment (registered frequency in control subjects, 0 of 106 individuals; frequency in first-degree relatives, 4.7%). Interestingly, in the subgroup of ICA^+ women with GDM, the prevalence of IAAs was higher than in ICA^- ones (11 versus 0.7%), so that in women with GDM and ICA positivity, the prevalence of IAAs was not different than in first-degree relatives. (Table 2) (3).

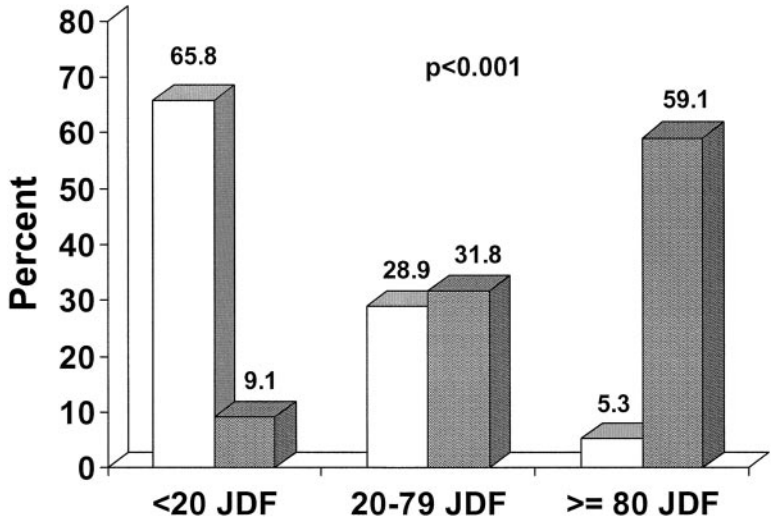

Figure 1—*ICA titers: GDM versus type 1 diabetes.* □*, GDM;* ■*, type 1 diabetes.*

Quite a different issue is the appearance of insulin antibodies (IAs) in women with GDM treated with exogenous insulin. Our group has reported that 44% of women receiving human insulin therapy for GDM develop IAs, which may persist up to 24 months after delivery (42). Similar findings have been described after treatment with lispro (43).

GADAs and IA-2As. GAD is the biosynthesizing enzyme of γ-aminobutyric acid. Pancreatic β-cells express this enzyme, among other cell types. The prevalence of these AAs in subjects with new-onset type 1 diabetes is 60–70% for GADAs, 40% for IA-2As, and 20% for IA-2βAs (44,45). All DRAs could be useful for screening of autoimmune diabetes. Because ICA measurement is time-consuming and semiquantitative, currently it is usually used for confirmation purposes. The combination of two antibodies offers a good yield with GADAs/IA-2As and GADAs/IAAs being used in adults and children, respectively (46). Our group has recently reported that nonisotopic alternatives for GADA65 and IA-2As are suitable for precise use of estimation of risk prediction and diagnosis of autoimmune diabetes (47).

A few reports have shown that the prevalence of IA-2As in GDM ranges from 0 to 6.2% (28–30,32,34,35,37). Four articles have compared the prevalence of IA-2As in women with GDM with that of a control population, the figures being higher in two articles (29,32) and similar in the other two (28,37). These antibodies are not frequent in this age range (48) and are associated with rapid progression to severe insulinopenia (49). IA-2A titers in women with GDM are lower than in children with type 1A diabetes (30).

The prevalence of GADAs in GDM has been reported to range from 0 to 10.8% (28–30,32–37,50–56), with an article from India describing a 41% prevalence of GADAs/IA-2As (57). Several reasons may account for these heterogeneous findings. First, each population has a different genetic and environmental background that confers different risks. Second, in each population, different ethnic groups may have different susceptibility for GDM and to β-cell autoimmunity. Third, methodological issues, such as study design or laboratory procedures, may justify these wide differences. As in the case of ICAs, their frequency has been reported to be higher than in the control population in some (29,32,36,37,55) but not all (28,52,53,56) articles, probably because of the low statistical power of the latter. As for other DRAs, titers of GADAs in GDM have also been reported to be lower when compared with type 1A diabetes, autoimmune pre-diabetes, and first-degree relatives (36,58).

A German multicentric study has shown that GADAs in GDM women bound fewer epitopes than GADAs in first-degree relatives (58). Whereas the prevalence and titers of GADAs to the major GAD65 COOH-terminal middle epitope were not significantly different (91 vs. 100%, 88.6 vs. 100%), AAs to epitopes GAD65-midb (middle epitope) and GAD67 were less frequently detected in patients with GDM (57 vs. 90%, 38 vs. 79%). AAs reactive to all epitopes of GAD65 tested in this study were also less frequent in subjects with GDM, in comparison to first-degree relatives (65 vs. 23%, $P < 0.01$). The observed reduction of binding to GAD epitopes in women with GDM, in comparison to young first-degree relatives, is also seen in LADA patients (59).

Similarly to LADA, in GDM, the combined presence of various AAs is infrequent (29,30,32,35,37), which is consistent with the concept of a slow progression form of autoimmune diabetes (58).

Transplacental passage of DRAs and related effects

DRAs are transferred to the fetus (42,60–66). They are mainly IgG and are actively transported by the placenta (67,68). Maternal and fetal levels are highly correlated for IAs (42,60,63–65), ICAs (60), GADAs (60,69), and IA-2As (60). This transplacental passage of antibodies lies behind the higher prevalence of DRA in cord blood from infants of diabetic mothers compared with infants of diabetic fathers (66). Postnatal elimination of transplacentally acquired DRAs has been prospectively investigated in infants born to type 1 diabetic mothers, with the mean elimination time being 3.1 months for ICAs and IAs, 4.5 months for GADAs, and 4.3 months for IA-2As (60).

Menon et al. (63) reported that the concentration of animal insulin in cord serum correlated with birth weight, but this observation has not been confirmed by other authors (42,64,65,70,71). The underlying mechanism would be an IA-facilitated maternal insulin transfer and, as a consequence, an enhancement of fetal hyperinsulinism and related morbidity (72). Maternal insulin-IA complexes have been associated with toxemia (18,73,74), HELLP syndrome (75), hypoglycemia (18,76), respiratory distress (18), and high hematocrit in the newborn (76). Nevertheless, other investigators have not observed a relationship between maternal levels of IAs and cord blood levels of insulin (71), 32–33 split proinsulin (71), or C-peptide (64). In our experience, fetal outcomes were not influenced by the presence or titers of IAs, IAAs, or ICAs (77).

In the nonobese diabetic mouse, the transplacental passage of maternal AAs increases the risk of experimental autoimmune diabetes in the offspring (78), whereas the transmission of AAs against activated T-cells is protective (79). Interestingly, in infants of diabetic mothers, the presence of GADAs and IA-2As, but

Table 1—*DRAs in women with GDM*

Author	*n*	ICA prevalence (%)	IAA prevalence (%)	GADA prevalence (%)	I-A2A prevalence (%)
Steel et al. (17)	50	10			
Ginsberg-Fellner et al. (20)*	88	35			
Fallucca et al. (18)	39	5			
Freinkel et al. (1)	160	7.5†			
Stowers et al. (19)‡	72	12.5			
Catalano et al. (21)‡	187	1.6			
Bell et al. (22)	181	2.8			
Stangerberg et al. (23)	55	1.8			
Mauricio et al. (24)	307	12.4†			
Ziegler et al. (25)	55	11			
Damm et al. (26)	139	2.9§	0§		
Tuomilehto et al. (50)	112			5.0	
Beischer et al. (51)‡	734			1.8	
Mauricio et al. (3)	203		1		
Petersen et al. (52)	139			2.2§	
Lapolla et al. (27)	68	2.9	1.5		
Dozio et al. (28)	145	10§	3.0§	0§	0§
Fuchtenbusch et al. (29)	437	8.5†		9.5†	6.2†
Fallucca et al. (53)	83			3.6§	
Whittingham et al. (30)	98	3		4	1
Panczel et al. (31)‡	68	14.7			
Kinalski et al. (32)‡	156	5.1†		7.0†	3.2†
Mitchell et al. (54)	100			6†	
Bartha et al. (33)‡	102	0.98		10.8	
Kousta et al. (55)‡	321			4.0	
Weng et al. (56)‡	66			4.5§	
Balaji et al. (57)	86			41 GADA/IA-2†	
Lapolla et al. (34)	70	2.8		1.4	0
Albareda et al. (35)	535	14		1.5	0.2
Bo et al. (36)	123	6.5†		4.1†	
Järvelä et al. (37)	435	12.5†	5.9†	4.7†	1.0§

Adapted from Lauenborg et al. (84). For groups with several articles on the subject, the first article reporting the prevalence of each autoantibody is included. *The method was later shown to produce false-positive results. †$P < 0.05$ vs. the control population. ‡Measurements were performed at different times after delivery; §NS vs. the control population. ‖Women had both GDM and a positive family history of diabetes.

not of IAs, in cord blood samples is associated with a lower risk of developing DRAs and type 1 diabetes (80). However, when present in infants of diabetic fathers, DRAs are not protective, which seems to imply an active fetus self-immune response in this case (80).

DRAs AND THE RISK OF MATERNAL GLUCOSE INTOLERANCE/DIABETES

— A major issue regarding the presence of DRAs in women with GDM is the potentially increased risk for the development of diabetes either at short term after delivery or at longer follow-up. The majority of reports have agreed that positivity for DRA during pregnancy increases the maternal risk of glucose intolerance/diabetes (Table 3).

In the first investigation on the prevalence of ICAs in GDM, three of five ICA^+ gestational diabetic women developed classic type 1A diabetes shortly after pregnancy (17). Additional studies have confirmed an increased risk of diabetes (24) or glucose intolerance (21) in women positive for ICAs. The association has also been extended to other DRAs: positivity for either ICA/IA-2A or GADAs increases the risk of type 1 diabetes 2 years after delivery, with the risk increasing with the number of positive antibodies (29). There are also articles reporting a lack of association of ICAs (23) or GADAs (56) with abnormal glucose tolerance at short term after delivery that could be attributable to a low statistical power of the studies. Nevertheless, it is important to highlight that only two of these articles performed statistical adjustment for other predictors (23,29).

In addition to ICAs being predictive of diabetes at the first assessment after delivery (24), our team reported an impairment of the acute insulin response to intravenous glucose in women with GDM with positivity for ICAs and normal glucose tolerance after delivery (81). The response was superimposable to that of ICA^+ first-degree relatives. Interestingly, a Finnish study on first-degree relatives of LADA patients demonstrated similar metabolic features that were described by us in women with GDM and positivity for ICAs. These individuals (family members of LADA patients) exhibited decreased insulin secretion, associated with an increased prevalence of risk genotypes (82).

At longer follow-up, an increased risk of type 1 diabetes has been demonstrated for ICAs (20,26,31,37,52), GADAs (37,49,52), and positivity for one or more islet cell antibodies (52,83–85), with the risk increasing with the number of antibodies (37), but not for IA-2 (29,37). Even for ICAs and GADAs, not all articles find a positive association between DRA positivity and diabetes at follow-up, which in some cases (19,34), but not others (35,55), can be attributed to a low statistical power. For example, in our population, despite the aforementioned association of ICA positivity with postpartum abnormal glucose tolerance, DRA positivity (ICA/GADA/IA-2, alone or in any combination) was not predictive of diabetes at mid-term follow-up (35). As in the case of short-term follow-up, only some studies have adjusted for other predictors (35,37,83).

AUTOIMMUNE GDM: A DISTINCT PRE-DIABETIC STAGE

— A recent publication investigated the differences in clinical character-

Table 2—*Prevalence of IAAs in women with GDM according to ICA status, as compared with first-degree relatives of subjects with type 1 diabetes*

	n	Prevalence
GDM		
ICA^+	27	11%
ICA^-	135	0.7%
FDR		
ICA^+	34	10%
ICA^-	23	4%

Adapted from Mauricio et al. (3).

Table 3—*Abnormal glucose tolerance at follow-up in women with GDM and DRAs*

Author	Follow-up	ICAs	IAAs	GADAs	IA-2As	Several DRAs
Steel et al. (17)	1 year	Predictive of type 1 diabetes				
Ginsberg-Fellner et al. (20)	Years	Predictive of type 1 diabetes				
Stowers et al. (19)	Up to 22 years	Not predictive of the final state of glucose tolerance				
Catalano et al. (21)	Up to 4 years	Predictive of IGT				
Stangerberg et al. (23)	2–4 months	Not predictive of abnormal OGTT*				
Mauricio et al. (24)	Months	Predictive of diabetes				
Damm et al. (26)	Up to 11 years	Predictive of type 1 diabetes				
Beischer et al. (51)	Years			GADAs at follow-up associated with type 1 and type 2 diabetes		
Petersen et al. (52)	Up to 11 years	Predictive of type 1 diabetes		Predictive of type 1 diabetes		DRA positivity predictive of type 1 diabetes
Fuchtenbusch et al. (29)	Up to 5 years	Predictive of type 1 diabetes*		Predictive of type 1 diabetes*	Not predictive of type 1 diabetes*	Risk of type 1 diabetes increases with the number of DRAs*
Panczel et al. (31)	Up to 14 years	Predictive of type 1 diabetes				
Kousta et al. (55)	Up to 45 months			GADAs at follow-up not associated with different FBG or HOMA estimations of insulin secretion and sensitivity		
Weng et al. (56)	1 year			No association with diabetes/IGT		
Lapolla et al. (34)	5 years					DRA positivity, borderline association to type 1 diabetes
Albareda et al. (35)	Up to 11 years					DRA positivity not predictive of diabetes, type 1 diabetes, or type 2 diabetes*
Järvelä et al. (37)	Up to 7 years	Predictive of type 1 diabetes*		Predictive of type 1 diabetes*	Not predictive of type 1 diabetes*	Number of DRAs predictive of type 1 diabetes*
Löbnner et al. (83)	Up to 11 years					GAD and/or IA-2 positivity predictive of diabetes*

For groups with several articles on the subject, only articles providing new information on the predictive ability of DRAs are included. *Adjusted for other predictors. FBG, fasting blood glucose; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

istics of women with GDM, whether associated with islet cell autoimmunity or not. A total of 207 women composed the total group of investigated subjects; 12.5% were carrying AAs in their sera, either ICAs and/or GADAs, usually at low titers. GDM women with autoimmune markers presented lower a priori risk for the development of GDM (were younger, had lower prepregnancy BMI, lower prevalence of diabetes in first-degree relatives, lower waist circumference, lower fasting plasma insulin, and lower weight increase during pregnancy). The rate of insulin treatment during pregnancy was significantly higher in the group positive for AAs (36). These observations led the authors to the conclusion that women with autoimmune GDM displayed fewer features of insulin resistance, required more frequent insulin therapy than negative women, and presumably had presymptomatic type 1 diabetes. Nevertheless, other authors have reported that women with GDM with or without GADA positivity at follow-up display similar clinical characteristics with the exception of BMI (55).

Freinkel et al. (2) foresaw the evolution of what may be defined as autoimmune GDM, when they wrote in 1987, that GDM entails genotypic and phenotypic diversity and may include patients with slowly evolving type 1 diabetes. Seventeen years after such publication, and considering today's new information, we believe that autoimmune GDM is a heterogeneous condition, covering for ~10% of all Caucasian women diagnosed with GDM. This condition may display the various types of expression of the immune reactivity against the β-cell. With these considerations, we propose that autoimmune GDM be regarded as a distinct clinical entity. This proposal does not only make reference to a special subtype of GDM for academic or classification purposes; it also addresses a peculiar and complex pre-diabetic status, susceptible of future new strategies for diabetes prevention.

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