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Case Report

Thyroid Antibody Associated Recurrent Spontaneous Abortion

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Abstract

Background: Recurrent spontaneous abortion (RSA) remains unexplained in about 50% of cases after a standard evaluation. A subset of unexplained RSA may be thyroid antibody associated recurrent spontaneous abortion (TAARSA).

Cases: The three cases illustrate TAARSA with elevated thyroid antibodies and a euthyroid state. Treatment with low molecular weight heparin (LMWH) and low dose aspirin (LDA) was associated with live birth.

Conclusions: A subset of previously unexplained RSA may be identified as TAARSA. Treatment may prevent future pregnancy loss.

Keywords: Recurrent spontaneous abortions; Thyroid autoimmunity; Low molecular weight heparin; Circulating microparticles

Abbreviations: RSA: Recurrent Spontaneous Abortion; TAARSA: Thyroid Antibody Associated Recurrent Spontaneous Abortion; LMWH: Low Molecular Weight Heparin; LDA: Low Dose Aspirin; APA: Antiphospholipid Antibody; ACA: Anticardiolipin Antibody; LA: Lupus Anticoagulant; ATA: Antithyroglobulin Antibody; ATPA: Antithyroid Peroxidase Antibody; SQ: Subcutaneous; rFSH: Recombinant Follicle Stimulating Hormone; DSI: Donor Sperm Insemination; IUI: Intrauterine Insemination; HCG: Human Chorionic Gonadotropin; cMP: Circulating Microparticles; APS: Antiphospholipid Syndrome; EVTC: Extravillous Trophoblast Cells; MMP: Matrix Metalloproteinases

Introduction

RSA, defined as 2 or more consecutive pregnancy losses, affects about 2-3% [1] of women achieving pregnancy. The experience takes a heavy emotional, physical and financial toll on patients and their families. Currently accepted testing for uterine anatomic abnormalities, Antiphospholipid antibodies (APA) and karyotypic abnormalities of the parents leave about 50% of RSA unexplained. The lack of clear causality and treatment to prevent repeat episodes adds to the burden of this diagnosis.

Testing for thyroid function is considered appropriate for RSA evaluation. Documentation exists that women with euthyroid states have a lower rate of miscarriage than those with overt or subclinical hypothyroidism. Thyroid autoimmunity and miscarriage risk has a pooled odds ratio of 2.55 [1]. The purpose of this report is to illustrate a basis for considering a diagnosis of TAARSA along with treatment and rationale for this approach.

Case

A 32-year-old G3P1021 presented with a full term spontaneous vaginal delivery, followed by a first trimester miscarriage and a biochemical pregnancy. She had an adequate ovarian reserve and TSH was 2.81 micro IU/ml Lupus anticoagulant (LA), Anticardiolipin antibody (ACA) and Antinuclear antibody (ANA) were negative. Antithyroid peroxidase antibody (ATPA) was 35 micro IU/ml and antithyroglobulin antibody (ATA) was 103 micro IU/ml (normal<60 micro IU/ml for both antibodies). Enoxaparin (LMWH) 30 mg subcutaneous (SQ) and LDA 81 mg daily was started 2 days after the LH surge was noted on the ovulation predictor kit. This treatment was continued until 36 weeks of gestation and resulted in successful vaginal delivery at 37 4/7 weeks.

A 27-year-old, G0, had a first trimester miscarriage after a clomiphene citrate cycle and donor sperm insemination (DSI). L-thyroxine of 0.025 mg improved her TSH from 5.36 to 3.53 micro IU/mL. (Normal range- 0.35 - 5.5 micro IU/mL). Repeat clomiphene citrate with DSI resulted in a biochemical pregnancy. Her ATPA and ATA were 389 micro IU /mL and 134 micro IU/mL respectively. LA, ACA and ANA were negative. She conceived the third time with the use of recombinant follicle stimulating hormone (rFSH) and the L-thyroxine was increased to 0.05 mg. LMWH 30 mg SQ and LDA daily was started on the night of DSI and was continued until 10 days prior to delivery. She delivered vaginally at 39 1/7 weeks. Before the fourth conception, L-thyroxine 0.05 mg daily brought the TSH from 4.99 to 2.28 micro international units/ml. ATPA and ATA remained elevated at 348 micro IU/ml and 237 micro IU/ml respectively. She conceived again with rFSH, using LMWH and LDA during pregnancy until 38 weeks and delivered at 40 weeks.

A 31-year-old G2P0020, presented with two 6-week Spontaneous Abortions (SAB). Her TSH was 2.56 micro IU/mL, ATPA elevated at 68 micro IU/ ml and negative ATA, ANA, LA, ACA. Her third pregnancy resulted in first trimester miscarriage at 9 weeks with LDA and vaginal progesterone. Two clomiphene citrate cycles with Intrauterine Insemination (IUI) and LDA resulted in a biochemical pregnancy and a negative pregnancy test. Treatment with rFSH and IUI resulted in a twin conception. LMWH 30 mg SQ daily and LDA daily was initiated after two human chorionic gonadotropin (HCG) levels showed a rise. LMWH was changed to heparin a week prior to the cesarean section, which was performed at 35 5/7 weeks.

Comment

The case reports illustrate that thyroid antibody elevations mark an effect associated with an increased risk of SAB despite a euthyroid state, whether that euthyroid state is achieved with or without treatment. The

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pathology occurs with elevations of ATPA, ATA or both. The effect is also seen at both low and high levels of elevations of the thyroid antibodies above the normal range.

Each of these patients experienced biochemical pregnancies. These pregnancies should be accounted for in documenting RSA in this population. Discounting biochemical pregnancies in clinical practice or research underestimates the burden of SAB associated with TAARSA. All of these patients present with TSH in the upper normal range. This is typical of patients with thyroid autoimmunity and portends an increased future risk of hypothyroidism [2].

Treatments involving LMWH and LDA were reported in two studies involving unselected populations of recurrent aborters. Neither of the studies tested to identify thyroid antibodies. Tzafettas et al. reported a 92.2% live birth rate in 38 women with unexplained RSA using LMWH and LDA [3]. Dolitzy et al. used either LMWH 40 mg (n=54) or 100 mg aspirin (n=50). Both treatment groups had similar overall live birth rates (81.5% vs 84%) and in primary aborters (94% vs. 81%) [4].

Several theories have been proposed to explain the pathogenesis of RSA in euthyroid women with thyroid autoantibodies including heightened autoimmunity against the feto-placental unit, direct involvement of thyroid antibodies, higher age and presence of a concomitant subtle degree of subclinical hypothyroidism. Overall, it could be an expression of a more general maternal immune system abnormality [5].

Alterations in Circulating Microparticles (cMP) may be the common link joining TAARSA with the observed success of treatment with LMWH and LDA as seen in Antiphospholipid Syndrome (APS). The location of dysfunction in TAARSA, like APS, may be at the uteroplacental interface where cMP are thought to be an important communicator in maternal-placental cross talk. Elevated cMP, especially endothelial cell

derived, is associated with RSA in APS [6]. These cMP are derived from exocytic budding from platelets, B and T lymphocytes, endothelial cells and antigen presenting cells and result in exposing new negatively charged phospholipids from cell membranes [7]. These newly exposed phospholipids on the outer membrane leaflet offer multiple binding sites for the coagulation factors II, Va, Xa and tissue factor thus providing cMP pro-coagulant activity. The cMP also serve as protein and lipid receptor transporters from parental cells to the acceptor cells and render them responsive to new stimuli. They can promote recruitment of inflammatory cells and trigger inflammation by activating the complement cascade and cytokine release. Thus, cMP may play a role in the pathogenesis of vascular placental injury, with possible endothelial and trophoblastic cell dysfunction and induction of RSA [8].

Implantation is a complex process, which involves the selectin adhesion system for the initial step. At the time of implantation, Extravillous Trophoblast Cells (EVTC) proliferates and then invades once they come in contact with the maternal decidua. The addition of LMWH to *in vitro* preparations of EVTC derived from SABs induced increased cellular invasion by reducing E-cadherin expression [9]. LMWH also seems to significantly enhance *in vitro* total and active Matrix Metalloproteinases (MMPs) and decrease tissue inhibitors of MMPs (TIMP-1 and TIMP-2) thereby promoting normal placentation [9]. Furthermore, heparin conferred resistance to apoptosis triggered by proinflammatory cytokines and thrombin and increased tissue factor pathway inhibitor secretion from endothelium and trophoblasts thereby blocking the coagulation cascade [10]. *In vivo* studies in pregnant mice with APS demonstrated that treatment with heparin prevented the complement activation induced by APA, and inhibited chemotaxis and adhesion limiting tissue injury [9]. Heparin is proangiogenic and possesses the ability to inhibit lipopolysaccharide-induced proinflammatory cytokines (TNF-a, interleukin 6, 8, and 1b), involved in recurrent fetal loss of a murine model [11].

It is common to have multiple contributory factors to RSA and it may be difficult to isolate a single clear cause. Despite the intent to use "clean" cases for illustration purposes (age < 35, no obesity, diabetes, hypertension, other known systemic disease, APA, ANA, no history of infertility, diminished ovarian reserve or anatomic abnormality), patents 2 and 3 had ovulation induction which could influence their results.

Ideally, future study should document that TAARSA occurs in euploid fetuses. This population should then be prospectively randomized to a treatment or no treatment group with LMWH and LDA. Additionally, basic science research should continue to elucidate the mechanisms of dysfunction at the uteroplacental interface for better understanding of TAARSA. Investigations can evaluate whether thyroid antibodies are associated with elevations or changes in cMP and mediate reactions like those of APA and LA.

In summary, clinical observation suggests that TAARSA may be a subset of currently unexplained RSA. LMWH and LDA may be effective in mitigating the increased risk of pregnancy loss in TAARSA. Validation awaits clinical trials and further explanation of pathophysiology.

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