Journal of Reproductive Immunology 99 (2013) 17–23

Contents lists available at SciVerse ScienceDirect

Journal of Reproductive Immunology

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

Skin test reactivity to female sex hormones in women with primary unexplained recurrent pregnancy loss☆

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ARTICLE INFO

Article history:
Received 24 January 2013
Received in revised form 10 April 2013
Accepted 23 April 2013

Keywords:
Estrogen
Progesterone
Recurrent pregnancy loss
Sex hormone hypersensitivity
Skin test

ABSTRACT

The objective was to examine the hypothesis that primary unexplained recurrent pregnancy loss might be associated with an inappropriate immunologically mediated response to progesterone and/or estrogen. This prospective study included 47 women with two or more documented consecutive early pregnancy losses of unknown etiology, and no previous history of deliveries. Intradermal skin testing was performed in the luteal phase of the cycle (days 16–20) using estradiol benzoate, progesterone, and a placebo of refined sesame oil. Immediate (20 min) and late (24 h and 1 week) skin test readings for all cases were compared with those of 12 parous women of comparable age with no history of spontaneous miscarriages, premenstrual disorders, pregnancy, or sex hormone-related allergic or autoimmune diseases. Main outcome measure was skin test reactivity to estradiol and/or progesterone. Immediate skin test reactivity to both hormones was observed among half of the cases at 20 min. A papule after 24 h, which persisted for up to 1 week, was observed among 32 (68.1%) and 34 (72.3%) cases at the sites of estrogen and progesterone injection, respectively. 55.3% of cases had combined skin test reactivity to both estradiol and progesterone at 1 week. All women in the control group showed absence of skin test reactivity for both estradiol and progesterone at 20 min, 24 h, and 1 week. None of the subjects in either group showed skin test reactivity to placebo. There is an association between primary unexplained recurrent pregnancy loss and skin test reactivity to female sex hormones.

1. Introduction

The American Society of Reproductive Medicine (ASRM) practice committee recently redefined recurrent pregnancy loss (RPL) as the occurrence of two or more documented failed clinical pregnancies (Practice Committee of the American Society for Reproductive Medicine, 2013). The incidence of RPL is estimated to be 1–2% of fertile women (Bricker and Farquharson, 2002), and unfortunately more than 40% of the cases of RPL have unidentifiable causes (Jaslow et al., 2010).

Progesterone is a key player in the initiation and maintenance of pregnancy through complex endocrine and immune interactions (Li et al., 2004) and via contributing to complex regulatory pathways responsible for fetal

Abbreviations: ASRM, American Society of Reproductive Medicine; BMI, body mass index; ESHRE, European Society of Human Reproduction and Embryology; IQR, interquartile range; RPL, recurrent pregnancy loss; SIGEP, Special Interest Group for Early Pregnancy; SPSS, Statistical Package for Social Sciences; Th-2, T helper 2; WMA, World Medical Association.

☆ This study was conducted in: Recurrent pregnancy loss clinic of Ain Shams University Maternity Hospital, Abbasiya square, Cairo, Egypt [one of the largest maternity hospitals in Egypt that has almost 18,000 deliveries yearly].

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http://dx.doi.org/10.1016/j.jri.2013.04.006

allograft survival (Arck et al., 2007). On the other hand, it is also known to accelerate some autoimmune processes (Herzberg et al., 1995).

Intolerance to sex steroid hormones is not uncommon, and an abnormal immune response to sex hormones has been described in relation to a variety of disorders. Hypersensitivity and abnormal immune response-related diseases are more common in pregnancy and situations characterized by the presence of excess exposure to female sex hormones (Itsekson et al., 2011). Successful pregnancy is dependent on the presence of an appropriate immune response (Ledee-Bataille et al., 2004). Sex hormone allergy has been found to be associated with a variety of adverse reproductive outcomes.

In our study, we examined the hypothesis that primary unexplained RPL may be associated with an inappropriate immunologically mediated response to progesterone and/or estrogen.

2. Materials and methods

2.1. Study design, setting, and ethics

This prospective study was conducted at Ain Shams University Maternity Hospital over a one-year period after being approved by the Local Institutional Ethics and Research Committee. All the procedures in this research were carried out in accordance with the ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki), as last revised in the 59th WMA General Assembly, Seoul, October 2008.

2.2. Study population

Cases were recruited from among young women (<35 years old) who attended the RPL clinic with two or more documented consecutive early pregnancy losses of unknown etiology and who had no previous history of deliveries (objective evidence of pregnancy was required either in the form of a positive human chorionic gonadotropin test, a histopathology report showing chorionic villi, or an ultrasound report showing evidence of pregnancy).

2.3. Exclusion criteria

Women were excluded if one of the following was found to be a possible contributing factor to their pregnancy loss, according to the European Society of Human Reproduction and Embryology (ESHRE) Special Interest Group for Early Pregnancy (SIGEP) (Jauniaux et al., 2006):

(1) History of diabetes mellitus or an abnormal diabetic oral glucose tolerance test.
(2) History of thyroid disorders or an abnormal thyroid-stimulating hormone level.
(3) History of hyperprolactinemia or an abnormal serum prolactin level.
(4) History of antiphospholipid antibody syndrome or elevated anticardiolipin or lupus anticoagulant antibodies.
(5) History of uterine anatomical disorders.
(6) Documented maternal or paternal carrier state of chromosomal abnormalities.
(7) Women with severe allergies or an inflammatory illness at the time of the study or in the antecedent 4 weeks (note that those who had previously had allergies or atopic diseases were not excluded).

2.4. Participants' evaluation

All participants were formally counseled as regards the type, methodology, and value of the study, and those who agreed to participate in the study were thoroughly evaluated for the study inclusion and exclusion criteria. The following aspects of medical history were determined for all patients: age, special habits, occupational hazards, menstrual history, obstetric history, history of medical conditions (i.e., thyroid diseases, diabetes mellitus, infectious disease, and hypersensitivity), drug history (especially for those affecting the immune system), and family history of similar conditions and consanguinity. General examination included thyroid examination and measurement of vital data, body weight, height, and body mass index (BMI). The abdomen was examined to discover any detectable pathological lesions or organomegaly. Vaginal examination and pelvic ultrasound were then performed to assess uterine size and position and to discover any cervical or pelvic pathological conditions. Laboratory investigations included oral glucose tolerance test, serum thyroid-stimulating hormone, serum prolactin, anticardiolipin and lupus anticoagulant antibodies, and karyotypes of both partners when the probability of carrier status of structural chromosome abnormalities was suspected. As the current study was conducted in a low resource setting, the policy of selective chromosome analysis was adopted. The following four factors were combined to calculate the probability of carrier status: low maternal age at second miscarriage, presence of more than two miscarriages, presence of more than one miscarriage in a brother or sister of either partner, and presence of more than one miscarriage in the parents of either partner (Franssen et al., 2005, 2007). Parental karyotyping was performed only if the carrier status probability was calculated to be $\geq$2.2% (Jauniaux et al., 2006).

2.5. Control group

The control group consisted of 12 healthy parous women of comparable age with the cases and with no history of spontaneous miscarriages, premenstrual disorders, pregnancy, or sex hormone-related allergic or autoimmune diseases.

2.6. Skin testing

Intradermal skin testing was performed for all subjects using estradiol benzoate dissolved in refined sesame oil (Folon®; Misr company for pharmaceuticals, Egypt), progesterone dissolved in refined sesame oil (Luton®; Misr