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## Skin test reactivity to female sex hormones in women with primary unexplained recurrent pregnancy loss<sup>☆</sup>

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### 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.

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**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.

<sup>☆</sup> 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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### 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

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

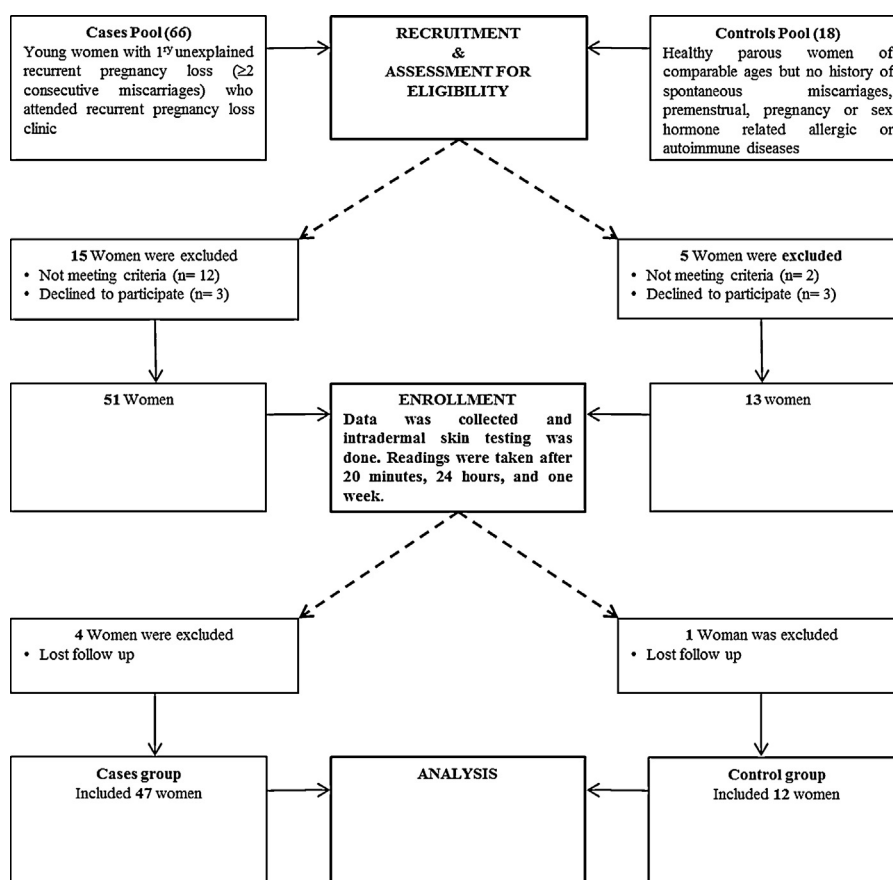


Fig. 1. Flowchart of the study participants.

Company for Pharmaceuticals, Cairo, Egypt), and a placebo of refined sesame oil (Salzgitter Mannesmann International GmbH, Germany). As a matter of standardization, and, because many allergic conditions have been reported to be exacerbated during the luteal phase (Caase and Reid, 2001), testing was performed during the luteal phase of the cycle (days 16–20). The test was performed according to the general considerations for skin test procedures in the diagnosis of drug hypersensitivity (Brockow and Romano, 2008). After sterilization with 70% ethyl alcohol, an intradermal injection of 0.02 mL estradiol benzoate, progesterone, and refined sesame oil was performed in the volar aspect of the forearm, raising a small bleb measuring 3 mm in diameter. Certain drugs including H<sub>1</sub>-antihistamines, imipramines, phenothiazines,  $\beta$ -adrenergic drugs, and glucocorticosteroids were discontinued prior to skin testing (Demoly et al., 1998), and the participants were free of any infectious diseases, fevers or inflammatory reactions at the time of testing.

Readings were taken after 20 min for immediate reactions. The method of documentation was outlining the injected area immediately after injection and then outlining the reaction area after 20 min on a translucent cellophane tape. Immediate reactions were considered

positive when the diameter of the initial wheal increased by 3 mm or greater and was associated with a flare or erythema. Readings were taken again after 24 h, for evidence of papules or induration. A persistent papule lasting for more than 24 h was required to consider a delayed reaction to the injected hormones (Itsekson et al., 2004). Accordingly, the participants were re-assessed after 1 week for evaluation of delayed reactions. Delayed reactions were assessed by morphological examination for the presence of erythema, edema or induration, and were documented by measuring the diameter of erythema, papulation/infiltrate.

## 2.7. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows, version 15.0. Variables were presented as mean and standard deviation for quantitative parametric data, median and interquartile range (IQR) for quantitative non-parametric data, and number and percentage for qualitative data. Variables of two groups were compared using Student's *t*-test for quantitative parametric data and Mann–Whitney *U* test for quantitative non-parametric data. *P* value < 0.05 was taken to denote statistical significance.

**Table 1**

Comparison of cases and controls as regards the parameters studied.

|                                   | Cases group (47) | Controls group (12) | P                 |
|-----------------------------------|------------------|---------------------|-------------------|
| Age (years)                       | 27.47 ± 5.63     | 25.58 ± 4.34        | 0.29              |
| Age at Menarche (years)           | 12.13 ± 0.99     | 11.91 ± 1.73        | 0.58              |
| Menstrual cycle duration (days)   | 29.51 ± 1.25     | 29.50 ± 2.71        | 0.98              |
| Menstrual period duration (days)  | 4.09 ± 0.78      | 4.50 ± 1.09         | 0.13              |
| Gravidity (number of pregnancies) | 3 (3–5)          | 2.5 (1.25–5)        | 0.20              |
| Parity (number of deliveries)     | 0 (0–0)          | 2.5 (1.25–5)        | 0.00 <sup>a</sup> |
| Weight (kilograms)                | 67.23 ± 5.59     | 65.75 ± 7.77        | 0.45              |
| Height (meters)                   | 1.57 ± 0.05      | 1.59 ± 0.04         | 0.18              |
| BMI                               | 27.15 ± 2.11     | 25.93 ± 3.34        | 0.12              |
| OGTT fasting (mg/dl)              | 82 (76–90)       | 84 (77.25–89)       | 0.54              |
| OGTT 1 h postprandial (mg/dl)     | 122 (110–135)    | 120 (99.25–129)     | 0.42              |
| OGTT 2 h postprandial (mg/dl)     | 100 (85–106)     | 95 (90–99)          | 0.84              |
| OGTT 3 h postprandial (mg/dl)     | 82 (73–87)       | 83.5 (78.5–99)      | 0.39              |
| Serum TSH level (μIU/ml)          | 2.55 ± 0.84      | 2.86 ± 0.77         | 0.25              |
| Serum prolactin level (ng/ml)     | 7.77 ± 5.84      | 10.87 ± 3.53        | 0.09              |
| Anticardiolipin-IgG level (U/ml)  | 11.27 ± 6.33     | 11.02 ± 4.57        | 0.90              |
| Anticardiolipin-IgM level (U/ml)  | 5.72 ± 3.12      | 6.32 ± 2.31         | 0.54              |
| Lupus anticoagulants (seconds)    | 33.11 ± 3.39     | 35.00 ± 3.07        | 0.09              |

All values are presented as mean ± standard deviation, SD, except for parity, gravidity and OGTT results, which are presented as median (Interquartile range, IQR)

<sup>a</sup> Statistically significant; BMI: body mass index; IgG: immunoglobulin G; IgM: immunoglobulin M; OGTT: oral glucose tolerance test; SD: standard deviation; TSH: thyroid-stimulating hormone.

### 3. Results

The participants' flowchart is shown in Fig. 1; the data of 59 women were statistically analyzed, including 47 cases and 12 healthy controls. As shown in Table 1, both cases and controls were of comparable age. There was no statistically significant difference between them regarding age at menarche, duration of menstrual periods or cycle, weight, height, or BMI. All the laboratory parameters studied were comparable in cases and controls. The median (IQR) of the total number of miscarriages among cases was 3 (IQR, 3–5), and those of the first trimester, the second trimester, spontaneous and induced miscarriages were 3 (IQR, 2–4), 0 (IQR, 0–1), 3 (IQR, 2–4), and 1 (IQR, 0–2) respectively. Parental karyotyping was performed for 39 cases as their carrier status probability was calculated to be ≥2.2%. The remaining 8 cases had a score of 1.6; thus, parental karyotyping was not performed.

Results of skin test reactivity to estrogen and progesterone at 20 min, 24 h, and 1 week among cases are shown in Table 2. Almost half of the cases had an immediate hypersensitivity reaction to both hormones at 20 min. Furthermore, the majority of cases showed a papule or induration at the site of hormone injection after 24 h. This delayed reaction persisted after 1 week among 32 (68.1%)

and 34 (72.3%) cases at sites of estrogen and progesterone injection respectively. After 1 week, 26 (55.3%) cases had a positive reaction for both estradiol and progesterone (Fig. 2). In contrast, none of the controls had any positive skin test reactivity to either estradiol or progesterone at 20 min, 24 h, or 1 week. None of the subjects in either group showed positive skin test reactivity to placebo, suppuration at the site of injection, draining lymph node enlargement or anaphylactic reactions.

### 4. Discussion

According to some experts, almost 20% of women with RPL have autoimmune etiologies, and a further 50% have unknown causes including non-antiphospholipid antibody-related thrombophilic tendencies (Ford and Schust, 2009). Following this reasoning, around 65–70% of RPL cases have immunological causes, including autoimmune and cellular immune abnormalities (Kwak-Kim et al., 2010).

Premenstrual dermatoses have been attributed to estrogen hypersensitivity (Shelley et al., 1995). Progesterone dermatitis presents with cyclic premenstrual urticaria and angioedema due to hypersensitivity to the endogenous progesterone (Snyder and Krishnaswamy,

**Table 2**

Skin test reactivity to estradiol and progesterone at 20 min, 24 h and one week among cases.

| Hypersensitivity skin test result |                |              |            |            |
|-----------------------------------|----------------|--------------|------------|------------|
| Material injected                 | Reading result | Reading time |            |            |
|                                   |                | Immediate    | Delayed    |            |
|                                   |                | At 20 min    | At 24 h    | At 7 days  |
| Estradiol                         | Positive       | 24 (51.1%)   | 32 (68.1%) | 32 (68.1%) |
| Progesterone                      | Positive       | 22 (46.8%)   | 36 (76.6%) | 34 (72.3%) |

All values are presented as number (%).

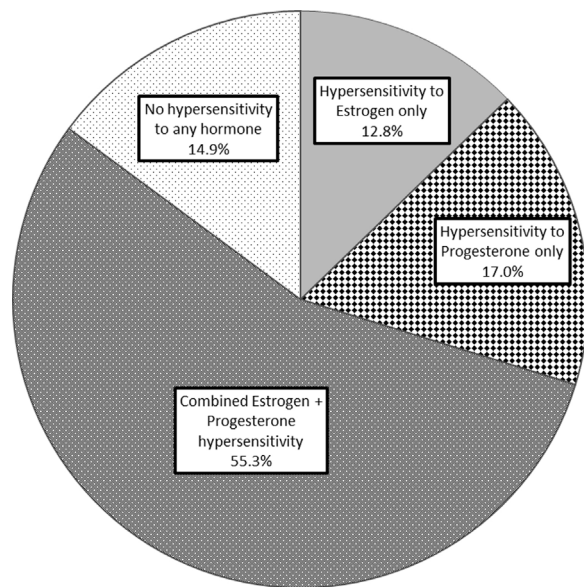


**Fig. 2.** Skin test reactivity to estradiol and progesterone among cases after one week.

2003). Hypersensitivity to estrogen or progesterone plays an important role in women with premenstrual syndrome and its related skin diseases (Itsekson et al., 2004).

Disorders related to hypersensitivity and abnormal immune responses are more common in situations characterized by the presence of excess exposure to female sex hormones like pregnancy, menstrual cycle, use of contraceptive pills, or exposure to environmental estrogens (Itsekson et al., 2011). Also, sex hormone allergy has been found to be associated with a variety of adverse reproductive outcomes such as hyperemesis gravidarum (Mabray et al., 1982), increased risk of preterm delivery in women with prior dysmenorrhea, (Juang et al., 2007), and infertility secondary to peri-implantation pregnancy failure in women with progesterone hypersensitivity (Cheesman et al., 1982; Prieto-Garcia et al., 2011). Uterine receptivity, implantation, and a subsequent successful pregnancy are all dependent on the presence of an appropriate immune response that is regulated by several growth factors and cytokines (Ledee-Bataille et al., 2004).

Over 80% of subjects with autoimmune diseases are female (Eaton et al., 2007; Gleicher and Barad, 2007); one of the proposed factors in this predominance are the female sex hormones (Selmi, 2008). Urticaria, angioedema, and anaphylaxis are all more frequently encountered in adult females than in males, with reversed gender difference among children (Poulos et al., 2007). Also, the predominance of eczema among females is limited to the reproductive age (Osman et al., 2007); thus, differences in sex hormones may be the playmaker in this phenomenon (Kasperska-Zajac et al., 2008).

The presence of IgG, IgM or IgE antibodies against steroid hormones has been previously described. Although high levels of antibodies against 17-hydroxyprogesterone were detected, followed by progesterone, hydrocortisone, and then estrogen, none was detected against the

parent compound of steroids (cholesterol), indicating the specificity of these antibodies toward certain chemical structures (Roby et al., 2006). Sex steroids may also induce the immune system leading to autoantibody formation (Beagley and Gockel, 2003). This inadequate immune response to sex hormones, especially progesterone, may lead to some sort of luteal phase defect by hindering progesterone from performing its physiological actions (Itsekson et al., 2007), with subsequent implantation and pregnancy failure. This point should be considered by obstetricians who give empirical progesterone supplementations to support pregnancy in women with unexplained RPL.

The development of an abnormal immune response to sex steroids may develop during a previous miscarriage or a previous exposure to contraceptive pills, or as a result of a cross-reaction to typically used corticosteroids (Schoenmakers et al., 1992; Wilkinson and Beck, 1994). Unfortunately, there is no simple laboratory test that can diagnose hormone hypersensitivity. As the skin is the most common organ that manifests the signs of hormone allergy, skin testing was used by several authors to diagnose the presence of hypersensitivity to sex hormones (Miura et al., 1989; Shelley et al., 1995; Itsekson et al., 2004, 2007; Farage et al., 2009; Prieto-Garcia et al., 2011). Itsekson et al. (2004) further concluded that estradiol and/or progesterone hypersensitivity played a pathogenic role in women with premenstrual syndrome and skin diseases related to it, and that intradermal skin testing with estradiol and progesterone represented a valuable diagnostic method for women with premenstrual syndrome and related dermatological conditions.

To our knowledge, there is only one study in the literature on the relationship between unexplained RPL and hypersensitivity to female sex hormones (Itsekson et al., 2007). Similar to that study, our results showed a significant association between primary unexplained RPL and skin test reactivity to the female sex hormones estrogen and progesterone. Positive skin test reactivity to both estradiol and progesterone was observed at 20 min in almost half of the cases. The frequency of this reactivity further increased among cases at 24 h, and for up to 1 week. There are several possible mechanisms for this hormone allergy. One of these mechanisms includes the binding of estrogen, progesterone, or their metabolites to blood proteins, thus acting as antigens. This promotes the development of T helper 2 (Th-2) lymphocytes, stimulating synthesis of IgE or other antibodies. When these antibodies bind to mast cells with their corresponding antigens (hormones or metabolites), mast cell or basophil degranulation ensues, leading to the release of histamine, leukotrienes, and Th-2 cytokines. The resultant reaction is an immediate hypersensitivity reaction observed after 20 min or a late-phase reaction occurring within several hours. A second mechanism implies that a lymphocytic reaction to the complex occurs when the hormone binds to proteins. This reaction stimulates lymphocyte proliferation and cytokine synthesis. The resultant reaction is a delayed hypersensitivity reaction, observed from 24 h up to several days later (Roby et al., 2006). These mechanisms may also resemble those of drug hypersensitivity (Schnyder and Pichler, 2009).

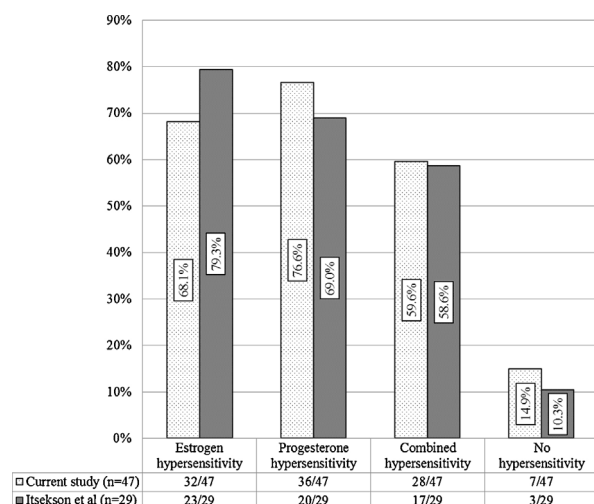


**Fig. 3.** Results of the current study in comparison to those of Itsekson et al. (2007).

Fig. 3 compares the results of the current study with those of the study by Itsekson et al. (2007). We observed that skin test reactivity to female sex hormones in our study was caused more frequently by progesterone than by estrogen, and late reactions recorded at 24 h were greater than immediate ones for both estrogen and progesterone. On the other hand, Itsekson et al. found greater skin test reactivity to estrogen than to progesterone, and they observed no difference between skin reactions at 24 h, 48 h or after 5 days. The dissimilarity to our study results can be partially attributed to the difference in population ethnicities between the two studies.

In the current study we used estradiol benzoate, progesterone, and a placebo of refined sesame oil, while Itsekson et al. (2007) used estradiol valerate, progesterone, made up in ethyl oleate with 10% benzyl alcohol, and a placebo of ethyl oleate with 10% benzyl alcohol. Refined sesame oil was used as a control because it was the vehicle in which the hormone was dissolved; thus, to confirm that any positive skin test reactivity was due to the injected hormone and not to the vehicle. Itsekson et al. (2007) used ethyl oleate for the same reason. We recruited only women with unexplained RPL of the primary type, as the presence of a previous successful pregnancy with a live birth was against our study hypothesis; this point has not been mentioned in the study by Itsekson et al. (2007).

In 2006, Roby et al. suggested the possibility of treating some hormone-related disorders by diagnosing the presence of hormone hypersensitivity and subsequently initiating desensitization (Roby et al., 2006). Progesterone-exacerbated chronic idiopathic urticaria was previously treated using a novel desensitization protocol (Poole and Rosenwasser, 2004). Desensitization therapy was also used effectively to alleviate premenstrual symptoms in women with hypersensitivity to female sex hormones (Itsekson et al., 2004). Rapid desensitization protocols have also been utilized successfully to achieve viable pregnancies in women with autoimmune progesterone dermatitis requiring in vitro fertilization (Prieto-Garcia et al., 2011).

From the present study, we conclude that there is a clear association between the presence of positive skin test reactivity to estrogen and progesterone and the occurrence of primary unexplained RPL. We recommend further larger studies to confirm this association, which could pave the way for considering clinical trials of desensitization as a treatment modality for women with primary unexplained RPL and hypersensitivity to female sex hormones.

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