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SPECIAL ARTICLE

Pregnancy Immunology: Decidual Immune Cells

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SUMMARY Human pregnancy is a complex process. Placental development depends on the function of secretory molecules produced by placental trophoblast cells as well as by maternal uterine immune cells within the decidua. These decidual immune cells are T cells, natural killer cells, macrophages and dendritic cells. The interactions between the trophoblast cells and the maternal immune cells have an impact on the outcome of the pregnancy. Knowledge about the phenotypes and functions of the maternal immune cells in normal and pathological pregnancies including recurrent spontaneous abortions, preeclampsia and hydatidiform moles may improve our understanding of the immunobiology of the normal pregnancy as a whole and may provide approaches for improving the treatment of pathological pregnancies.

Viviparous animals bear living babies that are nourished in close contact to their mothers' bodies. Human pregnancy classified as viviparity has evolved into a complex process and has been investigated by reproductive immunologists regarding the role of the immune system for the feto-placental development. The surrounding environment of the developing placenta includes maternal blood and decidual cells. These comprise leucocytes potentially providing various biological molecules, particularly cytokines and growth factors, to support placental growth and function. Revealing the function of maternal uterine immune cells is important to our understanding of the success or failure of a pregnancy. The phenotypes and functions of maternal immune cells in normal and pathological pregnancies may provide clues to better treatment approaches.

Decidual immune cells in normal pregnancy

Decidualisation begins at about 8 days after ovulation and is well developed by the 14th day of pregnancy, at the time of the first missed menstrual period. The decidua basalis lies underneath the placenta and is infiltrated by invasive interstitial trophoblast cells.[1] The function of the decidua is probably to control trophoblast invasion. This function largely depends on maternal immune cells as well as their secreted products within the decidual microenvironment. There are four major populations of leucocytes present in the early pregnancy decidua: T cells, uterine natural killer (uNK) cells, macrophages and dendritic cells. This review is focused on the phenotypic and functional characteristics of each immune cell type in the pregnant human uterus.

T cells

In a normal early pregnancy, the ratio of CD8+ and CD4+ T cells is around 2.5-3:1.[2] The

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numbers of T cells decrease in the early decidua compared to a non-pregnant endometrium.[3] It has been reported that decidual CD8+ T cells have cytolytic activity, do not evoke a predominant local intrauterine Th2 type cytokine environment, and regulate trophoblast invasion into the decidua.[4] The decidual T cells express various activation markers including CD45RO, CD69, HLA-DR and the IL-2 receptors.[5-8] The decidual and peripheral blood T cells differ phenotypically in that the decidual CD3+, CD4+ or CD8+ cells express higher CD45RO and lower CD45RA levels compared to peripheral blood T cells from the same pregnant women.[9] A larger percentage of decidual CD3+ T cells expresses VLA-1, HLA-DR and CD38 than of peripheral blood CD3+ T cells.[10]

Most decidual T cells express αβ T cell receptors (TCR) whereas γδ T cells comprise only a small proportion.[3,11-13] The numbers of TCRαβ-positive T cells reduce in the early pregnancy decidua compared to the non-pregnant endometrium.[3] Decidual γδT cells are CD4-CD8- double negative and are positive for CD2, CD69, CD45RO, CD94 and CTLA-4.[14-16] Decidual γδT cells may be cytotoxic as they express perforin, granzyme A, granzyme B, granulysin and Fas ligand (FasL).[17] Therefore, these cells may protect the maternal-fetal unit from infections, control trophoblast invasion, and create a local immune tolerance toward the semiallogeneic conceptus by killing fetal reactive lymphocytes. Decidual γδT cells undergo selective and diverse expansion, similar to that in the peripheral blood γδT cells, since they are heterogeneous in expressing seven receptor types as well as exhibiting an extensive junctional diversity.[18,19]

The first encounter and antigen presentation of fetal antigens to the immune system occurs in the decidua. The fetal-antigen-primed immune cells in the decidua then circulate in the peripheral blood of the pregnant woman.[20] Since temporary thymic involution during pregnancy results from decreased thymocyte proliferation without affecting thymocyte precursors in the bone marrow,[21,22] the decidua as an extrathymic maturation site may compensate the thymic changes by extrathymic differentiation of T cells primed by fetal antigens in the decidua leading to an elimination of fetal reactive T cells. The expression of transforming growth factor (TGF)-β1 and interleukin (IL)-10 by decidual γδT cells suggests their immunoregulatory functions.[23] Human decidual γδT cells express CD56[20] and are potentially cytotoxic.[17]

The decidua also contains regulatory T cells (Treg). The CD4+ Treg cells have been categorized into two major subgroups based on their ontogeny. The first consists of the naturally occurring forkhead box P3 (FOXP3)+CD4+CD25+ Treg cells, which develop in the thymus and are present in healthy individuals from birth. The other is comprised of the inducible Treg cells, which can be generated under various tolerogenic conditions. One type of these cells, called the T regulatory type 1 (Tr1) cells, produce high levels of IL-10.[24] In women, the numbers of Treg are modulated by sex hormones. Increased numbers of CD4+CD25+FoxP3+ Treg cells are found in the late follicular phase of the menstrual cycle of fertile non-pregnant women correlating with serum estradiol levels and their numbers are decreased at the luteal phase.[25]

Decidual CD4+CD25+ Treg cells constitute about 14% of the total decidual CD4+ T cells and they express GITR, OX40 and CTLA-4.[26] CTLA-4 expression on Treg cells may up-regulate IDO (indoleamine 2,3-dioxygenase) expression by decidual and peripheral blood dendritic cells and monocytes.[27] IDO is involved in the maternal tolerance to the fetus by limiting the availability of tryptophan for T cells in the local uterine microenvironment.[28] Human pregnancy also involves an expression of L-arginase that depletes arginine in the microenvironment of the fetoplacental unit, thus downregulating maternal T cell activity.[29] A successful pregnancy may be associated with cytokine production by decidual T cells. The Th1/Th2 paradigm for pregnancy[30] is supported by several observations. The Th1/Th2 ratio is highest in the proliferative endometrium, significantly decreases during the secretory phase and is lowest in the early pregnancy decidua.[31] The Th1 responses in human pregnancy may be suppressed *via* down regulation of NF-κB and T-bet transcription.[32]

Uterine natural killer (uNK) cells

The decidualization is closely related to the presence of uterine natural killer (uNK) cells. The uNK cells are found wherever decidual tissue is formed even in ectopic pregnancies.[33] In humans, the

numbers of uNK cells are related to sex steroid hormone production.[34] In the early pregnancy, uNK cells comprise about 70% of decidual leucocytes but their numbers decline in the second half of the pregnancy, with only a small number detected at term.[35] Originally, the uNK cells were recognized by the activity of the E-rosette receptor, CD2 as well as CD38. The uNK cells are mostly negative for CD3, CD5, CD4 and CD8.[36] Later, an unusual antigenic phenotype of these cells has been found including CD56+[37], CD38+, CD16-, CD3- and CD5-.[38] Some of them have also been found to express CD8.[39] The uNK cells may control trophoblast invasion into the decidua, myometrium and uterine spiral arteries.[33]

uNK cells isolated from the early pregnancy decidua proliferate strongly in response to IL-2, produce high levels of IL-2 upon stimulation with phytohemagglutinin (PHA) and can kill the NK cell target, the K562 cells,[40,41] the proliferative response to IL-2 involving increased IL-2 receptor β. The cytolytic activity of the uNK cells against the K562 cells is enhanced by IL-2.[42,43] IL-2 stimulated uNK cells can lyse cultured trophoblast and choriocarcinoma cell lines.[44,45] The uNK cells contain perforin, suggesting their cytolytic potential.[46]

CD56+CD16-uNK cells isolated from both early pregnancy decidua and non-pregnant endometrium have cytotoxic activity against the K562 targets comparable to CD56+CD16+ NK cells from the peripheral blood.[47] In the presence of decidual stromal cells, a sub-optimal dose of IL-2 can stimulate the proliferation of decidual CD56+ cells.[48] Since IL-2 is rarely detected in either the first trimester placenta or decidua,[49-51] studies have focused on the effects of IL-15 on the function of uNK cells.[52-54] This is because the biological actions of IL-15 are largely similar to those of IL-2 and IL-15 is produced by decidual macrophages and by placental trophoblast cells in the first trimester pregnancy.

The uNK cells produce various soluble products including the angiogenic cytokines angiopoietin-2 and vascular endothelial growth factor C.[33] NK cells distinguish between target cells and self cells by their expression of several families of class I MHC binding receptors.[55] Killer inhibitory receptors specific to class I MHC molecules of uNK cells[56-58] may be involved in the survival as well as invasion of trophoblast cells. Nevertheless, others have suggested that uNK cells are proper residents of the maternal-fetal interface because they may have a unique function in supporting the adaptation of blood vessels of the pregnant uterus.[59]

Despite the earlier finding of a CD3-negative phenotype of uNK cells, another later study has reported an unusual population of human uNK cells, the invariant CD1d-restricted NKT cells (iNKT).[60] Evidence suggests that the number of decidual NKT cells was 10 times higher than the peripheral blood NKT cells in humans.[61] Some iNKT cells in the decidua are a CD4+ NKT subset producing predominantly a Th1 type cytokine,[61] thus suggesting their immunoregulatory role at the maternal-fetal interface. However, in mice the NKT cells in the decidua may differ from those in the peripheral blood and the liver by their absence of CD4 and CD8 markers.[62] The uterine NKT cells differ from other NKT cell populations in that the former can recognize a class I/class I-like molecule other than CD1,[63] suggesting that the feto-placental unit may regulate maternal NKT cells by providing them with MHC class I/class I-like molecules.

Macrophages

Macrophages are a major cell type within both the non-pregnant and the pregnant endometrium. Decidual macrophages express CD14[64] and HLA-DR, -DP and –DQ.[65] In a normal early pregnancy macrophages increase in number compared to the cyclic endometrium and constitute approximately 30% of the decidual leucocytes. Since decidual macrophages are closely associated with the extravillous trophoblast[66,67] and are also MHC class II positive, they may have an immunological role in the control of the trophoblast invasion. Decidual macrophages can present alloantigen in MLRs[68] and they express acid phosphatase, non-specific esterase, α_1-anti-protease and α1-anti-chymotrypsin, suggesting their phagocyte activity.[64,69] They also have a role in pathogen recognition and clearance during pregnancy by producing superoxide radicals and tumor necrosis factor-α (TNFα) upon stimulation with bacteria. This may help in protecting the fetus against intrauterine infections that could lead to preterm labor.[70]

The immunosuppressive function of the decidual macrophages involves their production of prostaglandin-E_2 (PGE_2) which may block the activation of decidual cytotoxic leucocytes with potential anti-trophoblast lytic activity.[71] Decidual macrophages isolated from normal women in their early pregnancy had a higher inhibitory effect on the PHA-induced proliferation of mononuclear cells than peripheral blood monocytes from the same individuals; this difference is not observed in spontaneous aborters.[68] This study has shown no difference in the PGE_2 production of decidual macrophages and peripheral blood monocytes from both normal pregnant women and spontaneous aborters but decidual macrophages from normal pregnant women secreted lower levels of IL-1α and IL-1β than those from spontaneous aborters. Immunosuppression by decidual macrophages may also be due to their high levels of IL-10 and IDO.[72] The decidual macrophages do not differentiate into dendritic cells under the influence of IL-4 and GM-CSF, thus suggesting an immunoinhibitory rather than antigen presenting function.[72] Thus, any immunoregulatory role of the decidual macrophages may be due to the production of several factors as well as their unusual function in the pregnant uterus.

B cells

B cells are rarely found in either the pregnant or non-pregnant endometrium and their role in the placental development is largely unknown.[73]

Dendritic cells

Decidual dendritic cells (DC) express HLA-DR, CD83 and CD1a and play a role in allogeneic T cell stimulation similar to that found in blood monocyte derived DC.[74] Decidual DC which express DC-SIGN are identified as immature decidual DC.[75] However, other studies have shown that decidual DC, comprising 1.7% of decidual CD45+ cells, are immature myeloid DC expressing HLA-DR, DEC-205/CD205, CD40 and CD11c but not CD123 and CD1a. Decidual DC express the leukocyte immunoglobulin receptor binding protein-1 (LIRB1), a ligand for HLA-G molecules, suggesting that decidual DC may be functionally regulated by trophoblast cells expressing HLA-G. These decidual DC may promote the development of Th2 cells[76] and may inhibit the development of Th1 and allogeneic T cell responses,[77] suggesting that decidual DC play a role in the immunologic tolerance leading to a successful pregnancy.

Decidual immune cells in pathologic pregnancies

Recurrent pregnancy loss

Recurrent pregnancy loss is one of the most common complications of pregnancy and is defined as three or more spontaneous abortions before 20 weeks of gestation.[78] Potential etiologic factors for recurrent pregnancy loss include genetics, anatomical, endocrinological and immunological factors as well as infections. Immune mechanisms may be involved in recurrent pregnancy loss since maternal immune recognition of pregnancy associated with changes of lymphocyte functions is essential to support the survival of the semi-allogeneic fetus. However, pregnant women are not generally immunosuppressed and randomised therapeutic studies have not confirmed the usefulness of immunizing mothers with paternal antigens to prevent fetal loss.[79]

Decreased numbers of CD8+ T cells are found in the secretory endometrium of recurrent aborters compared to fertile women.[80] However, others have associated increased numbers of CD4+ and CD8+ leucocytes with recurrent abortion.[81] *In vitro* studies have shown that the cytotoxic effect of peripheral blood from women with unexplained recurrent miscarriages on mouse embryos is associated with Th1-type cytokines including IFN-γ, IL-2 and LT-α.[82] A low IL-4 production is found in unexplained recurrent miscarriages.[83] The levels of Th1 cytokines are higher and of the Th2-type cytokine IL-6 are lower in women with recurrent miscarriages compared to healthy women. However, periimplantation cytokine levels can not predict the outcomes in women with recurrent miscarriages.[84]

The uNK cells may be associated with recurrent miscarriages as their numbers were increased in such cases compared to controls.[81,85] Peripheral blood CD56+ NK cells were also increased in recurrent miscarriages[86,87] and their activity was higher than in a normal pregnancy.[87,88] The number of peripheral blood NK cells may be a predictor for the pregnancy outcome in women with recurrent miscar-

riages.[89,90] It is not clear whether the high numbers and activity of CD56+ NK cells found in women with recurrent pregnancy losses are a cause or a result of recurrent abortions.[91,92] There is no difference in the NKT cell population in the decidua or in the peripheral blood of recurrent aborters.[93,94]

Although the numbers of CD3+ T cells do not differ between women with recurrent miscarriages and normal fertile women,[80,81] differences between subpopulations of T cells associated with recurrent abortions can not be excluded.[95] There are similar numbers of macrophages in the deciduas of normal pregnancies and recurrent miscarriages.[96] However, the increased activation of these cells demonstrated by markers such as CD25 and CD69 may be associated with recurrent miscarriages.[96-98] Recurrent miscarriages are related to changes in the Th1/Th2 cytokine profile with a low IL-4 and IL-10 production by CD4+ T cells and a low IL-4 production by CD8+ T cells.[83] Recurrent abortions also involve lower IL-10 and IL-6 but higher IFN-γ levels in the peripheral blood and endometrium.[99] A decreased production of leukemia inhibitory factor (LIF) may also be associated with recurrent miscarriages.[100] Recurrent aborters have higher levels of CD4+ and CD8+ cells, both expressing IL-4, than normal pregnant women.[93]

Preeclampsia

Preeclampsia is a specific human pregnancy disorder associated with a significant maternal mortality and morbidity. It is characterised by hypertension, abnormal proteinuria, and other systemic disturbances. Preeclampsia can occur in the second half of the pregnancy, during labor, or the early period of delivery.[101] Preeclampsia can be divided into a maternal and a placental form. Placental preeclampsia arises from the hypoxic conditions associated with oxidative stress. Maternal preeclampsia is due to the interaction between a normal placenta and a maternal constitution affected by microvascular disease. However, mixed presentations combining maternal and placental contributions are common.[101]

Placental preeclampsia results from poor placentation. A subsequently hypoxic placenta leads to maternal hypertension, proteinuria, and clotting and liver dysfunction. In severe cases, particularly with an early onset of the disease before 34 weeks of gestation, the affected fetus suffers from nutritional and respiratory insufficiency, asphyxia, or death.[102] In the second two trimesters of pregnancy, the placenta requires increasing access to the maternal blood supply associated with spiral artery remodeling.[102-104]

Immunological considerations of preeclampsia involve trophoblast signaling to decidual immune cells.[105,106] The involvement of uNK cells with preeclampsia has been raised because of the findings that preeclampsia is more prevalent in women who are homozygous for the group A KIR haplotype than in women homozygous for the group B KIR haplotypes, the more complex B group having additional genes for stimulating NK cells.[101] Nevertheless, the role of uNK cells in the pathogenesis of preeclampsia remains to be elucidated.

Patients with preeclampsia have increased B cells, CD4+CD29+ T cells, CD4+CD45RO+ memory T cells and CD8+S6F1+ as well as CD8+CD28+ cytotoxic T cells, with decreased CD4+CD45RA+ T cells, resulting in an over-production of autoantibodies and immune complexes.[107-109] In preeclampsia, NK cell numbers are also increased in both the peripheral blood and the decidua.[108,109] Decreased $CD4+CD25^{high}$ Treg cells have been found in preeclampsia compared to normal pregnancies.[110] Regarding the cytokine production of NKT cells, they consist of IL-4-IFN-γ+NKT1 and IL-4+IFN-γ-NKT2 cells. The ratio of peripheral blood NKT1/NKT2 cells is higher in preeclamptic women than in normal pregnant women.[111] The percentage of decidual CD3+FoxP3+ T cells in preeclampsia decreases compared to normal pregnancies,[110] indicating a deviated function of Treg cells that could lead to a loss of maternal tolerance to the fetus in preeclampsia. Impaired endovascular invasions of the trophoblast in preeclampsia may be due to excessive recruitment of macrophages into the decidua.[112]

Hydatidiform mole

Hydatidiform mole is a gestational trophoblastic disease in which trophoblast cells proliferate abnormally. Complete hydatidiform moles are usually diploid with a 46, XX karyotype resulting entirely from the paternal genome, and are character-

ized by generalized trophoblastic hyperplasia with no fetus.[113,114] In contrast, partial hydatidiform moles are triploid, with an extra paternal chromosome component. Partial hydatidiform moles usually result from the fertilisation of a normal ovum by two spermatozoa,[115] and affect only part of the placenta. A fetus, often with congenital malformation, is usually found. A rare type of complete hydatidiform mole has a biparental origin and can be associated with a disturbed expression of imprinted genes, of which literature reviews can be found elsewhere.[116,117] Similar to a normal early pregnancy, invasive extravillous trophoblast cells of complete and partial hydatidiform moles are reactive to the monomorphic determinant but not to polymorphic determinants of class I HLA antigens.[118] Villous trophoblast cells of hydatidiform moles do not express class I HLA antigens. Class II HLA antigens are not expressed by any molar trophoblast subpopulation.[118,119]

Because its chromosomes are entirely paternal in origin, unlike the normal semiallogeneic conceptus, a complete hydatidiform mole is an absolute intrauterine allograft that should be expected to stimulate maternal immune responses. In hydatidiform moles, lymphocytes which are positive for CD8, CD3 and mast cell tryptase are increased, NK cells are decreased and macrophages are unchanged.[120] This suggests a dysfunction in the control of the trophoblast invasion by decidual leucocytes, perhaps *via* their production of cytokines and growth factors, in gestational trophoblastic diseases. Studies on formalin-fixed paraffin-embedded tissues of uterine curettages using a double immunoperoxidase-alkaline phosphatase staining have shown no difference in the proportion of decidual T cells, macrophages and uNK cells co-expressing TGF-β in partial and complete hydatidiform moles as compared to normal early pregnancies (Fig. 1, Table 1). This suggests that despite the known immunosuppressive effect of TGF-β, this cytokine may not be primarily responsible for the abnormal proliferation of the molar trophoblast.

Decidual CD4+ T cell numbers are increased in complete and partial hydatidiform moles compared to a normal early pregnancy, and these CD4+ T cells are activated/memory cells expressing CD45RO.[2] These findings suggest an altered maternal immune response against the molar trophoblast compared to a normal pregnancy. IL-17, produced by Th-17 cells, has been shown to increase the invasion of trophoblast cell lines,[121] although the *in vivo* role of this cytokine in pregnancy remains unclear.

Fas/FasL signalling is involved in the apoptosis of leucocytes and there is an increased proportion of Fas+ and FasL+ CD4+ T lymphocytes in both complete and partial hydatidiform moles.[122] In contrast, Fas+ CD8+ decidual T cells are decreased in hydatidiform moles suggesting that CD8+ T cells may not be primarily responsible for the immunity against the molar trophoblast.[122] Nevertheless, there is no difference in the apoptosis of decidual immune cells in hydatidiform moles compared to normal pregnancies.[123] Hydatidiform moles are associated with increased inhibitors of granzyme B, suggesting its role in the downregulation of the maternal cytotoxic lymphocyte response[124], thus supporting the survival of the molar trophoblasts.

Conclusion

A successful pregnancy and placental development depend on the function of secretory molecules produced by the placental trophoblast cells as well as by maternal uterine immune cells within the decidua. The decidual T cells, uNK cells, macrophages and dendritic cells interact with trophoblast cells through cytokine networking and growth factors which they produce locally within the uterine microenvironment. The phenotypes and functions of the maternal immune cells can affect the pregnancy process and subsequently the pregnancy outcome. Abnormal pregnancies such as recurrent spontaneous abortion, preeclampsia and hydatidiform mole all have evidence of alterations in decidual immune cells and research on these abnormalities may help to understand the immunobiology of the normal pregnancy and may provide approaches to improve the treatment of pathological pregnancies.

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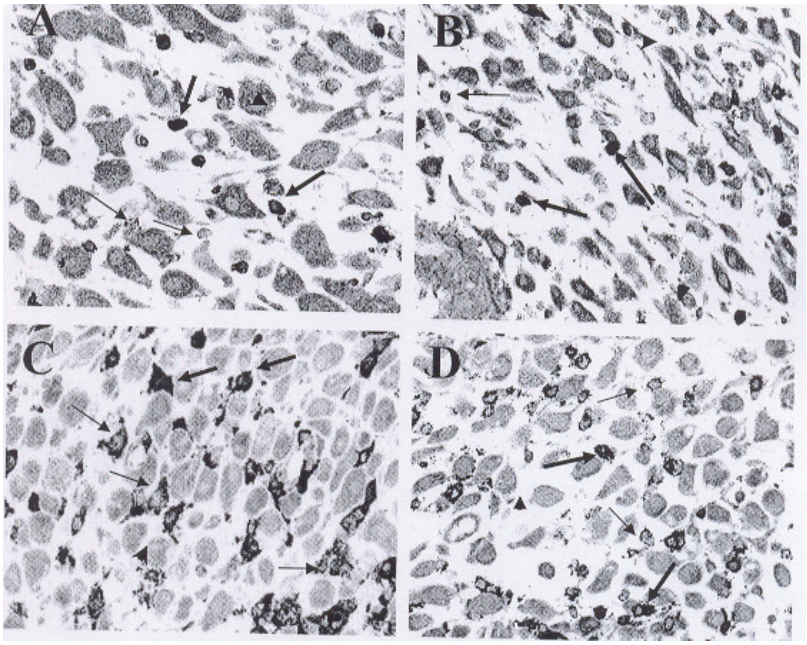

Fig. 1 Double immunoperoxidase-alkaline phosphatase staining of the decidua from a partial hydatidiform mole shows CD3+ T cells (A), CD8+ T cells (B), CD14+ macrophages (C), and CD56+ NK cells (D) double positive for TGF-β (thick arrows). The thin arrows show single positive leucocytes and the arrow heads show decidual stromal cells. All CD antigens were detected with mouse monoclonal antibodies (Novocastra Laboratories, Newcastle upon Tyne, UK) followed by a peroxidase detection system (ABC Vector Elite kit, Vector Labortatories, Petorborough, UK). TGF-β was detected by rabbit polyclonal antibody (SC-90; Santa Cruz Biotechnology, Santa Cruz, CA, USA) followed by an alkaline phosphatase development kit (Vector Laboratories). The photographs were taken at ×400 magnification. The study using paraffin tissues was approved by the Naresuan Ethical Committee no. 4602040010.

Table 1 The median and range of the percentages of decidual leucocytes co-expressing TGF-β in normal early pregnancy and in partial and complete hydatidiform moles

Decidual leucocyte populations	**Normal early pregnancy** (n = 5)	**Partial hydatidiform mole** (n = 10)	**Complete hydatidiform mole** (n = 6)
CD3	45 (14-52)	38 (25-66)	28 (7-88)
CD4	70 (26-84)	67 (8-90)	40 (1-74)
CD8	91 (74-96)	81 (49-89)	55 (17-95)
CD14	51 (28-60)	42 (14-55)	36 (26-75)
CD45RO	69 (57-89)	41 (24-85)	63 (52-84)
CD56	38 (16-45)	24 (8-64)	30 (15-46)

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