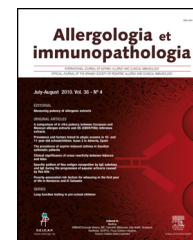


Allergologia et immunopathologia

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RESEARCH LETTER

Adverse reaction after administration of progesterone

To the Editor,

Progesterone is a hormone that inhibits contractions of uterus, facilitates the implantation of the embryo and maintains the pregnancy. In the pregnant uterus, progesterone plays a role in controlling the development of endometrial receptivity and in the processes of an angiogenesis and trophoblast invasion.^{1,2}

An inadequate secretion of progestogens in the early phases of pregnancy seems to be related to many cases of miscarriage. Therefore, a progesterone supplementation therapy has been used to prevent spontaneous pregnancy loss and also to prevent the preterm birth.³ There is some evidence, too, to indicate that women with idiopathic recurrent miscarriage may benefit from the immunomodulatory properties of progesterone in early pregnancy.⁴ In some cases vaginal progesterone therapy has been demonstrated effective to reduce the risk of miscarriage and without important side effects.⁵ However, until now there has been uncertainty about the real utility of routine use of progestogens to prevent miscarriage in pregnancy.⁶

We report a case of a 23-year-old Caucasian woman, with no significant past medical history, admitted to our Division of Allergy and Clinical Immunology, referring to an adverse reaction which occurred during the 9th week of her first pregnancy, to progesterone administered to prevent miscarriage. She had never before taken estroprogestins. She reported that after 2 h of intravaginal administration of 100 mg of progesterone, labial and hands angio-oedema appeared. Twenty-four hours after progesterone treatment, miscarriage occurred. Thus she underwent uterine curettage intervention, performed under general anaesthesia induced by administration of propofol and fentanyl. Before surgery she underwent premedication protocol, as indicated from "Memorandum SIAIC (Italian Society of Allergology and Clinical Immunology) on the diagnosis of allergy/intolerance to drugs". Premedication consists of the administration of prednisone 13 h, 7 h and 1 h associated to the intramuscular administration of chlorpheniramine maleate 1 h before surgery.⁷ When the woman came to our observation, after a physical examination which did not show any remarkable abnormality, a challenge test for the progesterone derivative hydroxyprogesterone was performed, with

a positive result (a wide itching wheal) 3 h after the intradermal injection of the undiluted drug. The tolerance test for the alternative medication is a procedure characterised by intradermal injection of scalar dilutions of the drug, followed by the administration of the whole dose of the drug.⁸

There are several data supporting the effective use of progesterone to prevent spontaneous miscarriage.⁹ We retain this case of interest because miscarriage, this time, seems to be a consequence of administration of progesterone.

To evaluate the causality connection between the adverse reaction and progesterone administration we applied the Naranjo adverse drug reaction probability scale.¹⁰ This algorithm permits to assign the likelihood of a drug to be the cause of an unexpected event. Through a ten-item questionnaire it assigns numerical values to arrive at an overall total score for probability assignment. Depending on the score obtained, the causality connection may be indicated as certain, probable, possible, unlikely. The total score of our case was 6, so the causality connection can be considered probable.

Hypersensitivity to progesterone is a rare clinical condition in which patients display hyper-sensitivity to endogenous or exogenous progesterone. It seems to occur as the result of an autoimmune response to endogenous progesterone production but can also be caused by exogenous intake of a synthetic progestin. This disorder has been reported to occur during pregnancy, in the postpartum period, in post-menopausal women taking hormone replacement therapy, and even in men taking exogenous synthetic progesterone.^{11,12}

The relationship between progesterone activity and the immune system has been investigated. Peripheral blood gamma delta T cells of pregnant women and peripheral natural killer cells express lymphocyte progesterone receptors. This recognition of foetal antigens is required for the initiation of progesterone-dependent immunoregulatory mechanisms.¹ Quite uncommon progestinic-induced side effects are hypersensitivity reactions. Cases of autoimmune progesterone anaphylaxis and dermatitis, due both to an autoimmune reaction to endogenous progesterone production, and to exogenous intake of a synthetic progestogen, have been reported. Moreover, progesterone-induced urticaria has also been described.¹³⁻¹⁵ However, progesterone seems to have a discrepant action because even if it contributes in suppressing the histamine release, still it

can cause potentiation of the IgE formation.¹⁶ The risk profile of progestogens is characterised by non-specific reported adverse effects (with incidence rates between 1% and 10%) common to substances belonging to this class of drugs. The most frequently-reported adverse effects are bleeding problems, headache, breast and pelvic pain, altered or depressed mood, nausea, acne and weight gain.¹⁷

In conclusion, we report a case of miscarriage probably caused by a hypersensitivity reaction to progesterone in a woman whose anamnesis revealed a link between the appearance of symptoms and the timing of the event. Successively, a positive response to an intradermal test with progesterone derivative hydroxyprogesterone was demonstrated. In the light of the common use of progesterone supplementation therapy to prevent spontaneous abortion and preterm birth and according to the possibility of occurrence of hypersensitivity reactions to progestogens, we suggest to evaluate the opportunity to ascertain this individual predisposition in pregnant.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

Patients' data protection.

Confidentiality of data

The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors have no conflict of interest to declare.

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