Journal of Reproductive Immunology 88 (2011) 72–79

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jreprimm

Seroconversion to islet autoantibodies between early pregnancy and delivery in non-diabetic mothers

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ARTICLE INFO

Article history:
Received 28 June 2010
Received in revised form 13 October 2010
Accepted 28 October 2010

Keywords:
Autoimmunity
Pregnancy
Seroconversion
Glutamic acid decarboxylase autoantibody
Islet antigen-2 autoantibody
Insulin autoantibody

ABSTRACT

Islet autoantibodies are currently used to classify type 1 diabetes at diagnosis as they reflect the autoimmune pathogenesis of the disease. The presence of maternal autoantibodies reactive with pancreatic islet antigens is thought to increase the risk for type 1 diabetes in the offspring. The objective of this study was to determine seroconversion to islet autoantibodies in non-diabetic mothers during pregnancy. Screening of 33,682 mothers between September 2000 and August 2004 in the Diabetes Prediction in Skåne (DiPiS) study showed that at delivery, 242 non-diabetic mothers had increased titers of islet autoantibodies reactive with glutamic acid decarboxylase (GADA), islet antigen-2 (IA-2A) or insulin (IAA), alone or in combination. Control mothers ($n = 1419$), who were islet autoantibody negative at delivery, were randomly selected and matched by age, parity and pregnancy sampling date. Mothers positive for GADA (92%), IA-2A (84%) or IAA (65%) at delivery had increased titers already evident in early pregnancy. Titers declined for GADA ($p < 0.0001$), IA-2A ($p < 0.0001$) and IAA ($p < 0.0001$). Seroconversion during pregnancy was observed for GADA in 10 (8%), IA-2A in 3 (16%) and IAA in 37 (35%) mothers. It is concluded that non-diabetic mothers with islet autoantibodies at delivery had significantly higher titers during early pregnancy than at delivery. As the statistical power in the seroconverting mothers was insufficient, further studies are needed to determine if the risk for type 1 diabetes in the offspring differs between mothers who already had increased titers of islet autoantibodies during early pregnancy or acquired them during pregnancy.

1. Introduction

Several studies suggest that gestational events are important for development of type 1 diabetes in the offspring, These include enterovirus infection (Dahlquist et al., 1995; Hyoty et al., 1995), blood group incompatibility (ABO) (Dahlquist and Kallen, 1992), preeclampsia (Jones et al., 1998) and high intake of nitrosamine compounds (Helgason and Jonasson, 1981). Even though previous studies have found that these events are associated with increased risk for type 1 diabetes, other studies have shown inconsistent results (Viskari et al., 2002; Stene et al., 2003). Islet autoantibodies at diagnosis are currently used to classify type 1 diabetes as they reflect the autoimmune

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doi:10.1016/j.jri.2010.10.002

pathogenesis of the disease (Alberti and Zimmet, 1998; ADA, 2003). Incomplete and sometimes complete beta cell failure has been shown in islet antibody positive patients, whereas a lack of GADA or low titer IA-2A indicated preservation of beta cell function (Borg et al., 2002).

It is controversial whether islet autoantibodies against glutamic acid decarboxylase (GADA), islet antigen-2 (IA-2A), or insulin (IAA) in cord blood increase the risk for type 1 diabetes (Lindberg et al., 1999; Elfving et al., 2008; Koczwara et al., 2004). As cord blood islet autoantibodies primarily emanate from the mother (Lynch et al., 2008), it was speculated that non-genetic factors may contribute to the development of these islet autoantibodies (Lynch et al., 2008). Alternatively, the mother may be islet autoantibody positive from the outset of pregnancy. To answer this question it is necessary to analyze blood samples obtained from early pregnancy. There is limited information about GADA, IA-2A and, to our knowledge, none about IAA in non-diabetic mothers during pregnancy. A previous study on seroconversion of ICA, GADA and IA-2A during pregnancy showed a tendency towards lower titers of all detected islet autoantibodies in samples at delivery compared to the samples from the early pregnancy, but none of the differences were statistically significant (Hamalainen et al., 2001). An additional study investigating patterns of GADA and IA-2A during type 1 diabetes pregnancy illustrated stability in islet autoantibody titers throughout pregnancy (Novak et al., 2000). Contradictory results on autoantibody titers in other autoimmune diseases during pregnancy have also been reported. Thyroid antibodies were shown to decrease (D'armiento et al., 1980), SLE associated autoantibodies to increase (Levy, 1982) while other autoantibodies did not change with gestational age (El-Roeiy and Shoenfeld, 1985).

In the Diabetes Prediction in Skåne (DiPiS) study (Larsson et al., 2005), cord blood samples as well as serum samples from the mother were obtained from 35,683 mothers at delivery (Lynch et al., 2008). In the present study, it was possible to obtain early pregnancy samples from the same islet autoantibody positive and matched control mothers DiPiS study mothers, from the Southern Sweden Microbiological Biobank (SSM-Biobank) (Ryding et al., 2008).

The objective of this study was to utilize these samples from the SSM-biobank to test the hypothesis that mothers with islet autoantibodies at delivery developed these during pregnancy. We therefore determined the end-point titers of GADA, IA-2A and IAA in serum samples from early pregnancy (gestational weeks 10–16) and at delivery from non-diabetic mothers who gave birth to children born with islet autoantibodies and compared them to islet autoantibody negative matched control mothers.

2. Materials and methods

2.1. Study population

The DiPiS-biobank has emerged from the population-based study Diabetes Prediction in Skåne and consists of serum samples collected from September 2000 to August 2004 and stored at −20 C. Serum samples from this study were thawed and an aliquot was removed and analyzed immediately for islet autoantibodies (Lynch et al., 2008; Larsson et al., 2005). In parallel to the DiPiS effort, serum samples were collected from all pregnant women in Region Skåne at their first visit to their Maternity Care Center during early pregnancy (gestational weeks 12–16). The serum samples from this public health test were used to screen for antibodies against rubella, hepatitis, HIV and syphilis. Leftover serum samples were stored at −20 °C in the SSM-biobank (Ryding et al., 2008). As with the serum samples in the DiPiS-biobank, the samples from the SSM-biobank were thawed and an aliquot was removed for islet autoantibody analysis.

Of the 48,058 recorded live births, cord blood and serum samples were obtained from 35,683 mothers at the time of delivery (Fig. 1). The selection criteria for islet autoantibody positive mothers at delivery have been detailed elsewhere (Lynch et al., 2008). A total of 2001 mothers were excluded because they had diabetes (gestational, type 1, type 2, unknown type or uncertain diagnosis). The delivery sample from the non-diabetic mothers was analyzed once the cord blood was found to be positive for any of the three islet autoantibodies (Lynch et al., 2008; Larsson et al., 2005). As the cord blood islet autoantibody results have been published previously (Lynch et al., 2008; Larsson et al., 2005) these results are not reported in the present study. A total of 532 mothers gave birth to children with cord blood islet autoantibodies (Fig. 1). Due to the fact that the mothers' serum sample at delivery was missing from 103 mothers, a total of 429 islet autoantibody positive mothers were available (Fig. 1). However, in the SSM-biobank, 187 samples were missing, hence it was possible to analyze a total of 242 early pregnancy samples (gestational week 10–16) (Fig. 1).

The mean ± SD gestational age of autoantibody positive mothers was 39.6 ± 12.3 weeks (range 27.5–43) and the mean birth weight was 3651 ± 681 g (range 1245–5745). Of the 32,294 islet autoantibody negative mothers we initially selected 1716 control mothers at random (four controls per islet autoantibody positive mother), matched for age, parity, and sampling date during early pregnancy ± 1 week (Fig. 1). As serum samples from early pregnancy were not accessible for 297 control mothers, our final number of mothers included as controls were 1419 islet autoantibody negative control mothers. For the control mothers the mean ± SD gestational age was 39.6 ± 11.4 weeks (range 28–43) and the mean birth weight was 3616 ± 538 g (range 1215–5950). All end-point titers were corrected for a 45% increase in maternal plasma volume expansion in the mother at delivery.

The Regional Ethical Review Board in Lund, Sweden approved this study. All mothers gave informed consent to participate in the SSM-Biobank and the DiPiS-biobank.

2.2. Antibody analyses

2.2.1. Glutamic acid decarboxylase 65 autoantibodies (GADA) and islet antigen-2 autoantibodies (IA-2A)

GADA and IA-2A antibody titers were determined in radioligand binding assays as described previously (Falorni et al., 1995). We previously defined GADA and IA-2A titers in the serum samples obtained at delivery from the