

# Spontaneous abortions with increased CD5 positive cells in the placental tissue during the first trimester of gestation

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## Summary

Most spontaneous abortions occur before 12 weeks' gestation, and most are due to chromosomal errors in the conceptus. Relatively few truly spontaneous abortions take place between 12 and 20 weeks' gestation. Thereafter, between 20 and 30 weeks another type of premature spontaneous termination due to ascending infection becomes prevalent. The number of cells expressing the various lymphocytic markers changes throughout pregnancy. In the present study, we investigated the immunohistochemical expression of mononuclear infiltrations in paraffin-embedded placentas, from fetuses after spontaneous abortion (8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> week of gestational age), and those after therapeutic abortion at the same time, using a panel of monoclonal antibodies for the identification of leukocytes (CD45/LCA), B-lymphocytes (CD20/L-26), T-lymphocytes (CD45RO/UCHL1) and CD5 cells.

Immunologic factors in human reproductive failure are plausible mechanisms of infertility and spontaneous abortion. Approximately 25% of cases of premature ovarian failure appear to result from an autoimmune etiology. Unfortunately, current therapeutic options for these women are limited to exogenous hormone or gamete substitution. Local inflammation at the sites of endometriosis implants are postulated to mediate the pain and reduce fecundability associated with this clinical syndrome. The recruitment of immune cells, particularly monocytes and T cells, neovascularization around foci of invading peritoneal lesions, and the possible development of antiendometrial autoantibodies support an immunologic basis of this disorder.

To date, treatment of pain and infertility associated with endometriosis is primarily surgical, although immune-based adjuvants are theoretical possibilities for the future.

Finally, although hypotheses supporting immunologic mechanisms of recurrent pregnancy loss have been popular over the past decade, most clinical investigations in this area do not provide compelling evidence for this position. Reputable specialists in reproductive medicine use experimental immunotherapies judiciously in selected cases of repetitive abortion. For example, the use of anticoagulation therapy can be beneficial in cases with documented antiphospholipid antibodies. At present, however, efficacious immunotherapy protocols for general application have not been established. Despite these caveats, continued strides in our understanding of human reproductive immunology, should yield considerable future progress in this field.

We conclude that, 1) maternal cells, probably CD45RO/UCHL1 positive cells, cross the maternofetal barrier and participate in spontaneous (involuntary) abortions, 2) a small proportion of maternal cells (approximately 30%), probably CD5 positive cells, also cross the maternal fetal barrier and cause growth delay and recurrent reproductive failure. The results were statistically significant ( $p < 0.0001$ , Student's t-test).

**Key words:** CD5 positive cells; Spontaneous abortion; First trimester of gestation.

## Introduction

Spontaneous abortion, or miscarriage, is generally defined as the involuntary termination of an intrauterine pregnancy before 20 weeks' gestation. A serious but relatively uncommon complication of early pregnancy is recurrent pregnancy loss (RPL). The definition of RPL is controversial, but most investigators suggest that two or three consecutive miscarriages constitute this diagnosis [1, 2]. Data derived from epidemiologic surveys indicate that the risk of a third spontaneous abortion after two miscarriages is 30%. Given a 10% to 15% chance that any clinically recognized pregnancy will result in spontaneous abortion, this rate is at least twice that which would be expected stochastically. Thus, specific repetitive risk factors are likely to underlie RPL.

A variety of possible etiologies of RPL have been proposed, including chromosomal, anatomic, endocrine, infectious, and immunologic mechanisms. Among the immunologic factors associated with spontaneous abortion are inflammatory activation of endometrial immunocytes by bacteria (e.g., chlamydia and listeria) [3, 4], viruses (e.g., parvovirus B 19 and herpes simplex) [5, 6] and parasites (e.g., toxoplasma) [7].

An excessive maternal immune response to trophoblastic invasion may contribute to pregnancy failure in some recurrent aborters. Macrophages and T cells, which are actively recruited into the endometrium during the late secretory phase and in early pregnancy, may secrete excessive amounts of TH1 cytokines [8]. Interferon- $\gamma$  and TNF- $\alpha$  are examples of this family of potentially embryotoxic cytokines produced by decidual immunocytes [9]. High doses of progesterone can inhibit TH1 immunity to trophoblasts in vitro [10], but these have not been tested rigorously for clinical efficacy in vivo. By binding to

anti-idiotypes on the surface of activated maternal T cells, intravenous immunoglobulin (IVIg) may be of benefit in the therapy of recurrent pregnancy loss because of immune activation.

A massive recruitment of bone marrow-derived monocytes, T cells, and large granular lymphocytes into the uterus occurs during the late secretory phase of the menstrual cycle and first pregnancy trimester. The precise functions of these cells remain unknown, but they have been postulated to play an immunoregulatory role in the establishment and maintenance of early human pregnancy. Some authors have attempted to correlate the presence or absence of specific circulating immunocytes with the risk of recurrent miscarriage. Kwak *et al.* [11] studied peripheral blood lymphocyte subsets by flow cytometry and measured autoantibodies to phospholipids and nuclear components by enzyme-linked immunosorbent assay. Thirty-five pregnant and eighty-one nonpregnant women with recurrent miscarriages and seventeen nonpregnant and twenty-two normal pregnant controls were studied. NK cells (CD56<sup>+</sup>) were found to be significantly elevated in nonpregnant women with recurrent miscarriage compared with non-pregnant controls. Pregnant women with recurrent pregnancy loss also had significantly increased NK and B cells compared with pregnant controls.

NK cell activity in the uterine decidua is typically depressed in early normal pregnancy; however, decidual NK activity was found to be increased in anembryonic pregnancies and in recurrent spontaneous abortions [12]. Whether this difference reflects a primary pathogenic defect or a secondary response to embryonic failure can not be ascertained through observational clinical studies.

## Materials and Methods

Samples representing 15 placentas from fetuses after spontaneous (involuntary) abortion and 15 placentas from fetuses after therapeutic or voluntary abortion were obtained at the 8<sup>th</sup>, 10<sup>th</sup> and 12<sup>th</sup> week of gestation. No hydropic changes in the chorionic villi of the placental tissue were observed in our material. Placentas were cut as thick as 3 mm, then fixed in 10% neutral buffered formaldehyde at 4°C for 24 hours and processed for routine paraffin embedding. Paraffin blocks were available in all cases, and 3-µm thick tissue sections were stained routinely with hematoxylin-eosin, PAS and Giemsa, and subsequently, using immunohistochemistry. The immunoperoxidase method was performed as follows: sections were deparaffinized in 70% alcohol and endogenous peroxidase was blocked with 3% H<sub>2</sub>O<sub>2</sub> in methanol. Sections were preincubated in 20% serum of the species from which the secondary antibody was raised and the primary antibody was applied. After overnight incubation at room temperature, the secondary biotinylated antibody was applied for 30 minutes. Staining was visualized using the Vector Elite System (Vector Laboratories, Burlingame, CA) with diaminobenzidine as the chromogen. Sections were counterstained in dilute hematoxylin. The primary monoclonal antibodies (Mab) used in the study were as follows: Leukocyte common antigen (CD45/LCA), mouse monoclonal antibody (Dako), B-lymphocytes (CD20/L-26), mouse monoclonal antibody (Dako), T-lymphocytes (CD45RO/UCHL1), mouse monoclonal antibody (Dako) and CD5 cells (Novocastra).

*Analysis of lymphocyte subsets:* For each sample, the cellular infiltrate in both the endometrial and decidual stroma was assessed by enumeration of labeled cells in each tissue compartment for a minimum of five random fields per section viewed at 40-fold magnification through a grid. Cell number was calculated per 1 mm<sup>2</sup> of tissue section. For reliable assessment of the lymphocyte subset ratios, similar areas were counted on serial sections. The counted areas were selected from random placental tissue sections, taking into account that the ratio of the area of the endometrial and decidual stroma according to the area of the chorionic villi was representative of the entire field. Areas with obvious necrosis or hemorrhages were excluded. Statistical analysis was undertaken using the student's t-test.

## Results

Five microscopic fields of the placentas were evaluated in each case without knowledge of the clinical data. The sections were examined independently by two observers, and positive cellular staining for each antibody was manifested as fine red cytoplasmic granularity and/or surface membrane expression.

The microscopic examination of the placentas (H-E, PAS, and Giemsa), in the cases of therapeutic or voluntary abortions, showed small focal or diffuse infiltrations of rounded mononuclear cells of approximately 10 µm in diameter with an eccentric, kidney-shaped nucleus. These infiltrations were particularly localized around the endometrial glands and their percentages corresponded to 0.6%-1.0% (0.81% ± 0.12%) of all cells of the endometrial and decidual tissue (Figure 1). Especially, in the 8<sup>th</sup> week of gestational age, 0.9%-1% (0.94% ± 0.05%) of decidual tissue showed diffuse mononuclear infiltrations, while in the 10<sup>th</sup> and 12<sup>th</sup> week, 0.6%-0.8% (0.74% ± 0.08%) focal mononuclear infiltrations were observed, respectively. The immunohistochemical study of these infiltrations (total leukocytes) demonstrated a strong positivity for the leukocyte common antigen (CD45/LCA) in all our cases. The control for the identification of T and B cells showed a greater percentage of cells (75%) corresponding to the T-cell monoclonal antibody marker (CD45RO/UCHL1) and to a lesser extent (25%), to the B-cell monoclonal antibody marker (CD20/L-26). In contrast, the immunohistochemical examination for the detection of CD5 positive cells and activated lymphocytes (CD30) was negative.

The microscopic examination of the placentas in the cases of spontaneous (involuntary) abortions, the mononuclear infiltrations (focal or diffuse), were localized mainly in the decidual stroma and to a lesser degree around the endometrial glands, and their percentage corresponded to 3%-5% (4.02% ± 0.71%) of all cells of the decidual tissue (Figure 2). Especially in the 8<sup>th</sup> week of gestational age, 4.8%-5% (4.92% ± 0.08%) of decidual tissue showed diffuse mononuclear infiltrations, while in the 10<sup>th</sup> and 12<sup>th</sup> week, 3%-3.9% (3.57% ± 0.33%) focal and diffuse mononuclear infiltrations were observed, respectively, in the decidual stroma. The immunohisto-

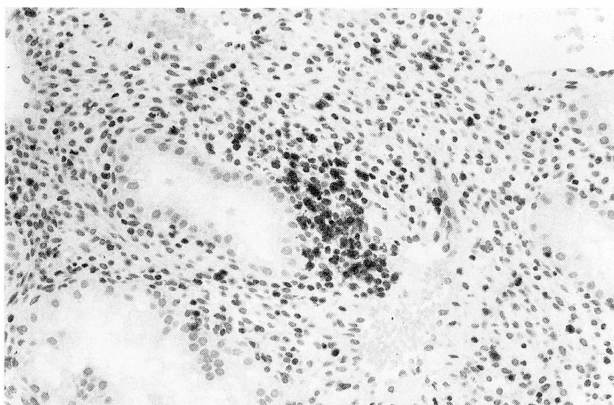


Figure 1. — Focal infiltrations of endometrial and decidual tissue by rounded mononuclear cells. LCA, x100 (Therapeutic or voluntary abortion).

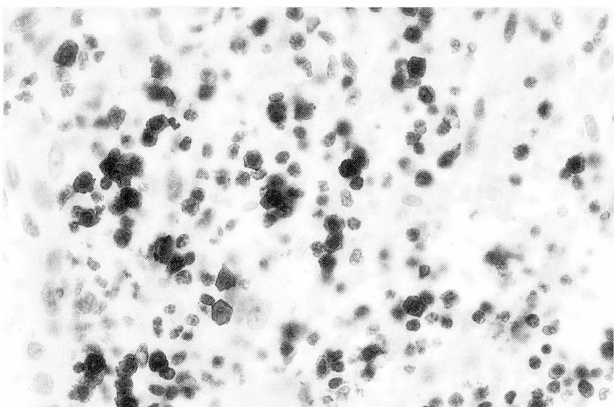


Figure 2. — Diffuse infiltrations of endometrial and decidual tissue by rounded mononuclear cells. LCA, x400 (Spontaneous or involuntary abortion).

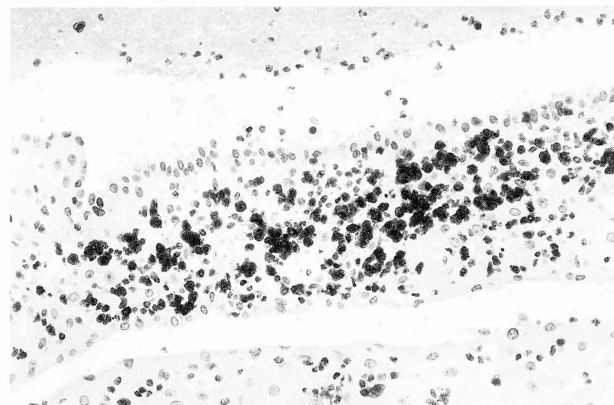


Figure 3. — Diffuse infiltrations of endometrial and decidual tissue by rounded mononuclear cells. CD5, x250 (Spontaneous or involuntary abortion).

### Discussion

Endometrial large granular lymphocytes are regular constituents of all implantation sites [13]. According to Kottsova *et al.* their number in the basal plate of normal pregnancies is rather low (0.5 - 1.0% of all cells of the decidual tissue); however, with severe forms of pre-eclampsia it increases to 12% [14]. Their typical granular inclusions stain characteristically with phloxine tartrazine [15]. During early pregnancy they form small, diffuse or focal infiltrates in the deep decidual layers and neighboring myometrium. They may be particularly impressively localized around the degenerating endometrial glands [15].

The large granular lymphocytes of the endometrium have been described under various names, causing considerable confusion. The classical name is granular cell (Kornchenzelle, K cell) [16-19]. Pijnenborg *et al.* [15] used the term endometrial granulocyte for this cell type, which appeared to be confined to the endometrium. These cells are equivalent to the metrial gland cells of rodents for which abundant literature exists [20]. There is now general agreement that these cells are derived from bone marrow, rather than from stromal stem cells, as had been assumed by Dallenbach-Hellweg [19]. The cells have been well characterized immunohistochemically [21, 22]. There has been some discussion whether they represent natural killer cells [23]. It now seems to be clear that they belong to a special subgroup of T lymphocytes that can be found among the large granular lymphocytes of the peripheral blood [24]. Among others, they express the T cell markers CD2 and CD7, but not natural killer cell markers such as CD16 and Leu7. The number of cells expressing the various lymphocyte markers changes throughout pregnancy [25]. It still remains to be established, however, whether these changes are of any importance for the mechanisms involved in fetal allograft protection.

Kawagoe analyzed 85 cases of tubal pregnancies and found that the nidatory site is often, but not always, surrounded by a band of lymphocytes. He discussed their

chemical study of these infiltrations (total leukocytes) demonstrated a strong positivity for the leukocyte common antigen (CD45/LCA) in all our cases while the control for the identification of T and B cells showed mainly positivity to T cell monoclonal antibody (CD45RO/UCHL1). The immunohistochemical examination of the above cellular population showed in five cases a mild to strong positivity to the monoclonal antibody CD5 (Figure 3). Further microscopic examination of the placentas of these cases demonstrated a mild vasculopathy with intimal hyperplasia, fibrinoid deposition in the walls of the spiral arteries, associated with foamy macrophages and mononuclear inflammation.

A statistically significant difference was found ( $p < 0.0001$ ) concerning the presence of mononuclear cell infiltrates expressing a CD45/LCA, CD45RO/UCHL1 (mainly), CD20/L26 (secondarily) and CD5 phenotype (30%) in the decidual and endometrial stroma, to the advantage of spontaneous abortions. No CD5 positive cells were demonstrated in the cases of voluntary miscarriages.

immunological importance at this unusual implantation site [26]. As was demonstrated by Sengupta *et al.* [27], granular infiltration of the decidua is not restricted to pregnancy; rather, it was part of the hormone-induced decidual response in ovariectomized rhesus monkeys. Moreover, Bulmer *et al.* [28] concluded from their studies on decidua in molar pregnancy and on choriocarcinomas that these cells are associated with the hormonal conditions of decidualization rather than with trophoblastic invasion. Correspondingly, they are also present in late proliferative and secretory endometrium [29], where they also may undergo mitosis [30].

Sengel and Stobner [31] gave a detailed ultrastructural account of these cells. They suggested that the K cells are involutive relaxin-secreting cells and that the actively relaxin-producing cells may have some different morphological features. In 1964 Dallenbach and Dallenbach-Hellweg showed that basal trophoblasts and the granules of Kornchenzellen stained positively for relaxin immunoreactivity. They therefore inferred that granular cells produce relaxin. Trophoblast and decidual tissue are still considered the major sources for relaxin secretion during pregnancy [32]. There are, however, no clear indications that the large endometrial granular lymphocytes contribute to this secretion. Rather, placental relaxin is likely to be synthesized by decidual and trophoblastic cells [33]. The same is true for the secretion of GM-CSF, a potent stimulator of myelopoiesis and trophoblastic growth; some findings point to secretion by the granular cells [34], but most authors favor a decidual and trophoblastic origin [35]. Other definitive suggestions for a functional importance of these cells are still lacking [24].

CD5 is expressed in T cells and a subset (approximately 20%) of mature peripheral B cells. The CD5-positive B-cell subset is increased in autoimmune diseases and may be related to autoantibody production. CD5 is coexpressed with B-cell antigens on the cells of some B-cell neoplasms including B-cell chronic lymphocytic leukemia, B-cell small lymphocytic lymphoma and mantle cell lymphoma.

In some diseases the number of CD5+ B cells is markedly raised. These include rheumatoid arthritis and auto-immune thrombocytopenic purpura. Neoplastic B cells in chronic lymphocytic leukemia and, to a lesser extent, other low-grade B-cell non-Hodgkin's lymphomas characteristically express CD5 antigen. Analysis of the specificity of antibodies on CD5+ B cells has shown that it is often of broad reactivity, including affinity for auto-antigens. The physiological and pathological significance of this subset of B cells is still relatively unclear.

Our results show that maternal T-cells (UCHL1+, CD5+), and a subset of B cells (CD5+) also of female origin, play an important role in pregnancy loss through an autoimmune pathway. When these cell populations are raised, polyclonal antibodies against hormones, hormonal receptors, and neurotransmitters (thyroid hormones, estrogens, progesterone, gonadotropin, and growth hormones) are produced. Those females show no response to gonadotropin administration.

## References

- [1] Stirrat G. M.: "Recurrent miscarriage (see comments) I: Definition and epidemiology". *Lancet*, 1990, 336, 673.
- [2] Laufer M. F., Ecker J. L., Hill J. A.: "Pregnancy outcome following ultrasound detected fetal cardiac activity in women with history of multiple spontaneous abortion". *J. Soc. Gynecol. Invest.*, 1994, 2, 138.
- [3] Witkin S. S., Ledger W. J.: "Antibodies to chlamydia trachomatis in sera of women with recurrent spontaneous abortions (see comments)". *Am. J. Obstet. Gynecol.*, 1992, 167(1), 135.
- [4] Rappaport F., Rabinovitz M.: "Genital listeriosis as a cause of repeated abortion". *Lancet*, 1960, 1, 1273.
- [5] Rogers B. B., Singer D. B., Mak S. K. *et al.*: "Detection of human parvovirus B 191 in early spontaneous abortuses using serology, histology, electron microscopy, in situ hybridization and the polymerase chain reaction". *Obstet. Gynecol.*, 1993, 81, 402.
- [6] Gronroos M., Honkoma E., Terho P., Punnonen R.: "Cervical and serum IgA and serum IgG antibodies to Chlamydia trachomatis and herpes simplex in threatened abortion: a prospective study". *Br. J. Obstet. Gynecol.*, 1993, 81, 402.
- [7] Southern P. J.: "Habitual abortion and toxoplasmosis. Is there a relationship". *Obstet. Gynecol.*, 1972, 39, 45.
- [8] Ecker J. L., Laufer M. R., Hill J. A.: "Measurement of embryotoxic factors is predictive of pregnancy outcome in women with a history of recurrent abortion". *Obstet. Gynecol.*, 1993, 81, 84.
- [9] Hill J. A., Polgar K., Anderson D. J.: "T-helper 1-type immunity to trophoblast in women with recurrent spontaneous abortion (see comments)". *JAMA*, 1995, 273, 1933.
- [10] Schust D. J., Hill J. A., Anderson D. J.: "Progesterone-induced immunosuppression (letter)". *Hum. Reprod.*, 1997, 12, 1367.
- [11] Kwak J. Y., Beaman K. D., Gilman-Sachs A. *et al.*: "Up regulated expression of CD56+, CD56+/CD16+, and CD19+ cells in peripheral blood lymphocytes in pregnant women with recurrent pregnancy losses". *Am. J. Reprod. Immunol.*, 1995, 34, 93.
- [12] Chao K. H., Yang Y. S., Ho H. N. *et al.*: "Decidual natural killer cytotoxic decreased in normal pregnancy but not in anembryonic pregnancy and recurrent spontaneous abortion". *Am. J. Reprod. Immunol.*, 1995, 34, 274.
- [13] Durst-Zivkovic B.: "Endometrial granular cells in fetal membranes". *Anat. Anz.*, 1978, 143, 258.
- [14] Kottsova N. A., Bystrova O. A., Susloparov L. A., Mikhailov V. M.: "Changes in the cellular composition of the deciduous membrane in physiologic pregnancy and late toxicosis". *Arch. Anat. Gistol. Embriol.*, 1989, 97, 76.
- [15] Pijnenborg R., Dixon G., Robertson W. B., Brosens I.: "Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy". *Placenta*, 1980, 1, 3.
- [16] Hamperl H.: "Über die endometrialen Granulozyten (Endometrial Kornchenzellen)". *Klin. Wochenschr.*, 1954, 32, 665.
- [17] Hellweg G.: "Über Auftreten und Verhalten der endometrialen Kornchenzellen im Verlauf der Schwangerschaft, im Krankhaft veränderten Endometrium und außerhalb des Corpus Uteri". *Virchows Arch.*, 1957, 330, 658.
- [18] Dallenbach F. D., Dallenbach-Hellweg G.: "Immunohistologische Untersuchungen zur Lokalisation des Relaxins in menschlicher Placenta und Decidua". *Virchows Arch.*, 1964, 337, 301.
- [19] Dallenbach-Hellweg G.: "Histopathology of the Endometrium". Springer-Verlag, Berlin, 1971, 24.
- [20] Tarachand U.: "Decidualisation: origin and role of associated cells". *Biol. Cell.*, 1986, 57, 9.
- [21] Bulmer J. N., Sunderland C. A.: "Immunohistological characterization of lymphoid cell populations in the early human placental bed". *Immunology*, 1984, 52, 349.
- [22] Ritson A., Bulmer J. N.: "Isolation and functional studies of granulated lymphocytes in first trimester human decidua". *Clin. Exp. Immunol.*, 1989, 77, 263.
- [23] Saito S., Nishikawa K., Morii T., Enomoto M., Narita N., Motoyoshi K., Ichijo M.: "Cytokine production by CD16-CD56 natural killer cells in the human early pregnancy decidua". *Int. Immunol.*, 1993, 5, 559.
- [24] King A., Loke Y. W.: "Uterine large granular lymphocytes: a possible role in embryo implantation". *Am. J. Obstet. Gynecol.*, 1990, 162, 308.

- [25] Haller H., Radillo O., Rukavina D., Tedesco F., Candussi G., Petrovic O., Randi L.: "An immunohistochemical study of leucocytes in human endometrium, first and third trimester basal decidua". *J. Reprod. Immunol.*, 1993, 23, 41.
- [26] Kawagoe K.: "Immune reaction between maternal and fetal tissue at the nidatory site of tubal pregnancy". *Nippon Sanka Fujinka Gakkai Zasshi*, 1985, 37, 2691.
- [27] Sengupta J., Given R. T., Talwar D., Ghosh D.: "Endometrial response to decidualogenic stimulus in ovariectomized rhesus monkeys treated with oestrogen and progesterone: an ultrastructural study". *J. Endocrinol.*, 1990, 124, 53.
- [28] Bulmer J. N., Johnson P. M., Sasagawa M., Takeuchi S.: "Immunohistochemical studies of fetal trophoblast and maternal decidua in hydatiform mole and choriocarcinoma". *Placenta*, 1988a, 9, 183.
- [29] Bogaert L. J.: "Endometrial granulocytes in proliferative endometrium". *Br. J. Obstet. Gynaecol.*, 1975, 82, 995.
- [30] Pace D., Morrison L., Bulmer J. N.: "Proliferative activity in endometrial stromal granulocytes throughout menstrual cycle and early pregnancy". *J. Clin. Pathol.*, 1989, 42, 35.
- [31] Sengel A., Stobner P.: "Ultrastructure of l'endometre humain normal. III. Les cellules K. Z. Zellforsch, 1972, 133, 47.
- [32] Bryant-Greenwood G. D., Rees M. C. P., Turnbull A. C.: "Immunohistochemical localization of relaxin, prolactin and prostaglandin synthase in human amnion, chorion and decidua". *J. Endocrinol.*, 1987, 114, 491.
- [33] Hansell D. J., Bryant Greenwood G. D., Greenwood F. C.: "Expression of the human relaxin H1 gene in the decidua, trophoblast, and prostate". *J. Clin. Endocrinol. Metab.*, 1991, 72, 899.
- [34] Kanzaki H., Crainie M., Lin H., Yui J., Guilbert L. J., Mori T., Wegmann T. C.: "The in situ expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) mRNA at the maternal-fetal interface". *Growth Factors*, 1991, 5, 69.
- [35] Duan J. S.: "Production of granulocyte colony stimulating factor in decidual tissue and its significance in pregnancy". *Osaka City Med. J.*, 1990, 36, 81.

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