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Depletion of CD8⁺ Cells Abolishes the Pregnancy Protective Effect of Progesterone Substitution with Dydrogesterone in Mice by Altering the Th1/Th2 Cytokine Profile

Sandra M. Blois,* Ricarda Joachim,* Judith Kandil,* Ricardo Margni,† Mareike Tometten,* Burghard F. Klapp,* and Petra C. Arck²*²

One of the most remarkable immunological regulations is the maternal immune tolerance toward the fetal semiallograft during pregnancy, which has been referred to as immunity’s pregnant pause. Rejection of the semiallogeneic trophoblast cells must be selectively inhibited and pathways presumably include Th2 cytokines unopposed by Th1 cytokines. Steroid hormones, including progesterone, have similar effects. Low levels of progesterone and Th2 cytokines and high levels of Th1 cytokines are attributable for increased abortions in mammalian, which may be triggered by psychoemotional stress. Thus, the aim of the present study was to provide experimental evidence for the mechanism involved in the mediation of immune responses by endocrine signals during pregnancy and stress-triggered pregnancy failure. DBA/2J-mated CBA/J female mice were randomized in three groups: 1) control females, 2) mice exposed to stress on gestation day 5.5, and 3) mice exposed to stress and substituted with dydrogesterone, a progestogen with a binding profile highly selective for the progestogen receptor on gestation day 5.5. On gestation days 7, 9.5, and 10.5, mice of each group were sacrificed, and the frequency of CD8⁺ cells and cytokine expression (IL-4, IL-12, TNF-α, IFN-γ) in blood and uterus cells was evaluated by flow cytometry. Additionally, some mice were depleted of CD8 cells by injection of mAb. We observed that progesterone substitution abrogated the abortogenic effects of stress exposure by decreasing the frequency of abortogenic cytokines. This pathway was exceedingly CD8-dependent, because depletion of CD8 led to a termination of the pregnancy protective effect of progesterone substitution. The Journal of Immunology, 2004, 172: 5893–5899.

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Th1-type cytokines on mammalian pregnancy and on observations that pregnancy appears to be associated with a down-regulation of cell-mediated immunity manifested as reduced delayed-type hypersensitivity, it has been suggested that the Th1/Th2 balance could be a critical and a complex factor in the tolerance of the conceptus (8).

Data have indicated that a shift of Th1 to Th2 cytokines and suppression of NK cell cytolytic activity may be under the control of an immunomodulatory protein known as progesterone-induced blocking factor (PIBF)3 (27). PIBF is secreted by T cells, predominantly γδ TCRVα and CD8Vγ (24), upon interaction of progesterone with the progesterone receptors on such cells (28).

In successful pregnancies after immunotherapy (using the male partner’s blood as the source of leukocytes), systemic CD8Vγ-progesterone-receptorVγ cells were found to be significantly increased compared with preimmunotherapy (29). Because much of our understanding of early human pregnancy is inferred from studies in animals, we recently performed a pilot study to investigate the effect of the progesterone derivative dydrogesterone (6-dehydroretroprogesterone), a progesterone with a binding profile highly selective for the progesterone receptor (30), in stress-triggered murine abortion (31) and observed that stressed animals present lower systemic levels of progesterone and PIBF and a reduced expression of progesterone receptor at the fetomaternal interface (30). Injection of dydrogesterone increased levels of plasma PIBF in stressed mice, but did not affect progesterone levels.

Based on the notion that stress perception decreased levels of progesterone which in turn may result in a Th1-Th2 predominance with consequent abortion, we now investigated—upon confirming that stress during early gestation (day 5.5) boosts the abortion rate, which can be abrogated by the progesterone derivative dydrogesterone—whether 1) the percentage of CD8Vγ uterine cells was affected in stressed mice with and without dydrogesterone treatment over a period of 5 days after stress exposure, 2) the relative numbers of Th1 (TNF-α, IFN-γ, IL-12) and Th2 (IL-4) cytokine-producing cells in the uterus would be affected by stress or dydrogesterone treatment, respectively, and 3) depletion of CD8Vγ cells by injection of anti-Lyt 2.1 Ab would abolish the protective effect of dydrogesterone on the abortion rate in stressed mice by affecting the Th1/Th2 cytokine profile.

Materials and Methods

Animals

Mice were purchased from Charles River Breeding Laboratories (Sulzfeld, Germany) and maintained in an animal facility with a 12 h light/dark cycle. Animal care and experimental procedures were followed according to institutional guidelines and conformed to the requirements of the state authority for animal research conduct (LaGeSi, Berlin, Germany). DBA/2J-mated CBA/J female mice were randomized in different groups of females: 1) control mice that received s.c. injection of sterile filtered sesame oil (200 μl) on gestation day 5.5. The mice were sacrificed either on gestation day 7.5 (n = 7), 9.5 (n = 7), 10.5 (n = 7), or 13.5 (n = 7) for evaluation of the abortion rate and number of implants; 2) mice that were exposed to sound stress on gestation day 5.5 and also received a s.c. injection of 200 μl of sterile filtered sesame oil. Again, the mice were sacrificed either on gestation day 7.5 (n = 7), 9.5 (n = 7), 10.5 (n = 7), or 13.5 (n = 7) for evaluation of the abortion rate and number of implants; 3) mice that were exposed to gestation day 5.5 and received a s.c. injection of dydrogesterone (provided by Solvay Pharmaceutical, Hannover, Germany) at a concentration of 1.25 mg/200 μl of sterile filtered sesame oil on gestation day 5.5, before exposure to sound stress was commenced. As in 1) and 2), the mice were sacrificed either on gestation day 7.5 (n = 7), 9.5 (n = 7), 10.5 (n = 7), and 13.5 (n = 7) for evaluation of the abortion rate and number of implants; 4) in a second experiment, an additional group of mice (n = 20) was treated as in 3), and divided into two subgroups (n = 10 each) which received s.c. injection of anti-Lyt 2.1 (cat. no. 558733) (85 μg/200 ml PBS) CD8 depletion on day 6.5 or PBS alone. Because we knew from the previous experiments on the mice described in 1)-3) that gestation day 7.5 was a crucial day with respect to changes of the uterine cytokine equilibrium, we exclusively focused on the presence of cytokines on this particular day in the CD8 depletion experiments in five mice per subgroup in addition to the evaluation of the abortion rate and number of implants on day 13.5 (n = 5 for each subgroup).

Application of stress

The CBA/J mice were exposed to sound stress for the duration of 24 h starting on gestation day 5.5. The sound stress was emitted by a rodent

3 Abbreviations used in this paper: PIBF, progesterone-induced blocking factor; RT, room temperature.
FIGURE 3. CD8-positive decidual lymphocytes are decreased after stress exposure, dydrogesterone treatment restores them. A, The percentage of CD8⁺ cells within the uterine lymphocyte population in the various experimental groups on gestation days 7.5, 9.5, and 10.5. The data were obtained by flow cytometry and are presented as mean ± SEM. *, p < 0.05, **, p < 0.01, ***p < 0.001, as analyzed by the nonparametric Mann-Whitney U test. B, The percentage of CD8⁺ cells within the uterine lymphocyte population in stressed, dydrogesterone-treated mice with and without CD8 depletion on gestation day 7.5.

Abortion rate

Mice were sacrificed by neck dislocation on day 13.5, the uteri were removed, and the total number of implantations and resorbing sites (signs of abortion) was recorded. The abortion rate was calculated as percentages of resorption sites calculated from total number of implantations based on the following formula: % abortion rate = A/(A + V) × 100, whereby A means the number of dead placental units and V means viable placental units.

Blood cells

On gestation days 7.5, 9.5, and 10.5, mice of the respective groups were narcotized and blood cells were obtained by retro-orbital punction and collected in tubes containing heparin. After treatment with ammonium chloride lysis buffer for 10 min to deplete erythrocytes, the cells were washed twice with sterile PBS.

Blood cells were used for determination of phenotype (surface expression) and cytokine expression on cells by flow cytometry.

Uterus cell isolation

Utleri were removed and uterus cells were isolated by the method described by Marquez et al. (32), with some modifications. In brief, the uterus was washed with sterile PBS, carefully cut into small pieces, and collected in tubes containing HBSS and digested for 20 min at 37°C under slight agitation in HBSS with 1 mM DTT (cat. no. D-0632; Sigma-Aldrich, Munich, Germany). After that, the isolated cells were collected in a fresh tube through a 100-μm net (BD Biosciences, San Diego, CA) and washed with RPMI 1640 complemented with 10% FCS. The procedure was repeated twice, with HBSS medium containing no DTT. Mononuclear cells were purified by Lympholyte/M (cat. no. GT5030XX; Cedarslane Laboratories, Hornby, Ontario, Canada) gradient centrifugation. These cells were used to characterize surface and intracellular expression by flow cytometry.

Flow cytometric analysis

For flow cytometry, the blood and uterus cells were incubated for 3 h with brefeldin A (10⁶ cells/ml medium with 1 μl of Golgi Plug, 55-23011K; BD PharmMingen, Heidelberg, Germany) in RPMI 1640 with FCS in a humidified incubator at 37°C with 5% CO₂. Flow cytometry was performed using our standard protocol (31): briefly, uterus cells were washed twice with FACS buffer (PBS supplemented with 1% BSA (cat. no. A-9418; Sigma-Aldrich) and 0.1% sodium acide (Sigma-Aldrich)). Cells were then incubated for 30 min at room temperature (RT) with FITC-labeled Ab against CD8-α (cat. no. 553030). After the cells were washed and fixed using Fix solution (BD Biosciences, Erembodegem, Belgium), they were incubated for 30 min at RT in the dark. Subsequently, the cells were washed and permeabilized, using FACS Permeabilizing Solution (BD Biosciences), followed by incubation with intracellular Ab PE-labeled TNF-α (cat. no. 554419), IL-4 (cat. no. 554435), INF-γ (cat. no. 554412), IL-12 (cat. no. 554479), and IL-10 (cat. no. 554467) for 30 min at RT in the dark. As a control, cells were stained with the corresponding isotype-matched mAb. All mAbs were purchased from BD Biosciences. The cells were then washed and read. The acquisition was performed using a FACS Calibur (BD Biosciences). Instrument compensation was set in each experiment using single-color stained samples. Data were analyzed by using CellQuest software. Flow cytometry results were expressed as the percentage of cells positive for the surface marker evaluated.

Statistical analysis

Statistical significance was determined using the nonparametric Mann-Whitney U test. Significance was set at p < 0.05.

Results

Stress-triggered increase of the abortion rate could be abrogated by the progesterone derivative dydrogesterone

As depicted in Fig. 1A, we reproduced our previous findings that exposure to stress on gestation day 5.5 significantly boosts the abortion rate in DBA2/J-mated CBA/J females, as analyzed on gestation day 13.5, when resorption = abortion sites are visible (31). Further, substitution of progesterone with 1.25 mg of dydrogesterone on gestation day 5.5 significantly abrogated the stress-triggered increase of abortions. Neither stress nor dydrogesterone solution (BD Biosciences, Erembodegem, Belgium), they were incubated for 30 min at RT in the dark. Subsequently, the cells were washed and permeabilized, using FACS Permeabilizing Solution (BD Biosciences), followed by incubation with intracellular Ab PE-labeled TNF-α (cat. no. 554419), IL-4 (cat. no. 554435), INF-γ (cat. no. 554412), IL-12 (cat. no. 554479), and IL-10 (cat. no. 554467) for 30 min at RT in the dark. As a control, cells were stained with the corresponding isotype-matched mAb. All mAbs were purchased from BD Biosciences. The cells were then washed and read. The acquisition was performed using a FACS Calibur (BD Biosciences). Instrument compensation was set in each experiment using single-color stained samples. Data were analyzed by using CellQuest software. Flow cytometry results were expressed as the percentage of cells positive for the surface marker evaluated.

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<table>
<thead>
<tr>
<th>Treatment of Mice</th>
<th>Days</th>
<th>CD8⁺</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.5</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>Stress</td>
<td>7.5</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>Stress/dydrogesterone</td>
<td>7.5</td>
<td>13 ± 5</td>
</tr>
<tr>
<td>Control</td>
<td>9.5</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>Stress</td>
<td>9.5</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Stress/dydrogesterone</td>
<td>9.5</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>Control</td>
<td>10.5</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Stress</td>
<td>10.5</td>
<td>18 ± 6</td>
</tr>
<tr>
<td>Stress/dydrogesterone</td>
<td>10.5</td>
<td>15 ± 4</td>
</tr>
</tbody>
</table>

* Number of mice was n = 7 for each group.
* Numbers indicate day of gestation.
* Percentage of CD8⁻ lymphocytes among gated lymphocyte population, identified by size and granularity.

FIGURE 4. Stress exposure up-regulates the percentage of TNF-α-positive decidual cells; dydrogesterone abolishes this proinflammatory response. Percentage of TNF-α-positive cells within the uterine lymphocyte population of the various experimental groups on gestation days 7.5, 9.5, and 10.5. TNF-α-positive cells were identified by flow cytometry for intracellular proteins. The data are presented as mean ± SEM. *, p < 0.05, **, p < 0.01, as evaluated by nonparametric Mann-Whitney U test.
On gestation day 10.5, 5 days after stress exposure, levels of CD8+ cells had been restored back to levels seen in control mice. Interestingly, on day 9.5, mice exposed to stress presented a significant change (p ≤ 0.05) when compared to the “Control” groups for the respective gestational day. Bold numbers in the “Stress/dydrogesterone” groups reflect significant changes when compared to the “Stress” groups. Significance of difference was analyzed by the Mann-Whitney U test.

Differential expression of CD8+ cells in stressed mice

Now, we wished to determine the relative number of uterine CD8+ cells, because this population has been suggested to have a crucial role in pregnancy maintenance (8, 29, 33). As shown in Fig. 3A, stressed mice presented a significant decrease of the percentage of CD8+ uterine cells, as analyzed by flow cytometry, on day 7.5 of gestation compared with control mice. Strikingly, in stressed mice which received dydrogesterone, the percentage of CD8+ uterus cells had been restored back to levels seen in control mice. Interestingly, on day 9.5, mice exposed to stress presented a significantly higher percentage of CD8+ uterus cells, compared with control or stressed and dydrogesterone-treated mice. However, the percentages of CD8+ cells where at a lower level, compared with day 7.5 of gestation. On gestation day 10.5, we observed that the significant differences between the percentages of CD8+ uterine cells in the groups tested were no longer detectable.

We further looked at the expression of CD8+ in the peripheral blood cells by flow cytometry and found no significant effect of stress or dydrogesterone treatment with respect to CD8+ cells (Table I).

Influence of stress and dydrogesterone treatment on cytokine profile in uterus cells

As mentioned earlier, Th2-like cytokines appear to contribute to the maintenance of pregnancy, whereas Th1 cytokines have been shown to be deleterious for pregnancy. In the present study, we observed that on gestation day 7.5 and 9.5, stressed mice showed a significantly increased percentage TNF-α+ CD8+ uterine cells (Fig. 4).

On gestation day 10.5, 5 days after stress exposure, levels of TNF-α were back to the percentage seen in control mice. Interestingly, injection of dydrogesterone significantly lowered the relative number of TNF-α-producing uterine cells on days 7.5, 9.5, and even on 10.5. The absolute numbers of CD8+/TNF-α+ uterus cells are presented in Table II.

Further, we investigated the presence of the Th1 cytokines IFN-γ and IL-12 in uterus cells. As depicted in Fig. 5, nonstressed mice presented a significantly greater percentage of IFN-γ+ cells immediately after stress exposure, on gestation day 7.5, compared with stressed as well as stressed dydrogesterone-treated mice. However, on day 9.5, when the percentages in controls significantly decreased compared with day 7.5, this Th1 down-regulation was not present in stressed mice. When the stressed mice were treated with dydrogesterone, IFN-γ down-regulation did occur in uterine cells. On day 10.5, significant differences with respect to IFN-γ+ uterus cells were no longer detectable as the relative number was rather low compared with day 7.5. The absolute numbers of CD8+/IFN-γ+ and IL-12+ uterus cells are presented in Table II.

As presented in Fig. 7, stressed mice treated with dydrogesterone showed significantly higher percentages of pregnancy protective IL-4+ uterus cells beginning on gestation day 7.5 and, even more strikingly, maintained until day 10.5. The absolute numbers of CD8+/IL-4+ uterus cells are presented in Table II.

Depletion of CD8+ cells abolished the protective effect of dydrogesterone on the abortion rate in stressed mice by affecting the Th1/Th2 cytokine profile

To investigate whether the protective effect of progesterone substitution with dydrogesterone may be mediated by CD8+ cells, we specifically depleted this cell population using a mAb (33). As presented in Fig. 1B, we observed that the decrease of stress-triggered abortion in dydrogesterone-treated mice could be significantly abrogated if these mice have been CD8-depleted. Further,
the dydrogesterone-induced down-regulation of the Th1 cytokines TNF-α, IFN-γ, and IL-12 present in uterus cells has been abolished in the CD8-depleted mice (Fig. 8A). Depletion of uterine CD8⁺ cells by injection of Lyt 2.1 has been confirmed by flow cytometry, as presented in Fig. 3B. Interestingly, the ratio between Th1/Th2 cytokines in stressed mice changed upon depletion of CD8 cells; Fig. 8B depicts the predominance of Th1 cytokine levels in stressed, dydrogesterone-treated and CD8-depleted mice with a ratio of 1, compared with a ratio of 0.4 in stressed, dydrogesterone-treated mice with no CD8 depletion.

Discussion
It is well known that progesterone mediates effects which are beneficial for the onset, development, and maintenance of pregnancy (10–14). In contrast, stress interferes with the course of pregnancy and may lead to abortions, putatively via decrease of progesterone (15, 16). Previous studies in our laboratory have demonstrated that stress-triggered abortion can be therapeutically approached by application of a progesterone derivative (31).

In this study, we now deliver evidence that stress exposure induces a decrease of uterine CD8⁺ cells within 24 h. This decrease can be restored by application of the progesterone derivative dydrogesterone, an observation which is clearly in agreement with the observations of a pregnancy protective CD8⁺ T cell subpopulation preventing abortion, which are present between days 4.5 and 8.5 of gestation (8, 33). These CD8⁺ cells, which have been suggested to coexpress the γδ TCR, appear to play a crucial role in Th1/Th2 balance (8, 34), which determines success and failure of pregnancy. Because we were able to restore this population by dydrogesterone, it appears that these cells are highly regulated by adequate levels of progesterone and express progesterone receptors. In our CD8 depletion experiments, we observed that the pregnancy protective effect of dydrogesterone treatment with respect to the abortion rate is almost abolished, thus, we conclude that the protective effect of progesterone and dydrogesterone is predominantly mediated by uterine CD8⁺ cells (Fig. 9).

Interestingly, the population of uterine CD8⁺ cells changes subsequently (gestation days 9.5 and 10.5) from pregnancy protective to abortogenic, suggesting the presence of different functional subpopulations of uterine CD8⁺ cells throughout gestation. Functional CD8 is a dimeric protein made of either two α-chains (CD8αα) or an α-chain and a β-chain (CD8αβ) (35–37). Importantly, CD8αα and CD8αβ are differentially expressed on a variety of lymphocytes. CD8αβ is expressed predominantly on the surface of αβ TCR⁺ T cells and thymocytes (38–41). Expression of CD8αα has been identified on a subset of γδ TCR⁺ intestinal intraepithelial lymphocytes, NK cells, dendritic cells, and a small fraction of CD4⁺ T cells, but αα-chains are essentially absent on cells of the circulation (41–44). The differential distributions of CD8αα and CD8αβ suggest that these two forms of CD8 are likely to mediate distinct functions. Based on the experimental set-up in our present study, we cannot differentiate whether the CD8 cells express an αα or αβ-chain. However, from preliminary results, we know that ~25% of uterine CD8 cells also express CD11c, thus belonging to the family of uterine dendritic cells. The percentage of CD8⁺CD11c⁺ cells slightly diminished with stress and could be restored by dydrogesterone application (data not shown). Gorczynski et al. (45) suggested that CD8⁺ γδ T suppressor cells and CD8αα indoleamine 2, 3 dioxygenase-producing suppressor cells could be stimulated by CD200⁺ CD8⁺ dendritic

![FIGURE 6.](image) Stress or dydrogesterone do not significantly alter levels of uterine IL-12. Percentage of IL-12-positive uterine lymphocyte populations from nontreated, stressed, and dydrogesterone-treated, stressed mice on gestation days 7.5, 9.5, and 10.5. Bars show mean ± SEM. Data were analyzed by nonparametric Mann-Whitney U test.

![FIGURE 7.](image) Dydrogesterone treatment up-regulates IL-4 in uterus cells. Percentage of IL-4⁺ uterine lymphocyte population of the various experimental groups on days 7.5, 9.5, and 10.5 of gestation. Data are represented as the mean ± SEM. *, p < 0.05, **, p < 0.01, as evaluated by nonparametric Mann-Whitney U test.

![FIGURE 8.](image) Depletion of CD8 abrogates the pregnancy protective effect of dydrogesterone treatment via an increase of proinflammatory cytokines and the Th1/Th2 ratio. A. Percentage of uterine lymphocyte population positive for the cytokines TNF-α, IFN-γ, IL-12, IL-4, and IL-10 in stressed mice treated with dydrogesterone, compared with mice that were CD8⁺ depleted in addition to stress and dydrogesterone treatment. Data are represented as the mean ± SEM. *, p < 0.05, **, p < 0.01, as evaluated by nonparametric Mann-Whitney U test. B. Th1/Th2 ratio has been calculated as follows: sum of percentages for TNF-α⁺, IFN-γ⁺, and IL-12⁺ uterine cells, divided by 3 (to obtain the mean Th1 value). The sum of percentages for IL-4⁺ and IL-10⁺ uterine cells was calculated and divided by 2 (to obtain the mean Th2 value). The Th1/Th2 ratio has been obtained by dividing the mean Th1 value by the mean Th2 value.
cells. These CD8$^+$ cells represent an important subset for the induction of cytokines such as IL-4, IL-10, and TGF-β that inhibit macrophages. TCR αβ$^+$ cells and NK or NK γδT cells, which produce IFN-γ, TNF-α, and IL-12 and induce placental hemorrhage by up-regulation of fgfl2$^+$ prothrombinase (25). However, CD8 depletion did not entirely abrogate the protective effect of progesterone and mimicked an abortion rate as seen in the stressed mice. This could be due to cellular infiltration of the fetomaternal interface by progesterone receptor-negative macrophages and NK cells, which are also capable of producing high levels of abortogenic cytokines. Another possible reason may be the existence of a T regulatory cell subpopulation, e.g., Johansson et al. (46) recently described a novel population of small CD3$^+$CD8$^+$ regulatory cell subpopulation, which produce high levels of abortogenic cytokines, possibly via PIBF secreted by uterine CD8$^+$ cells. These CD8$^+$ cells represent an important subset for the induction of cytokines such as IL-4, IL-10, and TGF-β that inhibit macrophages. TCR αβ$^+$ cells and NK or NK γδT cells, which produce IFN-γ, TNF-α, and IL-12 and induce placental hemorrhage by up-regulation of fgfl2$^+$ prothrombinase (25). However, CD8 depletion did not entirely abrogate the protective effect of progesterone and mimicked an abortion rate as seen in the stressed mice. This could be due to cellular infiltration of the fetomaternal interface by progesterone receptor-negative macrophages and NK cells, which are also capable of producing high levels of abortogenic cytokines. Another possible reason may be the existence of a T regulatory cell subpopulation, e.g., Johansson et al. (46) recently described a novel population of small CD3$^+$CD8$^+$ regulatory cell subpopulation, which produce high levels of abortogenic cytokines, possibly via PIBF secreted by uterine CD8$^+$ cells. In our previous experiment, we revealed that the percentage of cells producing IL-4 was increased in stressed mice and could be restored by treatment of dydrogesterone (31).

In our present experiments, the percentage of IL-12-producing uterus cells did not change over the days investigated in the various groups, bringing into question the function of IL-12 as a Th1 inducer on the uterine level. We suggest that the physiologic function of IL-12 in pregnancy may rather be around the time of blastocyst adhesion, and additional studies are necessary to elucidate the role of this cytokine in the regulation of the immune system during pregnancy maintenance.

In conclusion, our data imply that stress leads to increased abortions by an alteration of the hormonal system with a consecutive dysregulation of the Th1/Th2 ratio via CD8$^+$ cell-dependent pathways. Progesterone substitution by dydrogesterone can abrogate this effect by inducing a pregnancy protective Th2-biased immune response in the decidua.

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References