

# Hormone Allergy

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Allergy, hormone, IgE, IgG, IgM

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## Background

Estrogen and progesterone have been associated in women with symptoms that include asthma, migraine, dermatitis and pain.

## Objective

We suggest a connection between symptoms associated with hormone changes to a hormone antibody response.

## Methods

For IgG, IgM and IgE antibodies to progesterone, blood samples were obtained from 288 healthy control subjects by a commercial lab in California. Blood from 270 patients in Texas with changes in symptoms associated with menstrual cycles was examined. For IgE antibodies to both progesterone and estrogen, blood samples were obtained from an additional 32 healthy control subjects who had no symptoms related to menses and from 98 patients with symptoms associated with menstrual cycles. The symptoms were asthma, migraines and joint pain.

## Results

At 2 S.D. above the mean values of control subjects, a significant number of patients show high levels of IgG, IgM and IgE antibodies to progesterone and estrogen.

## Conclusions

This paper describes evidence of antibodies to the hormones estrogen and progesterone. Progesterone, estrogen and their metabolites, after binding to human tissue proteins, such as albumin or globulin, may act as antigens and promote Type 2 helper cell development, thereby regulating antibody synthesis and allergy. This leads to the possibility of treating a wide variety of disorders by determining hormone allergy and initiating desensitization. Two obvious applications for determination and treatment of hormone allergies are pre-menstrual asthma and menstrual migraines.

## Introduction

Many disorders have been associated with menstrual cycle influences, including acne, asthma, hereditary angioedema, aphthous ulcers, Behçet syndrome,

porphyria, epilepsy, myasthenia gravis, allergic rhinitis and migraines.<sup>1–10</sup> A recent review of autoimmune progesterone dermatitis<sup>11</sup> describes an allergic reaction to progesterone that can lead to severe dermatitis and anaphylaxis. Geber<sup>12</sup> described the first

documented case of cyclic urticaria associated with the menstrual cycle in 1921. He suggested a terminology of hormone allergy after demonstrating a flare in the disease by administering the patient's own pre-menstrual serum.<sup>1</sup>

As early as 1935, Riebel,<sup>2</sup> first, and then, in 1945 and 1947, Zondek and Bromberg<sup>13, 14</sup> advanced the concept of allergy to ovarian hormones. They performed skin tests on a healthy population and on patients with endocrine disturbances and found positive skin tests to endocrine test materials only in individuals with endocrine abnormalities. Furthermore, they were able to passively transfer this reaction to healthy individuals using sera from patients with hormone sensitivity. This positive skin reaction indicated that the serum contained specific antibodies to hormones.<sup>13</sup> While all these actions supported the theory of hypersensitivity to hormones, only 22 and 35 years later, steroid-binding globulin,<sup>15</sup> and 17-hydroxyprogesterone-binding immunoglobulin<sup>16</sup> were identified in the serum of a woman with periodic rashes.<sup>16</sup> This patient suffered from primary infertility and a history of recurrent oral and perineal rashes that appeared just prior to the midcycle rise in basal body temperature and subsided with the onset of menses. Sera obtained during the follicular and luteal phases of her cycle were found to contain a progestin-binding component having properties of IgG.<sup>16</sup>

Other clinical entities have been associated with hormone variations. Miller<sup>17</sup> and Mabray et al.<sup>18</sup> treated headache, joint pain, backache, breast pain and hot flashes utilizing allergy management with progesterone as an antigen. A review of menstrual related migraines suggests connections between menstrual cycles and frequency and severity of migraines.<sup>3</sup>

An extensive review article provides a great breadth of references on the impact of estrogen and progesterone on asthma.<sup>4</sup> Between 33% and 52% of asthmatic women experience pre-menstrual increases in asthma symptoms.<sup>5-9</sup> Another 22% report increasing asthma symptoms during menses.<sup>8</sup> These women experience higher rates of hospitalization each year.<sup>6</sup> Nearly 50% of women admitted to the hospital for asthma have been perimenstrual.<sup>10</sup>

Our paper describes high levels of IgG, IgM and IgE antibodies against estrogen and progesterone in women patients with perimenstrual symptoms and discusses the possible mechanisms of action.

## Methods

### Blood

Hormone levels are examined as part of our routine work-up of all adult allergy patients. When prick and sublingual tests with hormones resulted in changes in symptoms of asthma, migraine or joint pain, we began to test for hormone antibodies. Over the last 3 years we have tested 368 female patients for hormone antibodies.

For the first 2 years we tested only for IgM and IgG antibodies to progesterone as that was the hormone most commonly associated with symptom changes when used as a test antigen. Blood samples were taken from 270 female patients who experienced a change in symptoms associated with their menstrual cycle. The women were 24–47 years of age. Blood samples were obtained from 288 healthy control subjects by a commercial lab (Immunosciences Lab., Inc., Beverly Hills, CA, USA). During the last year we checked for IgE against both estrogen and progesterone using 288 healthy control female subjects from Immunosciences Lab., and from our clinic 32 healthy control subjects and 98 patients who noted perimenstrual symptom changes.

### Hormones, Antibodies and Reagents

Estradiol-bovine serum albumin (BSA) and progesterone-BSA, hydrocortisone, BSA, cholesterol, human serum albumin (HSA), BSA, phosphate buffer saline (PBS) and substrate para-nitrophenyl phosphate (PNPP) were purchased from Sigma Chemicals (St Louis, MO, USA). Alkaline phosphatase-labeled goat anti-human IgG, IgM and IgE were purchased from KPL (Gaithersburg, MD, USA).

### Enzyme-Linked Immunosorbent Assay for Estrogen and Progesterone Antibody

Enzyme-linked immunosorbent assay (ELISA) was used for testing for antibodies against estrogen and progesterone in the sera of healthy control subjects and of patients with pre-menstrual asthma, migraine or joint pain. Different rows of microtiter plates (Corning Inc. Product # 2592, Corning, NY, USA) were coated with either 100  $\mu$ L of BSA concentration of 10  $\mu$ g/mL or 100  $\mu$ L of estrogen-BSA or progesterone-BSA optimal concentration of 10  $\mu$ g/mL in 0.1 M carbonate-bicarbonate buffer (pH 9.5). Plates were

incubated overnight at 4°C and then washed three times with 200 mL of Tris-buffered saline (TBS) containing 0.05% Tween 20, pH 7.4. The non-specific binding of immunoglobulins (Igs) was prevented by adding a mixture of 1.5% BSA and 1.5% gelatin in TBS and then incubating this mixture for 2 h at room temperature and then overnight at 4°C. Plates were washed with PBS-Tween 20 and then 100 µL of control or patient's serum was added to duplicate wells coated either with BSA alone or with estrogen or progesterone bound to BSA. The optimal dilution of serum was determined by checkerboard dilution and found to be 1:100 for IgG and IgM and 1:2 for IgE. Plates were incubated for 2 h (for IgG and IgM) and overnight (for IgE) and then washed four times with PBS-Tween 20. Alkaline-phosphatase-conjugated goat anti-human IgG, IgM or IgE F(ab')<sub>2</sub> fragment at optimal dilution of 1:700 (IgG); 1:500 (IgM) and 1:250 (IgE) was added to corresponding wells. The plates were then incubated for an additional 2 h at room temperature. After washing five times with TBS-Tween buffer, the enzyme reaction was started by adding 100 µL of para-nitrophenylphosphate in 0.1 mL of diethanolamine buffer (1 mg/mL) containing 1 mM MgCl<sub>2</sub> and sodium azide, pH 9.8. The reaction was stopped 45 min later with 50 µL of 1 N NaOH. The optical density was read at 405 nm (OD<sub>405</sub>) with a microtiter reader. Optical densities coated with BSA alone were not more than 0.2. However, this non-specific OD was subtracted from wells coated with estrogen or progesterone bound to BSA.

### Specificity of Hormone Antibodies

Absorption of sera with specific and non-specific antigens was used to demonstrate that these anti-hormone antibodies are specific. Microtiter plates were coated with hormones and blocked by the addition of 2% BSA in PBST. A 100 µL of serum diluent buffer was added to all wells. Estrogen, estrogen-BSA, progesterone-BSA, BSA, myelin basic protein (MBP) and HSA starting at concentration of 1 mg/mL were added to the second rows of one to eight strips and titrated down the column in 1/2 log dilution. After 60 min incubation, 100 µL serum anti-estrogen or anti-progesterone were added to all wells. Addition of enzyme-labeled second antibody, after incubation and washing, resulted in color development, which was measured at 405 nm. Results were calculated as percentage of inhibition in antigen-antibody reaction.

### Reaction of 17- $\alpha$ -Hydroxyprogesterone- and Estrogen-Binding Antibodies to Other Hormones

The ELISA inhibition method was used to determine specificity and cross-reactivity between different hormones and to ensure the degree of human IgG, IgM and IgE estrogen or progesterone binding to estrogen or progesterone in solid phase. Different microtiter plates were coated with optimal concentration (100 µg/mL) of 17- $\alpha$ -hydroxyprogesterone, progesterone, estrogen, hydrocortisone and cholesterol, and blocked with 1% BSA + HSA. A 100 µL of sera from three different patients with high IgG, IgM or IgE antibodies against 17- $\alpha$ -hydroxyprogesterone was added to all wells. After shaking and incubation for 1 h at room temperature, addition of enzyme labeled anti-human IgG, IgM or IgE, was followed by incubation, washing and addition of substrate. Color development was measured at 405 nm. Results were calculated as percentage of anti-17- $\alpha$ -hydroxyprogesterone binding to 17- $\alpha$ -hydroxyprogesterone and other hormones. Also, anti-estrogen binding to estrogen and other hormones in solid phase by progesterone in liquid phase was performed and calculated in a similar manner.

### Inter- and Intra-Assay Precision

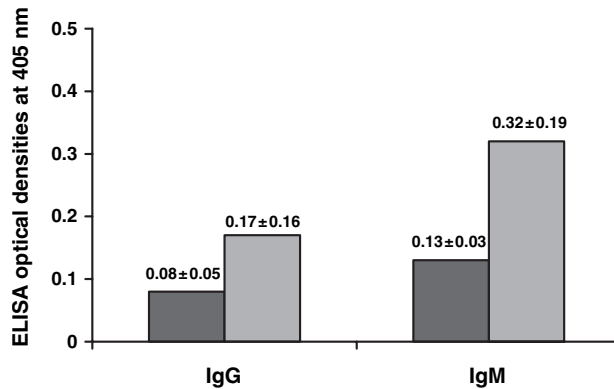
The inter-assay reproducibility was determined by assaying eight different samples in duplicate using the hormone antibody ELISA assay on each of five consecutive days. Each assay was performed using freshly prepared reagents. The % CV for samples with high OD (2.0 or greater) was between 5% and 8% and for the samples with optical densities of 0.5–1.0 was between 10% and 20%.

The intra-assay reproducibility was determined by assaying eight different samples, eight different times simultaneously. Each assay was performed using freshly prepared reagents. The percent CV for samples with OD between 1.0 and 2.5 was <10% and for the samples with optical densities of 0.5–1.0 was between 12% and 20%.

## Results

### IgG and IgM Against Progesterone

IgG, IgM and IgE antibodies against progesterone were measured in blood samples from 288 healthy females between the ages of 42–55 in the reference

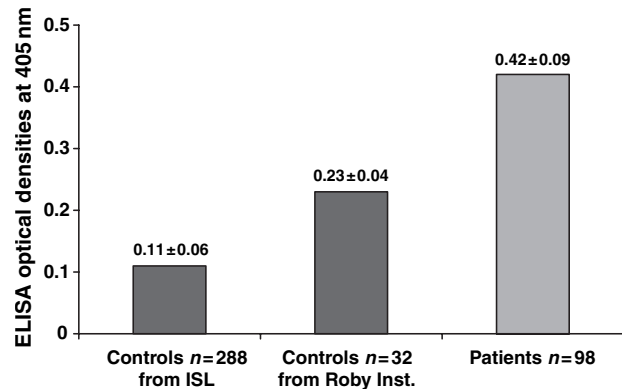


**Fig. 1** Mean  $\pm$  S.D. of ODs for IgG or IgM against progesterone in 288 controls ■ and 270 patients ■ with possible hormone allergy.

laboratory. Data presented in Fig. 1 shows that at a serum dilution of 1:100, ELISA OD values were  $0.08 \pm 0.05$  for IgG and  $0.13 \pm 0.03$  for IgM. At two standard deviations above the mean the ODs for the upper limit of normal was determined to be 0.18 for IgG and 0.19 for IgM. Based on these ranges 270 patients were tested for IgG and IgM. Their group mean OD was  $0.17 \pm 0.16$  for IgG and  $0.32 \pm 0.19$  for IgM. These values are statistically significant ( $P < 0.001$ ) when compared with controls. One hundred and thirteen (42%) patients had out of range high levels ( $>0.18$  OD) of IgG, IgM or both. Patients with out-of-range high for both IgG and IgM ODs (mean  $\pm$  S.D.), were  $0.75 \pm 0.11$  for IgM and  $0.62 \pm 0.09$  for IgG. Where IgG was out of range but not IgM, the average IgG score was  $0.57 \pm 0.08$  and where things were the converse, with IgM out of range but not IgG, the IgM score was  $0.57 \pm 0.04$ . It is interesting to note that the average scores for the group where both IgM and IgG were out of range are both larger than the corresponding average for out of range groups for IgG only or IgM only.

#### IgE against progesterone

The same 288 healthy female subjects were tested for IgE antibodies against progesterone; the OD mean  $\pm$  S.D. was found to be  $0.11 \pm 0.06$ . Sera from an additional 32 healthy female subjects from the same geographic region as the patients with possible hormone allergy area were tested; the OD mean  $\pm$  S.D. was  $0.23 \pm 0.04$ . At 2 S.D. above the mean (0.31 OD), four of the 32 control individuals were marginally above the normal range. In compar-

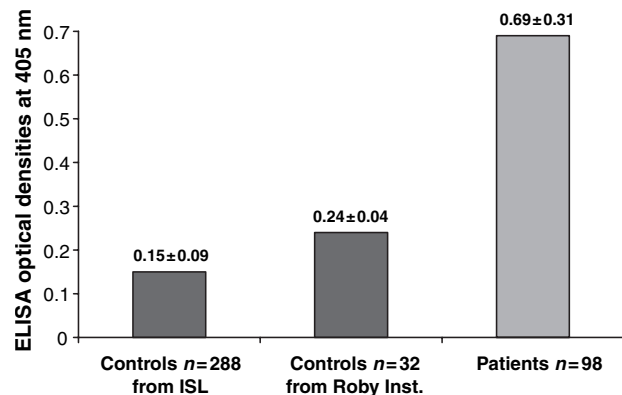


**Fig. 2** Mean  $\pm$  S.D. of ODs for IgE against progesterone in two groups of controls ■ and patients ■ with possible hormone allergy.

ison, the IgE antibody level against progesterone in sera from 98 patients was  $0.42 \pm 0.09$  (Fig. 2). Student's *t*-one tailed test gave highly significant differences between patients and controls ( $P < 0.0001$ ). 40 (41%) of 98 patients showed progesterone IgE levels greater than 0.31 OD, while 58 (59%) overlapped normal range but were predominantly 1 S.D. above the mean.

#### IgE Against Estrogen

Sera from 288 and 32 healthy female subjects and 98 patients were analyzed using ELISA assay for IgE against estrogen. The mean  $\pm$  S.D. for healthy groups was  $0.15 \pm 0.09$  and  $0.24 \pm 0.04$ . In sera from the 98 patients, the mean  $\pm$  S.D. for IgE antibody against estrogen was  $0.69 \pm 0.31$  (Fig. 3). Student's *t*-one tailed test gave highly significant differences between patients versus controls ( $P < 0.0001$ ).



**Fig. 3** Mean  $\pm$  S.D. of ODs for IgE against estrogen in two groups of controls ■ and patients ■ with possible hormone allergy.

**Table I** Percent Elevation of Antibodies Against Progesterone and Estrogen in Healthy Subjects and Patients with Possible Hormone Allergy at 2 S.D. Above the Mean of Optical Densities (ODs) Determined by ELISA

Antibody	Progesterone		Estrogen	
	Control [% (n)]	Patients [% (n)]	Control [% (n)]	Patients [% (n)]
IgG	3 (288)	21 (270)	N.D.	N.D.
IgM	7 (288)	33 (270)	N.D.	N.D.
IgE	11 (288)	41 (98)	2 (288)	54 (98)

N.D., not done.

At 2 S.D. above the mean (0.33 OD), six of 288 (2%) and 0 of the 32 control groups had estrogen IgE of >0.33 OD. When the same cutoff point was applied to the 98 patients' sera, 53 (54%) showed significant elevation in IgE anti-estrogen while 45 (46%) were within normal range. In seven different individuals, ELISA values as high as 1.5 or greater ODs were detected.

Table I summarizes the percent elevation of antibodies against progesterone or estrogen in healthy subjects and patients with possible hormone allergy at 2 S.D. above the mean of OD determined by ELISA.

#### Examination of Specificity of Estrogen and Progesterone Antibodies by Inhibition Studies

To examine whether antibodies to estrogen or progesterone are specific or cross-reactive, we performed competition ELISA by adding specific and non-specific antigens in liquid phase and examined prevention of serum antibody binding to the antigen in solid phase. Results showed that BSA, HSA, MBP and estrogen alone did not significantly absorb the serum IgG and IgE antibodies when they were added to the liquid phase. But addition of estrogen or progesterone-BSA significantly absorbed the IgG and IgE antibodies. This inhibition of anti-estrogen binding to estrogen by estrogen-BSA in liquid phase was between 52% and 67% and by progesterone-BSA was between 41% and 52%. For IgE anti-estrogen, this inhibition by estrogen-BSA was between 54% and 62% and with progesterone-BSA, from 37% to 43%. These results indicate that while antibodies against hormones are specific, they may be cross reacting between estrogen and progesterone. Similar results were obtained when progesterone antibodies

were absorbed with estrogen or progesterone bound to BSA.

#### Reaction of Progesterone- and Estrogen-Binding Antibodies to Different Hormones and Cholesterol

Human sera containing 17- $\alpha$ -hydroxyprogesterone IgG-, IgM- and IgE-binding antibodies were reacted against progesterone, estrogen, hydrocortisone and cholesterol. In comparison with 100% binding of anti-17- $\alpha$ -hydroxyprogesterone-binding to 17- $\alpha$ -hydroxyprogesterone, the IgG anti-17- $\alpha$ -hydroxyprogesterone-binding to progesterone, estrogen, hydrocortisone and cholesterol was 69–77%, 25–30%, 39–53% and <10%, respectively. The percent binding of serum IgM and IgE anti-17- $\alpha$ -hydroxyprogesterone to 17- $\alpha$ -hydroxyprogesterone, progesterone, estrogen, hydrocortisone and cholesterol were similar to the binding of IgG. Binding of anti-17- $\alpha$ -hydroxyprogesterone to progesterone was the highest, followed by hydrocortisone, then estrogen, to almost no binding with cholesterol. Similar to this, human sera with IgG, IgM and IgE binding antibodies against estrogen were reacted with progesterone, 17- $\alpha$ -hydroxyprogesterone, hydrocortisone and cholesterol, in the presence of estrogen. Results showed that the highest IgG, IgM and IgE anti-estrogen binding was first with estrogen (100%), then 17- $\alpha$ -hydroxyprogesterone (28–57%), followed by progesterone (26–35%). Binding of anti-estrogen antibodies to hydrocortisone and cholesterol was not significant.

#### Discussion

Many disorders have been associated with changes in the menstrual cycle. This data suggests the possibility of hormone allergy, which is supported by the following evidence:

- 1 As early as in 1945 first and then in 1947, only patients with endocrine disorders were found positive by skin test to different hormones. This reaction passively was transferred to healthy individuals. Positive skin reaction was attributed to specific antibodies to hormones. They were very successful in desensitizing this reaction.<sup>13, 14</sup>
- 2 Steroid-binding globulin antibodies were detected in women with periodic rashes.<sup>15</sup> These antibodies were detected during follicular and luteal phases of the cycle and reacted specifically with 17- $\alpha$ -hydroxyprogesterone.<sup>16</sup>

3 Different derivatives of estradiol and progesterone bound to serum proteins, including  $\beta$ -estradiol-6-carboxymethyl-BSA,  $\beta$ -estradiol-17-hemisuccinate, progesterone-11- $\alpha$ -BSA, progesterone-7-BSA, progesterone-3-carboxymethyl-BSA were prepared and are commercially available (Sigma Chemical Co., St. Louis, MO, USA). These derivatives were injected into animals, and monoclonal and polyclonal antibodies were prepared against them. Preparation of these antibodies is strong evidence for immunogenicity of estrogen and progesterone after their binding to carrier proteins.<sup>19, 20</sup>

Our data presented in this paper are the first to show the presence of IgM and IgE against different steroid hormones. When these antibodies were measured against progesterone, the highest levels were detected first against 17-hydroxyprogesterone, followed by progesterone, hydrocortisone and then estrogen. And where a patient demonstrated the highest levels of IgG, IgM or IgE antibodies against estrogen, these antibodies were detected significantly against 17-hydroxyprogesterone, followed by progesterone and hydrocortisone. No antibodies were detected against cholesterol. This lack of detection of antibodies against the parent compound of steroids (cholesterol) is the best indication of antibody specificity against certain chemical structures of steroids.

In a sample of three different patients IgG, IgM and IgE isotype antibodies were detected first at the highest level against 17- $\alpha$ -hydroxytestosterone, then against progesterone and hydrocortisone, these antibodies have an apparent binding affinity to OH-group at C<sub>11</sub> of 17- $\alpha$ -hydroxyprogesterone, estrogen or estrogen metabolites, including 2-HE, 4-HE and 16- $\alpha$ -HE. In relation to levels of these metabolites, carcinogenesis studies are informative. Most researchers agree that 4-HE and 16- $\alpha$ -HE can induce tumors in experimental animals.<sup>21, 22</sup> Researchers discovered that an enzyme known as cytochrome P-450 1B1 converts 17- $\beta$ -estradiol to 4-HE.<sup>23, 24</sup> Further, numerous enzymes can change 4-HE into compounds called 3,4-semiquinones and 3,4-quinones, which damages DNA and leads to tumor development.<sup>21</sup> In relation to 16- $\alpha$ -HE, epidemiological studies with 85 women showed that those who had lower 2-HE to 16- $\alpha$ -HE ratio in urine were more likely to go on to develop breast cancer than were women in whom that ratio was more in favor of 2-HE.<sup>25</sup> Critics cite the fact that estrogen is present in the body in too tiny quantities to produce enough by-products to worry about. But estrogen is also syn-

thesized directly in cells in target tissue, far exceeding the amount of the hormone in blood. As the tissue itself makes estrogen, there is enough present to make high levels of estrogen metabolism to make protein and DNA adducts. While the protein-hormone metabolite adducts may induce anti-hormone and anti-tissue antibodies, the DNA-hormone adducts may trigger DNA damage and cancer.<sup>19, 21, 22</sup>

The inhibition and cross-reaction of different sera containing IgG, IgM or IgE antibodies against estrogen and 17- $\alpha$ -hydroxyprogesterone with different hormone compounds presented in this study is further indication that hormone metabolites play a critical role in antibody production in these experiments.

Detection of high levels of IgG, IgM and IgE antibodies in the sera from a subgroup of patients and its inhibition by steroids-bound to BSA is an indication for reactions of steroids as haptens with body proteins and production of antibodies against this new antigenic epitope(s). And as the highest levels of antibodies were detected against 17- $\alpha$ -hydroxyprogesterone, we believe that OH-group at C<sub>11</sub> plays a role in the formation of this new antigenic material in a subgroup of patients with endocrine allergy. Data presented here clearly demonstrate that antibody formation against small molecules such as steroids occurs.

As early as 1957 estrogen and progesterone have been successfully bound to BSA or peroxidase.<sup>19, 20</sup> In fact, for these preparations, steroids were modified by the binding of amino acids of carrier proteins to OH-group of C<sub>11</sub>.<sup>26</sup> Therefore, when these hormones, whether from endogenous or exogenous source, rise to certain levels, hormone metabolizing enzymes get activated and form different metabolites. In individuals with specific HLA types and low or high levels of hormone metabolizing enzymes (cytochrome P150 1B1 and others) these metabolites bind to tissue proteins and induce immune response in a form of IgG, IgM and/or IgE production.

It is possible that several mechanisms of action are at work in the process of hormone allergy. One of these possibilities may be that estrogen, progesterone and their metabolites, after binding to different proteins, may act as antigens and promote T-helper-2 cell development, thereby regulating IgE or other antibody synthesis. The binding of these antibodies to mast cells with their corresponding antigens (hormones or metabolites) induce mast cell or basophil degranulation. This reaction leads to histamine release, TH2 cytokine and leukotriene secretion,

resulting in systemic anaphylaxis in the form of allergy or asthma.

A second possibility is that after hormones bind to blood proteins, different lymphocytes will react to this complex and induce lymphocyte proliferation and cytokine production, resulting in Type IV allergic reaction or delayed-type hypersensitivity. Based on the understanding of these mechanisms of actions, many disorders might be effectively treated by determining the presence of hormone allergy and the use of hormones as antigens to diminish symptoms by desensitization.

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