

# Clinical Recommendations for the Use of Islet Cell Autoantibodies to Distinguish Autoimmune and Non-Autoimmune Gestational Diabetes

Kadri Haller-Kikkatalo · Raivo Uiibo

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**Abstract** Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first recognized during pregnancy. The prevalence of GDM is highly variable, depending on the population studied, and reflects the underlying pattern of diabetes in the population. GDM manifests by the second half of pregnancy and disappears following delivery in most cases, but is associated with the risk of subsequent diabetes development. Normal pregnancy induces carbohydrate intolerance to favor the availability of nutrients for the fetus, which is compensated by increased insulin secretion from the maternal pancreas. Pregnancy shares similarities with adiposity in metabolism to save energy, and both conditions favor the development of insulin resistance (IR) and low-grade inflammation. A highly complicated network of modified regulatory mechanisms may primarily affect carbohydrate metabolism by promoting autoimmune reactions to pancreatic  $\beta$  cells and affecting insulin function. As a result, diabetes development during pregnancy is facilitated. Depending on a pregnant woman's genetic susceptibility to diabetes, autoimmune mechanisms or IR are fundamental to the development of autoimmune or non-autoimmune GDM, respectively.

Pregnancy may facilitate the identification of women at risk of developing diabetes later in life; autoimmune and non-autoimmune GDM may be early markers of the risk of future type 1 and type 2 diabetes, respectively. The most convenient and efficient way to discriminate GDM types is to assess pancreatic  $\beta$ -cell autoantibodies along with diagnosing diabetes in pregnancy.

**Keywords** Autoimmune diabetes · Tolerance · Islet cell autoantibodies · Gestation · Pregnancy complications

## Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first recognized during pregnancy. Its etiopathogenesis and prevalence have been studied since the 1960s [1]. The website of the National Center for Biotechnology Information lists more than 12,500 research articles and reviews published to date on GDM.

The prevalence of GDM is highly variable, depending on the population studied and diagnostic test and glycemic cutoff value used [2]. GDM development has been reported in association with 1 % of all pregnancies in Sweden [3] and in more than 20 or 30 % of pregnant women in Sardinia, Italy [4], and Asia [5]. The population-based prevalence of GDM generally reflects the underlying pattern of diabetes in the background population [4, 6]. The prevalence of diabetes in the general population of Europe is about 6–8 %; about 90 % of these cases are type 2 diabetes (T2D) and 10 % are type 1 diabetes (T1D), mostly autoimmune in origin [7].

GDM usually manifests by the second half of pregnancy, and it disappears after delivery in most cases. Normal pregnancy induces carbohydrate intolerance to mobilize more nutrients for fetal growth, which in turn creates an increased demand for insulin production by maternal pancreatic  $\beta$  cells.

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K. Haller-Kikkatalo · R. Uiibo (✉)  
Department of Immunology, Institute of Biomedicine and Translational Medicine, University of Tartu, Ravila Str. 19, Tartu 50411, Estonia  
e-mail: raivo.uiibo@ut.ee

K. Haller-Kikkatalo · R. Uiibo  
Competence Centre on Health Technologies, Tiigi 61b, Tartu 50410, Estonia

K. Haller-Kikkatalo  
Department of Obstetrics and Gynecology, University of Tartu, L. Puusepa 8, Tartu 51014, Estonia

K. Haller-Kikkatalo  
Women's Clinic, Tartu University Hospital, L. Puusepa 8, Tartu 51014, Estonia

Failure to meet this increased need for insulin due to insufficient glucose uptake by insulin-sensitive tissues [causing insulin resistance (IR)] and/or insufficient secretion of insulin by  $\beta$  cells results in increased blood glucose levels. Many researchers previously considered the pathophysiology of GDM to be similar to that of IR-mediated T2D [2], and GDM has been considered a high-risk factor for T2D development later in life in up to 70 % of affected women [8]. More recently, however, growing evidence has indicated that GDM is similar to autoimmune T1D or latent autoimmune diabetes of adults (LADA) in a proportion of patients [9], as reviewed comprehensively by Lapolla and colleagues in 2009 [10]. In the worst-case scenario, half of affected patients will develop autoimmune diabetes a few years after index pregnancy [11]. In addition, discrimination between GDM and other types of diabetes that were previously undiagnosed or develop coincidentally at the time of pregnancy represents a diagnostic challenge during pregnancy [10].

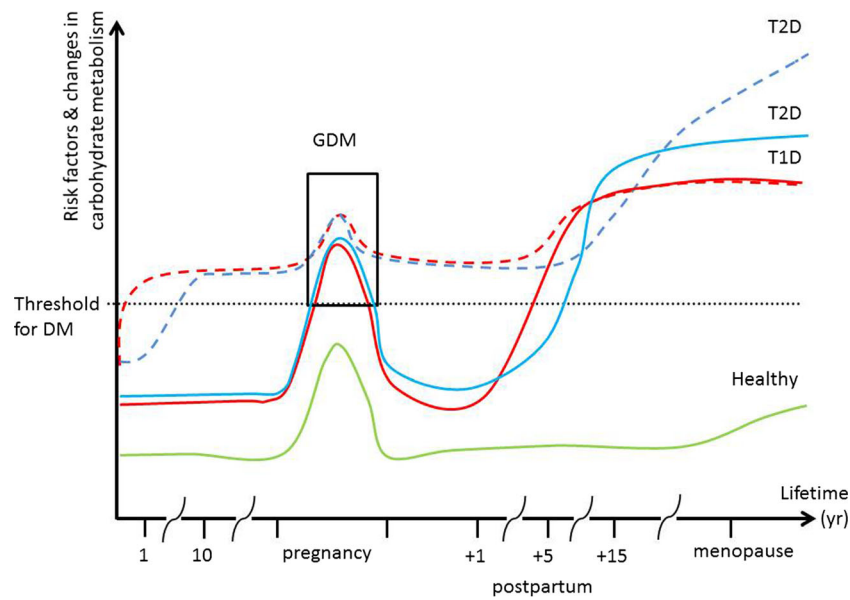
This review describes recent perspectives on GDM, with particular focus on the autoimmune aspects of GDM and pregnancy. The population of patients with GDM appears to consist of at least four subpopulations (Fig. 1): pregnant women with (i) autoimmune or (ii) non-autoimmune GDM (considered to be “true” GDM), who are at risk for postpartum T1D and T2D, respectively, and those with existing (iii) T1D or (iv) T2D that is first diagnosed during pregnancy (missed diabetes). The contribution of pregnancy in the sense of “true” GDM is probably to identify women at risk of developing diabetes later in life [12]. The pathophysiological mechanisms underlying autoimmune and non-autoimmune GDM are likely distinct, but they may overlap [13, 14] and the type of diabetes developed may depend on which risk factors dominate. Still, importantly, these two types of GDM require different treatments and have different prognoses with respect to postpartum maternal health [15, 16]. Pancreatic  $\beta$ -cell autoantibodies during and after pregnancy are useful markers for discrimination of these conditions and prediction of the probability of autoimmune diabetes development later in life, respectively. The diagnostic or predictive value of certain  $\beta$  cell autoantibodies in cases of autoimmune GDM has not yet been determined, and the prediction of T2D development following GDM is even more problematic.

### Healthy Pregnancy: Changes in Glucose Metabolism and Immune Mechanisms

The somatogenic and lactogenic hormones of the placenta and maternal pituitary gland integrate the metabolic adaptations of pregnancy with the demands of fetal and neonatal development. Healthy pregnancy is associated with IR and activation of an inflammatory response (Fig. 2). IR is transient during pregnancy to facilitate the mobilization of maternal nutrients for fetal

growth [17], and manifests as elevated postprandial glycemia, fasting hyperlipidemia (in the form of increased triglycerides, low-density lipoprotein particles, and free fatty acids), and accelerated ketosis [18]. Insulin sensitivity decreases by 50–70 % in normal and diabetic pregnancies; it returns to normal postpartum in women with normal glucose tolerance, but not in all cases of diabetic pregnancy [19]. Increased maternal obesity, hormones present in pregnancy [i.e., estrogen, progesterone, and prolactin], but especially placental growth hormone (GH) [17], human placental lactogen (hPL), leptin, and cortisol [20], as well as placental tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) [21], and magnesium cation (Mg<sup>2+</sup>) deficiency [22] may be responsible for increased IR in pregnancy.

Placental GH [17] and hPL [23] control embryo growth, likely via the opposing actions of insulin and insulin-like growth factors, inducing IR in humans [24]. hPL and prolactin increase maternal food intake by inducing central leptin resistance [17]. Resistin is one of the adipocyte-derived signaling molecules called adipokines. Adipokines and/or their receptors are expressed in the placental tissue, contributing to maternal IR and ultimately to fetal growth. The levels of leptin and resistin in serum and placenta increase as pregnancy progresses, and high levels of both adipokines have been detected in umbilical plasma [25]. Conversely, the serum level of the insulin-sensitizing adipokine adiponectin decreases. However, recent studies have shown that TNF- $\alpha$ , but no other maternal or placental hormone (including cortisol and hPL), is the primary mediator of progressive IR during pregnancy [21]. TNF- $\alpha$  has also been found to be the link between IR and the physiological increase in inflammatory response in normal pregnancy [26] via the stimulation of hepatic C-reactive protein (CRP) production [27, 28]. TNF- $\alpha$  is a pro-inflammatory cytokine produced by many cell types, including macrophages, lymphocytes, fibroblasts, keratinocytes, adipocytes, and placental tissue [29], in response to inflammation, infection, and other environmental stresses. Interleukin (IL)-15, another pleiotropic inflammatory cytokine, is produced by multiple tissues, including the placenta, skeletal muscle, kidney, lung, heart, pancreas, monocytes/macrophages, and numerous cell types under various stimulatory conditions [30]. IL-15 is a powerful T cell growth factor facilitating the activation of autoreactive cluster of differentiation (CD)8(+) T cells by weak autoantigens [31]. A constant increase in IL-15 level is expected during the progression of a healthy pregnancy, as the fetus [32] and placenta [33] produce IL-15 in the processes of fetal immune response development and preparation for delivery. Nevertheless, pregnancy is characterized by intracellular Mg<sup>2+</sup> depletion [34]. Mg<sup>2+</sup> regulates ion channels and cellular processes, and serves as a cofactor for many essential metabolic reactions. It is involved in multiple steps of insulin signal transduction pathways, such as insulin secretion, binding, and receptor activity [35], suggesting that reduced intracellular Mg<sup>2+</sup> decreases insulin receptor activity,



**Fig. 1** Putative changes in carbohydrate metabolism associated with pregnancy and aging in healthy and diabetes-prone women that contribute to the risk of diabetes. Healthy women (*green line*) who never develop diabetes still face increased insulin demand due to insulin resistance during pregnancy and weight gain later in life (e.g., due to menopause). However, the increased need for insulin is compensated by the pancreas, and the sum of diabetic risk factors never exceeds the threshold level. Women who are at risk of type 1 diabetes (T1D; *red line*) may exceed this threshold during pregnancy and develop autoimmune diabetes, which shows clinical

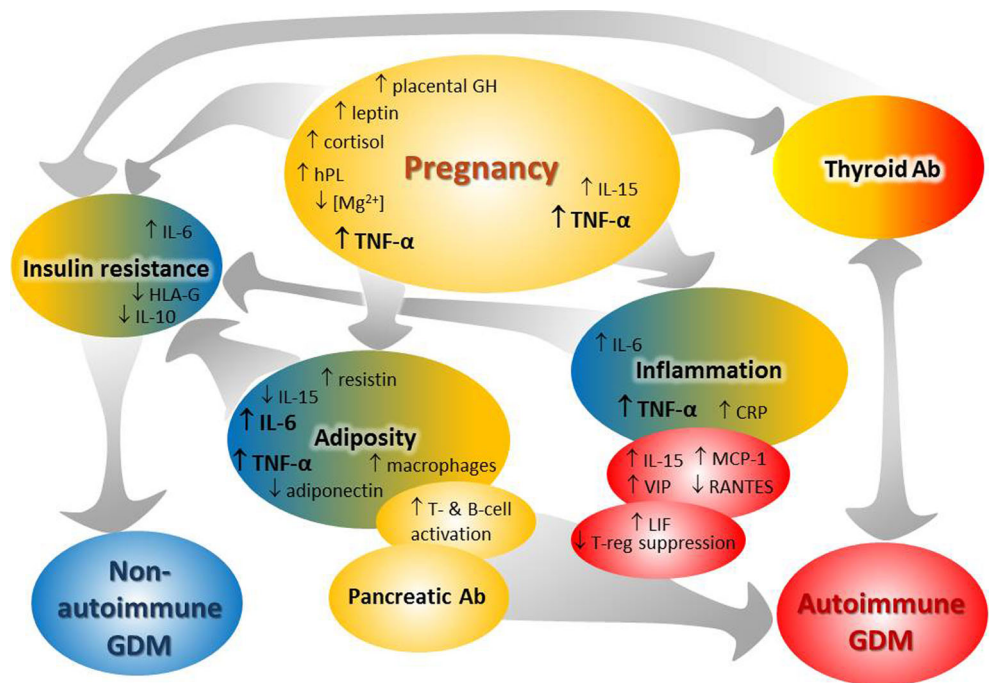
improvement after delivery in many cases, but leads to T1D development 1–4 years postpartum in some cases. Similarly, women at risk of type 2 diabetes (T2D; *blue line*) may develop non-autoimmune diabetes during pregnancy and again 5–15 years postpartum. In some cases, the diagnosis of diabetes during pregnancy reflects the presence of this condition before pregnancy. Missed T1D (*red dashed line*) usually manifests earlier in life than missed T2D (*blue dashed line*), and both groups of patients remain diabetic postpartum. Diabetes first diagnosed during pregnancy is defined collectively as gestational diabetes mellitus (GDM)

impairs post-receptor action, and results in increased IR during pregnancy [34].

In normal pregnancy, IR is compensated by expansion of the functional  $\beta$  cell mass in the pancreas, preventing chronic

hyperglycemia and GDM development [17]. This compensation is controlled by hPL and prolactin [17] and mediated by epigenetic regulation in islet cell genes. Rodent studies have revealed underlying changes in the expression of several islet

**Fig. 2** Overview of interactions between physiological adaptations during pregnancy (*yellow*) and conditions associated with the risk of type 1 (T1D, *red*) or type 2 (T2D, *blue*) diabetes in the manifestation of autoimmune or non-autoimmune gestational diabetes mellitus (GDM). *Ab* autoantibodies, *HLA-G* human leukocyte antigen G, *CRP* C-reactive protein, *GH* growth hormone, *hPL* human placental lactogen, *IL* interleukin, *LIF* leukemia inhibitory factor, *Mg<sup>2+</sup>* magnesium cation, *MCP-1* monocyte chemoattractant protein 1, *RANTES* regulated upon activation of normal T cells expressed and secreted, *TNF- $\alpha$*  tumor necrosis factor alpha, *T-reg* T regulatory lymphocytes, *VIP* vasoactive intestinal peptide



microRNAs in compensatory  $\beta$  cell expansion. Decreased expression of miR-338-3p was associated with the promotion of islet cell proliferation and the protection of these cells from apoptosis [36].  $\beta$  cell proliferation requires intact prolactin receptor signaling [37]. Any disturbance in  $\beta$  cell or insulin function, as expected in T1D and T2D, respectively, will challenge the compensatory mechanism underlying these physiological changes in pregnancy. The complexity of these mechanisms and inconsistent findings regarding metabolic changes in GDM have prevented us from drawing a comprehensive picture of diabetes-related metabolism in GDM [38]. For this reason, these aspects of GDM are not considered in detail in the present review. The role of microorganisms, including commensal microflora that may influence diabetes development during pregnancy and after delivery, is also not discussed. These factors are of general importance for diabetes development and have been discussed elsewhere [39, 40].

### **Pregnancy in Women at Risk of T1D may Result in Autoimmune GDM Development**

In general, the risk of T1D is determined by the magnitude of autoimmunity against pancreatic  $\beta$  cells. In patients with GDM, general risk factors for T1D (reviewed elsewhere [10, 41, 42]) combine with pregnancy-related physiological changes in glucose metabolism and immune system regulation. The likelihood of GDM development is positively related to the number of risk factors present at the time of pregnancy (Fig. 2). Women with autoimmune GDM are commonly normal weight [4] and young (aged <30 years); they are more likely to require insulin treatment during pregnancy beyond dietary adjustment. They are more likely than women with non-autoimmune GDM to show pancreatic autoantibody positivity [12] and increased prevalence of human leukocyte antigen (HLA) DR3-DQ2/x or DR4-DQ8/x haplotypes [43]. In healthy pregnancy or pregnancy at risk of diabetes, anti-pancreatic  $\beta$  cell autoimmunity is the primary autoimmune reaction triggered, while other forms of autoimmunity are suppressed to avoid maternal immune reaction to the semi-allograft fetus. Pancreatic  $\beta$  cells may be preferentially targeted due to a combination of the embryo's need for nutrients, which primarily involves the regulation of maternal carbohydrate metabolism, and the adaptation of maternal immune mechanisms to support the pregnancy, although this interpretation remains speculative.

Autoimmune GDM is associated with changes in chemokine concentrations in peripheral blood. The monocyte chemoattractant peptide (MCP)-1 level is increased, and, the regulated upon activation, normal T cell expressed and secreted (RANTES) level is decreased in diabetic pregnancy [44]. MCP-1 serves as a pro-inflammatory activator of various immune cells [45], and RANTES may act as an

immunomodulator suppressing the maternal allogeneic response [46]. Decreased expression of vasoactive intestinal peptide (VIP) at the implantation site has also been detected in prediabetic non-obese diabetic mice [47]. VIP is produced by trophoblast cells, where it induces a tolerogenic environment by increasing the expression of IL-10, transforming growth factor  $\beta$ , and Forkhead box P3 [48]. The expression level of VIP may serve as a link between placental trophoblasts, and the activation of autoimmune processes as a low VIP level activates proinflammatory leukemia inhibitory factor and T regulatory cells in contrast to VIP expression in healthy implantation [47]. Recent study findings suggest that certain subpopulations of T regulatory cells have reduced suppressive function in GDM [49]. These above-described mediators are needed to control excessive inflammation and moderate immune response, which are of vital importance for a successful and healthy pregnancy [50]. These changes augment inflammation during pregnancy, increasing the risks of T1D and unfavorable outcome of diabetic pregnancy; they may also activate adaptive immunity, further impairing pregnancy outcome.

Thus, in addition to the activation of innate immunity and inflammation, pregnancy may be accompanied by the activation of autoimmune reactions. GDM was previously thought not to be autoimmune in origin. This supposition was supported by similar frequencies of HLA DR2, DR3, and DR4 antigens in healthy pregnant women and those with GDM, as well as the low prevalence of markers of  $\beta$  cell autoimmune destruction in women with GDM [19]. However, adiposity is usually increased during pregnancy [20], and recent studies have shown that overnutrition under this condition results in the necrotic death of engorged adipocytes, leading to recruitment of classically activated macrophages to clear cellular debris [51]. These macrophages express molecules suitable for antigen presentation (major histocompatibility complex II, CD1d, costimulatory molecules, and CD11c), and necrotic cell-derived antigens can potentially be presented to T cells and B cells. This process activates adaptive immunity, resulting in clonal expansion of CD4<sup>+</sup> T helper (Th) 1 cells and recruitment of CD8<sup>+</sup> T cells. CD8<sup>+</sup> T cells produce cytokines that increase the recruitment of macrophages into adipose tissue, and interferon- $\gamma$  secreted by CD4<sup>+</sup> Th1 cells increases their activation, establishing a vicious cycle of inflammation [51]. Furthermore, B cells can produce cytokines that affect T cell development, which in turn drives B cells to produce pathogenic antibodies [52]. In addition, B-cell responses can deplete T regulatory cells [53], resulting in adiposity-associated inflammation. Thus, inflammation initiated in adipose tissues propagates a vicious cycle that further worsens IR [52, 53]. Escalating IR is toxic to pancreatic  $\beta$  cells and further facilitates the development of pancreatic  $\beta$ -cell autoimmune responses [51]. The present authors have recently demonstrated an association between adiposity and pancreatic antibodies in diabetes (unpublished results).



Regardless of whether pregnancy is associated with increased adiposity, the antigenic load of the fetus has been postulated to trigger the diabetogenic process [54]. Membrane-bound or soluble (s) HLA-G expressed on or by the placental trophoblast cells is a central regulator of maternal immune mechanisms during pregnancy [55]. Interaction between HLA-G and nuclear factor kappa B (NF- $\kappa$ B) has been suggested to be central in events leading to GDM development. In general, HLA-G has anti-inflammatory and tolerogenic properties, including the induction of T regulatory cells, modulation of CD8<sup>+</sup> T-cell cytotoxicity, and regulation of CD4<sup>+</sup> T lymphocyte function [56]. These functions are partially shared with IL-10, which regulates the expression of HLA-G. However, the level of IL-10 is reduced in IR states [57]. In addition, HLA-G likely protects pancreatic islet cells [56]. Probably as a compensatory event, an increased plasma sHLA-G level is associated with the degree of glucose tolerance and is directly related to the levels and action of IL-6, a cytokine involved in subclinical inflammatory status in T2D, obesity, early stages of altered glucose tolerance, and several autoimmune diseases [58]. Under physiological conditions, activated CD14<sup>+</sup> monocyte cells are primarily responsible for sHLA-G secretion into plasma in response to inflammatory stimuli [59].

As mentioned above, a constant increase in IL-15 level is expected during the progression of a healthy pregnancy due to fetal development. However, IL-15 production by mononuclear phagocytes and pancreatic  $\beta$  cells mediates inflammatory reactions in the pancreatic cells during the development of diabetes [60] by enabling autoreactive CD8<sup>+</sup> T-cell responses to weak antigens; in other words, this process changes the avidity of autoreactive T cells [31]. Increased serum IL-15 levels are common to many autoimmune diseases in humans, including T1D [61], but also to pregnancies with preeclampsia [62] and other situations in which the maternal immune system reacts against the fetus [43]. The inflammatory properties of IL-15 are opposed by vitamin D in many organs, including the pancreatic islets [63] and placenta [64]. Pregnancy, however, is associated with increased need for vitamin D, primarily for fetal bone development. The maternal kidneys, and possibly the placenta, decidua, and fetal kidneys, try to meet this increased vitamin D requirement by providing the necessary 1- $\alpha$  hydroxylase activity; this enzyme hydroxylates vitamin D metabolite 25-hydroxycholecalciferol into biologically active 1 $\alpha$ ,25-dihydroxycholecalciferol [1,25(OH)<sub>2</sub>D<sub>3</sub>]. The result of this process is a several-fold increase in serum vitamin D level in healthy pregnancy compared with the pre-pregnancy level [65]. However, the prevalence of vitamin D deficiency is increased among pregnant women, despite sufficient exposure to sunlight [66]. These data collectively suggest the supportive effect of pregnancy for anti-pancreatic  $\beta$ -cell autoimmunity development (in addition to underlying genetic susceptibility) [10, 41, 42].

The prevalence and profile of pancreatic  $\beta$ -cell autoantibodies among women with GDM mirror the prevalence of T1D outside of pregnancy and depend on the profile of HLA DQ8/DR3/DR4 haplotypes in the background population [67]. The Finnish population is unique because of the high incidence rate of T1D, but similar frequency of T2D to other countries in Europe [68]. In this population, the prevalence of autoantibodies to islet cells (ICA), glutamic acid decarboxylase-65 (GADA), and insulinoma-associated protein 2 (IA-2A; 12.5, 5.9 and 4.7 %, respectively) is significantly higher among pregnant women with than among those without GDM, whereas the prevalence of antibodies to insulin (IAA) is similar (1 and 0.5 %, respectively) [12]. The incidence rate of T1D is also notably high in Sardinia, Italy [69], where 29, 14.5, and 3.2 % of women with GDM show positivity for IA-2A, IAA, and GADA, respectively. Almost 40 % of patients with GDM in Sardinia show positivity for at least one pancreatic autoantibody [4], in contrast to <9 % of patients in northern Italy (where GADA was detected in only 1.4 % of women with GDM) [70] and 6 % of patients in Sweden (where GADA was detected in <6 %, ICA in about 3 %, and IA-2A in about 2 % of women with GDM) [11]. Only one published study has assessed the prevalence of antibody to zinc transporter 8 (anti-ZnT8) in women with GDM, and the authors concluded that anti-ZnT8 detection would contribute about 2 % to autoantibody positivity among women with GDM and GADA and IA-2A negativity [71]. The presence of pancreatic  $\beta$ -cell autoantibodies has been known for some time to be associated with the need for insulin treatment during GDM [72]. Collectively, evidence is sufficient to prove that pancreatic autoantibody screening would be informative in cases of GDM, and that the pattern and prevalence of particular pancreatic autoantibodies are population dependent.

The post-GDM risk of T1D development also depends on the prevalence of T1D in the background population, which in turn determines the prevalence of anti-pancreatic autoimmunity among women with GDM (Fig. 1). These antibodies are present years before T1D onset and can occasionally be revealed in association with GDM. However, the profiles of different pancreatic  $\beta$ -cell autoantibodies may indicate whether GDM is an early manifestation of LADA or T1D [4, 73]. About 5 % of all post-GDM patients, but about 50 % of post-GDM patients with positivity to three pancreatic antibodies, develop T1D within 6 years postpartum in the Finnish population. However, the presence of ICA during GDM is the best single marker for the prediction of postpartum T1D development; more than 60 % of women with post-GDM T1D showed ICA positivity during GDM, whereas 56 % of such women showed GADA positivity, 38 % showed IA-2A positivity, and 0 % showed IAA positivity [12]. In Northern Italy, where <9 % of patients with GDM have any type of pancreatic autoantibody, the overall postpartum T1D rate was 3.5 % [70].

Similar results were obtained in a Swedish population, where autoimmune GDM was present in 6 % of patients with GDM and the overall rate of T1D or LADA was 3 % [11]. However, the diabetes rate among antibody-positive women with GDM in this population was 50 % [11]. Overall, post-GDM autoimmune diabetes can be predicted best by assessing all three antibodies (GADA, ICA, and IA-2A); this method has shown 67–100 % sensitivity, and the use of ICA or IA-2A in combination with GADA has shown 60–90 % sensitivity [74].

T1D and LADA manifest rapidly after index pregnancy. About half of patients with post-GDM T1D develop the condition in the first year postpartum, and most other patients develop it within 4 years postpartum; only 2 % of patients develop T1D or LADA after this 4-year timepoint [11]. The first 2 years postpartum are thus most critical in terms of T1D development [74]. The timing of GDM manifestation also affects the probability of postpartum T1D development, with early pregnancy manifestation increasing this risk [15]. However, early pregnancy detection of diabetes may include patients with existing T1D that is not diagnosed before pregnancy [75].

In addition to pancreatic autoimmunity, GDM increases the risk of anti-thyroid antibody production. Anti-thyroid autoimmunity in GDM may be due to at least two conditions: pregnancy and a woman's general risk of autoimmunity (Fig. 2). Pregnancy with GDM [76] and healthy pregnancy [77] may be associated with increased production of thyroid antibodies and altered thyroid function. Normally, the levels of circulating thyroid antibodies decrease during pregnancy, and small changes in thyroid hormonal level may contribute to energy conservation [78]. Anti-thyroid autoimmunity during pregnancy seems to be far more prevalent than GDM; anti-thyroid peroxidase (TPO) or thyroid globulin antibodies have been detected in about 10–16 % of pregnant women [76, 79] and more than 80 % of those who underwent routine GDM screening (only anti-TPO), whereas only 26 % of the latter patients had GDM [80]. These data suggest that thyroid autoimmunity is induced primarily by pregnancy, and that diabetes represents an additional risk (Fig. 2). Autoimmune thyroid disease has been associated with T2D with GADA positivity (our unpublished data) and with T1D [81]. Anti-TPO antibody detection during pregnancy is correlated positively with the level of thyroid-stimulating hormone (TSH) [80], indicating the presence of (subclinical) hypothyroiditis during pregnancy. However, a combination of high TSH and thyroid autoimmunity in early pregnancy increases the risk of GDM more than four times, as well as increasing the risk of adverse pregnancy outcome [79]. Hypothyroiditis is associated with decreased rates of insulin-stimulated glucose transport into cells, which can lead to IR [82].

Several studies have examined thyroid antibodies in GDM, but data on the presence of other organ-specific or non-specific autoantibodies are very limited. In 1991, Bech and

colleagues [83] reported that parietal cell autoantibodies were present in 27 %, antibodies to TSH in 50 %, rheumatoid factor in about 18 %, and adrenal autoantibodies in 5 % of pregnant women with insulin-dependent diabetes. The limited data available suggest that pregnancy has no overall effect on autoimmunity development, despite the fostering of pancreatic  $\beta$ -cell or thyroid autoimmunity. This postulation is in agreement with the general understanding of immunomodulation during pregnancy to avoid unnecessary reaction to fetal allogeneic antigens.

### **Pregnancy in Women at Risk of T2D may Result in Non-Autoimmune GDM Development**

The risk of T2D is defined by the magnitude of IR (Fig. 2) [2]. In non-pregnant women, adiposity is the most significant mediator of IR. It is associated with increased inflammation and changes in metabolic function. The prevalence of weight gain is increasing constantly, and up to 40 % of women and more than 20 % of girls are obese worldwide [84]. In pregnancy, weight gain intensifies physiological changes in carbohydrate metabolism and can lead to the development of non-autoimmune GDM (discussed by Carpenter [18]). Just as the prevalence of autoimmune GDM reflects that of T1D, the prevalence of non-autoimmune GDM mirrors the prevalence of T2D in the background population [12, 42]. As expected, the phenotype of pregnant women with non-autoimmune GDM is opposite to that described for autoimmune GDM [4, 12].

In adipose women who become pregnant or when pregnancy is associated with increased adiposity, adipocytes are responsible for the initiation in inflammation, which together with adipokines contributes to IR. In contrast to a reasonable increase in adipose tissue in healthy pregnancy, extensive adiposity increases adipose tissue-specific inflammation and induces adipose tissue hypoxia [85] due to altered angiogenesis [86]. In women with GDM, adipocytes produce significantly higher levels of the adipokine resistin compared with those in pregnant women with normal glucose tolerance and much more than the same cells in non-pregnant women [26]. In GDM, resistin and IL-6 levels are correlated positively [26]. Inflammatory cytokines, such as TNF- $\alpha$  and IL-6, are produced by adipocytes as well as by monocytes and macrophages, and their levels are increased in obese individuals. These cytokines activate transcription factor NF- $\kappa$ B to increase, in turn, the expression of resistin, mainly by macrophages but also by adipocytes, in humans [87]. High levels of resistin selectively inhibit hepatic insulin action on glucose metabolism, thereby increasing glucose production by the liver and contributing to IR. Thus, the physiological function of resistin is believed to be the maintenance of blood glucose during fasting [88]. Another important protein, the hormone

adiponectin is secreted exclusively by white adipose tissue in inverse proportion to the extent of body fat mass. Adiponectin receptors are widely distributed in peripheral tissues and possess anti-diabetic, anti-atherogenic, and anti-inflammatory properties, among others [89]. Adiponectin also plays a key role in mediating IR and  $\beta$  cell dysfunction in the pathogenesis of diabetes [90]. Through ceramide deacylation stimulation, adiponectin promotes the survival of functional  $\beta$  cell mass, favoring insulin production to meet insulin demands [91]. Women with lower levels of adiponectin (adipose) in the first trimester of pregnancy thus have higher levels of IR and are more likely to develop GDM [92]. The increased level of CRP in GDM is also partly associated with increased adiposity [93] and IR [94]. These data indicate that adipocytes are capable of creating a low-grade inflammatory environment under conditions of adiposity.

However, chronic low-grade inflammation can be initiated by adipocytes in the absence of obesity, which can cause IR similar to that found in obese individuals. Our understanding of the origin of adipocytes has changed in the past 5 years. White and brown adipose tissues have been suggested to originate from distinct types of mesenchymal precursor or even from hematopoietic cells [95], explaining the central role of adipocytes in the initiation of inflammation. Research on rodents has shown that lean animals with chronic inflammatory disease develop IR at the level of muscle and liver tissue, and that this mechanism is mediated by lean adipose tissue [96]. In that experiment, adipose tissue was infiltrated by macrophages and the levels of MCP-1 and IL-6 were increased [96]. Another rodent study elegantly demonstrated that the infusion of free fatty acids into lean animals decreased insulin sensitivity in muscle cells [97]. Similarly, humans with some other chronic inflammatory conditions (chronic hepatitis C, rheumatoid arthritis, inflammatory lung disease) are at increased risk of diabetes because of elevated TNF- $\alpha$  [98] and IL-6 [99] levels. TNF- $\alpha$  elevation stimulates inhibitory phosphorylation of serine residues of the insulin receptor substrate family, promoting IR at the post-receptor level of insulin action [98]. Serum IL-6 elevation is also associated with diminished insulin secretion [99], indicating the role of inflammatory cytokines in promoting IR.

Opposite to T1D, the T2D-prone environment is characterized by a decreased serum IL-15 level. IL-15 is involved in the mechanisms that attenuate the deleterious effect of TNF- $\alpha$  to promote IR in muscle cells [100]. The actions of IL-15 are modulated by vitamin D in many regulations, including maturation of adipocytes capable of producing adipokines [101]. However, the vitamin D level in pregnant women is commonly very low [66], which also affects calcium metabolism. In the presence of a low calcium level, 1,25(OH) $_2$ D $_3$  favors the expression of inflammatory cytokines (TNF- $\alpha$ , IL-6, IL-15) and inhibits the expression of anti-inflammatory cytokines (adiponectin) by adipocytes and muscle cells [102]. These

data show that coincident vitamin D deficiency, pregnancy, and adiposity may further favor an inflammatory environment. The extent of inflammatory activation, in turn, encourages GDM development in women with pregnancy-associated IR [103]. Thus, excessive adiposity contributing to subclinical inflammation favors the development of GDM. However, as discussed above, escalating IR is toxic to pancreatic  $\beta$  cells, further facilitating the development of pancreatic  $\beta$ -cell autoimmune responses [13, 14, 51]. This effect closes the circle and suggests, at least theoretically, that a proportion of women with non-autoimmune GDM may develop autoimmune diabetes later in life or during subsequent pregnancy. Pancreatic  $\beta$ -cell autoantibody detection would be informative in this regard.

The prediction of T2D is far more difficult than the prediction of T1D by pancreatic  $\beta$ -cell autoantibody detection. In general, multiparity, the magnitudes of weight gain during and after pregnancy, low efficacy of IR maintenance, and postpartum insulin requirement are well-known markers of increased T2D risk [2]. However, an elevated fasting glucose level during pregnancy has been the most important risk factor for future T2D [8]. About 2 years after GDM, women continue to show significant deviations in several metabolic and inflammatory markers compared with women with normal glucose regulation during pregnancy. Importantly, higher serum triglyceride levels within the low-normal range (0.84–1.21 mmol/l) at 2–24 months after pregnancy with GDM have been associated with an increased risk of early impaired glucose intolerance [104]. Another study found that serum plasminogen-activator inhibitor-1 possessed similar prognostic value for impaired glucose intolerance and metabolic syndrome development by 12–24 weeks after delivery [105]. The overall risk of T2D within 5–16 years postpartum is 17–63 % for women with GDM [106]. The cumulative incidence of T2D increases markedly in the first 5 years after delivery and seems to plateau after 10 years (Fig. 1) [8].

## Conclusions

There is enormous literature on both main types of diabetes - T1D and T2D, including the role of microflora [107, 108], inflammatory responses, including gestational influences [109–112], interventional studies in both humans and animal models [113–117], the role of vitamin D and other nutritional factors [118–121], and better definition of genetic control, autoantibodies, and the implications of offspring of the diabetic mother [122–124]. In this manuscript, we have focused on the research data that reflects the metabolic conditions of pregnancy and adiposity. Both of these conditions favor the development of two strongly associated changes: IR and low-grade inflammation. The established highly complicated network of regulatory mechanisms during pregnancy may

primarily affect carbohydrate metabolism by promoting auto-immune reactions to pancreatic  $\beta$  cells and affecting insulin function, while suppressing other autoimmune mechanisms. As a result, diabetes development during pregnancy is facilitated. Depending on a pregnant woman's genetic susceptibility, autoimmunity or IR is the fundamental mechanism causing autoimmune or non-autoimmune GDM, respectively. Pregnancy may facilitate the identification of women at risk of developing diabetes later in life; autoimmune and non-autoimmune GDM may be early markers of the risk of future T1D and T2D, respectively. Importantly, metabolic changes occurring in T2D may, in turn, promote pancreatic  $\beta$ -cell autoimmunity, and the development of T1D cannot be excluded in such cases. Thus, the most convenient and efficient way to discriminate GDM types and to predict autoimmune diabetes is to assess pancreatic  $\beta$ -cell autoantibodies along with diagnosing diabetes during and after pregnancy.

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