Published in final edited form as:
Autoimmun Rev. 2010 January ; 9(3): 153. doi:10.1016/j.autrev.2009.06.001.

Pregnancy, postpartum autoimmune thyroiditis, and autoimmune hypophysitis: intimate relationships

Melissa A. Landek-Salgado[a], **Angelika Gutenberg**[b], **Isabella Lupi**[c], **Hiroaki Kimura**[a], **Stefano Mariotti**[d], **Noel R. Rose**[a,e], and **Patrizio Caturegli**[a,e,*]

[a]Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD

[b]Department of Neurosurgery, Georg-August University, Goettingen, Germany

[c]Department of Endocrinology and Metabolism, University of Pisa, Pisa, Italy

[d]Endocrinology, Department of Medical Sciences, University of Cagliari, Italy

[e]Feinstone Department of Molecular Microbiology and Immunology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Abstract

Autoimmune diseases comprise a group of about 85 heterogeneous conditions that can affect virtually any organ and tissue in the body. Many autoimmune diseases change significantly during pregnancy: some ameliorate, some worsen, and others are unaffected. Two autoimmune diseases present prominently in relation to pregnancy: postpartum autoimmune thyroiditis and autoimmune hypophysitis. This article will review the current state of knowledge of the immunological changes that occur during normal pregnancy, and will explore the striking temporal association with pregnancy observed in thyroiditis and hypophysitis.

Keywords

Pregnancy; Hypophysitis; Postpartum thyroiditis

1. Historical context and scope

The immune system changes significantly during pregnancy. Indeed, it is still a mystery why the mother does not reject the fetus who carries paternal antigens (semi-allograft) and thus should be subjected to the standard laws of transplantation. This immunological paradox of pregnancy has fascinated scientists for generations. In 1953 Medawar proposed three reasons for the lack of fetus rejection: the fetus is antigenically immature; the fetus is anatomically separated from the mother; the maternal immune system is “paralyzed” or “inert” during pregnancy. It is now well established that pregnant women make antibodies directed against paternal antigens, indicating the fetus is not antigenically immature [1]. And, in fact, the MHC antisera used extensively for tissue typing are obtained from multiparous women. Second, cells

*Corresponding author. Johns Hopkins University, Department of Pathology, Ross building room 632, 720 Rutland Av., Baltimore, MD 21205 Tel.: 443-287-8911; fax: 410-614-3548. *E-mail address:* pcat@jhmi.edu (P. Caturegli)..

traffic between mother and fetus during pregnancy, giving rise to microchimerism, with quantitatively greater transfer in the mother-to-fetus direction [2], proving that the fetus is not anatomically sequestered from the mother. Finally, the maternal immune system is not wholly suppressed during pregnancy since it is capable of mounting a response against live infectious agents or vaccines [3]. Medawar's postulates have, thus, been largely abandoned, but have stimulated the quest for fresh understanding of how the fetus evades maternal immune recognition. Modern studies focus on the fetal placenta and the maternal uterine decidua.

2. Placental mechanisms of immunoregulation

A brief review of placental anatomy is necessary to envision the site of action of immunoregulatory mechanisms (Table 1). The placenta is a dish-shaped fetal organ required to maintain pregnancy. The placenta, at term, is composed of three major zones called the basal plate, lacunar system, and chorionic plate.

The basal plate is the maternal surface of the placenta; it makes contact with the inner lining of the uterus (endometrium), which during pregnancy takes on the name of decidua basalis. After delivery of the placenta, some decidua basalis is left in the uterus and some is part of the basal plate. The basal plate is a mixture of maternal cells [uterine natural killer lymphocytes (70%), T lymphocytes (10%), macrophages and other myeloid cells (20%)] and fetal extravillous trophoblast cells (see below), all embedded in extracellular debris, fibrinoid, and blood clots. The surface of the basal plate is subdivided into 10-40 areas called cotyledons by a system of incomplete grooves. The grooves correspond histologically to the pillars that protrude into the lacunar system and subdivide it into 10-40 lobes.

The chorionic plate is the fetal surface of the placenta; it faces the amniotic cavity and the embryo, and gives rise to the umbilical chord. It consists of the amniotic layer and the chorion. The amniotic layer, which contacts the amniotic fluid, is a single layer of epithelial cells positioned above an avascular connective tissue stroma. The chorion is composed of a vascular stroma and trophoblast cells. Approximately 60-70 vascular villi (also called fetal lobules) emerge from the chorionic plate and protrude into the lacunar space, so that each lobe is occupied by one to four villi. Most villi are freely floating into the lacunar system, whereas others reach the basal plate anchoring the placenta to the maternal endometrium. Each villum consists of a stromal core covered by an epithelium-like layer called the villous trophoblast. The villous trophoblast has two components: cytotrophoblast and syncytiotrophoblast. The cytotrophoblast forms a complete, uninucleated layer of cells in direct contact with the basement membrane; as cells proliferate, they detach from the basement membrane, differentiate, and fuse to form the multinucleated villous syncytiotrophoblast. The syncytiotrophoblast is like a continuous blanket that envelopes the forest of villous trees. Its cells are polarized: the apical side of these cells, the one that contacts the maternal blood filling the lacunar system, has in fact numerous microvilli, which amplify the surface area about seven fold. Villous syncytiotrophoblast cells continue to differentiate after their formation, expressing proteins specific for this layer (HLA-G), but loose any proliferative activity so that the maintenance of this syncytial layer is totally dependent upon the cells from the villous cytotrophoblast.

The key mechanisms that induce tolerance at the placenta-decidua interface are summarized below.

Syncytiotrophoblast cells express a unique pattern of MHC molecules. They lack the classical MHC molecules (HLA-A, HLA-B, and class II molecules), even after interferon-gamma stimulation, but express classical HLA-C and non-classical HLA-E and HLA-G molecules [4]. This expression profile prevents NK cell activation and CD8 mediated cytotoxicity.

Syncytiotrophoblast cells and macrophages express high levels of indoleamine 2,3-dioxygenase [5], an enzyme that degrades and thus decreases the local concentration of tryptophan. T cells are extremely sensitive to tryptophan and do not proliferate when tryptophan levels drop [5].

Syncytiotrophoblasts express Fas ligand (CD95L) [6], a molecule that when bound to Fas (CD95) on activated lymphocytes induces their death, and complement regulatory proteins (like CD46, CD55, and CD59) that dampen complement activation [7].

The transformation of uterus into decidua is accompanied by a marked infiltration of NK cells [8]. In human peripheral blood, NK cells exist as two major subsets: $CD56^{dim}$ $CD16^{+}$ and $CD56^{bright}$ $CD16^{low\ or\ negative}$. The first and most abundant subset contains cells that are more cytotoxic, more refractory to IL-2-induced proliferation, and poor cytokine producers. In contrast, $CD56^{bright}$ $CD16^{low\ or\ negative}$ cells produce more cytokines, proliferate in response to low levels of IL-2, and have low cytotoxicity because of the absence or decreased expression of CD16. Uterine NK cells resemble the second subset because they express high levels of CD56, produce large amounts of immunoregulatory cytokines (e.g. IFNγ, GMCSF, TNF), and are less cytotoxic. Uterine NK cells likely originate from secondary lymphoid organs such as spleen and lymph nodes and then migrate to the decidua, homing through their Lselectin and α_4-integrin receptors [9]. The functions of uterine NK cells are still unclear. They might play a role in guiding the invading trophoblast into the decidual stroma, and in replacing the tunica media of the spiral arteries with fibrinoid material [8]. Mice deficient in uterine NK cells are prone to fetal losses, showing hypocellular decidual stroma and unmodified spiral arteries [10].

A lot of attention has been devoted lately to CD4 CD25 Foxp3 regulatory T cells (Treg), a population capable of suppressing proliferation and activation of other T cells, either through direct cell-cell contact or by release of immunosuppressive cytokines like IL-10 and TGF-β. Treg increase very early after conception, peak during the second trimester, and decline postpartum [11]. The increase is independent of paternal antigens since it can be seen also in syngeneic pregnancies [12]. Treg accumulate in the decidua, where they represent 30% of the total CD4 positive population [13]. The proportion of decidual Treg is significantly lower in specimens from spontaneous abortion than in those from induced abortions [14], indicating that Treg contribute to preventing fetus rejection. Recently, Schumacher and colleagues have shown that Treg are attracted to the implantation site by human chorionic gonadotropin (hCG) [15]. Once Treg are generated, they can suppress other immunological processes, rather than just controlling a response to the fetus semi-allograft.

The mechanisms highlighted above indicate that pregnancy is associated not with a state of immunosuppression, as previously believed, but rather with a state of selective tolerance. This selective tolerance is also transient [16]. Tafuri *et al* used mice transgenic for a T cell receptor recognizing the MHC molecule H-$2K^b$ (a class I MHC molecule homologous to the human HLAA), to follow the fate of T cells recognizing paternal alloantigens. These transgenic mice have a high number of cytotoxic CD8 T cells specific for the K^b antigen. When transgenic females are bred on a K^k MHC haplotype and then mated to K^b males, they harbor semi-allogeneic ($K^{k/b}$) fetuses. These pregnant females had reduced numbers of K^b-reactive T cells and accepted tumor grafts from K^b positive donors. After delivery, the T cell phenotype and responsiveness were restored, indicating that during pregnancy maternal T cells acquire a transient state of tolerance specific for paternal alloantigens [16].

3. Effect of pregnancy on thyroid and pituitary structure and function

Thyroid function and structure change profoundly during pregnancy, modifying the thyroid function tests [17] that thus need to be interpreted with greater attention.

The demand on thyroxine (T4) production from the thyroid gland increases as a consequence of the increased estrogen levels, which induce the hepatic production of thyroxin binding globulin. This carrier protein binds the T4 produced by the thyroid, decreasing the amount of free (bioactive) T4 in the circulation. The decrease stimulates the production of thyrotropin (TSH) from the pituitary gland until the total/free T4 equilibrium is re-established. Increased T4 production (or demand in hypothyroid women) continues even after thyroxine binding globulin levels plateau at mid gestation, reflecting the high thyroid hormone turnover secondary to fetal transfer of T4 and placental inactivation of thyroid hormones (see below).

Serum TSH levels (Figure 1A) decrease during the first trimester as a consequence of the placental production of hCG. This dimeric glycoprotein, the first marker of trophoblast differentiation, stimulates the production of progesterone by the ovary. The alpha chain of hCG is identical to that of TSH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH); whereas its beta chain is unique and responsible for the biologic activity. hCG also has a weak TSH-like activity so that high hCG levels during the first trimester (Figure 1B) induce a transient biochemical hyperthyroidism. TSH levels then increase during the second trimester and normalize in the third trimester.

Iodine, the essential element for thyroid hormone synthesis, decreases during pregnancy as a consequence of increased renal clearance and redistribution to the fetus. These changes are accentuated if the mother was iodine deficient before pregnancy, and can cause goiter and hypothyroidism [17].

Maternal thyroid volume increases during pregnancy (goiter) as a consequence of the iodine deficiency indicated above, the thyroid stimulatory actions of hCG, and the increased blood flow that induces a vascular intumescence of the thyroid [17].

The thyroid hormones produced by the mother enter the fetus via the placenta, which regulates this transfer through the expression of deiodinases [18]. The placenta expresses high levels of deiodinase 3, the inactivating enzyme, thus avoiding an unrestricted transfer of maternal thyroid hormones to the fetus. It is worth noting that in the first trimester the small amount of T4 escaping placental inactivation represents the only source of thyroid hormone in the fetus, before the appearance of a functional thyroid. This source is fundamental for the correct development of fetal brain. Low maternal T4 concentration due to hypothyroidism or iodine deficiency may lead to irreversible fetal brain damage [19]. Considering the pregnancy-related changes in thyroid function, most notable in the first trimester, gestation-specific reference intervals for TSH and T4 are recommended.

Pituitary structure and function also change significantly during pregnancy [20]. Pituitary weight increases by about 30% over the pregestational values of 0.5-1.0g [21], so that the mean pituitary height assessed by MRI increases from 5.5 to about 10 mm, peaking on day 3 after delivery [22]. Pituitary enlargement results from the hyperplasia and hypertrophy of the prolactin-secreting cells (lactotropes). Prolactin (PRL) is in fact the only anterior pituitary hormone that increases progressively during pregnancy (Figure 1A). No significant changes are seen for LH, FSH, and growth hormone (GH1) (Figure 1A). Corticotrophin (ACTH) increases progressively during pregnancy, peaking in labor (Figure 1A).

The increased estrogen levels modify the blood flow to the pituitary, so that more blood derives from the systemic circulation and less from the portal system [23].

4. Pregnancy and postpartum autoimmune thyroiditis

The occurrence of thyroid dysfunctions after delivery was published as early as 1825 by Dr. Caleb Hillier Parry, who reported the case of a woman with Graves disease appearing 3 months

postpartum, and 1888 by Dr. Horatio Bryan Donkin, who described a severe hypothyroidism 7 months after delivery. Postpartum autoimmune thyroiditis (PPAT) is a common endocrinological disorder that uniquely manifests itself within one year after delivery. The prevalence of 8% in the general population increases to 20% in women with type 1 diabetes or a family history of thyroid disease, and to 42% in women with a history of prior PPAT [24]. Symptoms may be subtle and confused with postpartum depression. Most patients (40%) become hypothyroid, a third hyperthyroid, either because of destructive thyrotoxicosis (24%) or Graves disease (11%), and the remaining patients (25%) develop a biphasic form characterized by an initial hyperthyroidism followed by hypothyroidism. PPAT is transient in most women but evolves to permanent hypothyroidism in 20% of the patients or, more rarely, to Graves disease.

The presence of serum antibodies against thyroperoxidase during the first trimester is the best predictor of PPAT development. In 2000, RC Smallridge reviewed 10 studies assessing the utility of this testing [25]. The odds of developing PPAT were on average 33-fold greater (range 10-59) in women with thyroperoxidase antibodies than in those without. Thyroperoxidase antibodies were absent in the majority of healthy women who did not develop PPAT (0.94 average specificity, range 0.90-0.98), and present in the majority of women who develop PPAT (0.71 average sensitivity, range 0.45-0.89). These sensitivity and specificity values, however, translated to a mediocre positive predictive value (average 0.57, range 0.31-0.78) so that a systematic screening of all pregnant women for thyroperoxidase antibodies is currently not recommended [26].

The mechanisms underlying PPAT remain unknown. Women who develop PPAT have a higher CD4/CD8 ratio in the peripheral blood [27] and the thyroid [28], and a greater number of activated T cells [29], suggesting a heightened immune activity during and after pregnancy, which could trigger PPAT.

Microchimerism is another possible explanation. Fetal immune cells cross the placenta and home to the maternal thyroid gland, triggering an autoimmune reaction akin to the graft-versus-host reaction [30]. Fetal cells have been reported in the thyroid of patients with autoimmune thyroid diseases, although studies looking specifically at PPAT are lacking. Ando and Davies propose that after delivery, when placental tolerogenic mechanisms are lost, intrathyroidal fetal immune cells are activated and initiate a graft-versus-host reaction against maternal antigens resulting in the activation of maternal autoreactive T cells which could eventually modulate autoimmune thyroid diseases in the postpartum [30]. In fact, a study on systemic sclerosis found that fetal T cells in the peripheral blood and skin lesions of women with systemic sclerosis are capable of proliferating in response to maternal MHC [31].

Genetic susceptibility has also been reported in PPAT, with candidate genes similar to those reported for Hashimoto thyroiditis (MHC class II DR3) [27]. In keeping with this susceptibility, PPAT associates with other autoimmune manifestations. For example, Manetti and colleagues have reported that pituitary antibodies are 5 times more common in PPAT cases than in healthy controls (27% versus 5% prevalence) [32].

5. Pregnancy and autoimmune hypophysitis

Autoimmune hypophysitis (AH) is an endocrine disease of more recent characterization. Even in the original reports in the 1960s, a striking temporal association with pregnancy was recognized. This association is clear in the form of AH that affects the anterior pituitary lobe. Of the 215 women thus far reported with adenohypophysitis at ages between 15 and 45 years, 149 (69%) manifested AH during late pregnancy or postpartum. The association is much weaker for infundibulo-neurohypophysitis and pan-hypophysitis [33]. AH usually presents in late pregnancy or early postpartum with neurologic symptoms due to compression of meninges

(headache) or optic chiasm (visual disturbances). Development of AH during pregnancy seems to have no adverse effects on the fetus or on the ability to become pregnant in the future [34-36]. In addition, when a subsequent pregnancy occurs in a patient with AH, the risk of disease recurrence is not increased by the history of AH. Numbers, however, are small and symptom recurrence has been reported during subsequent pregnancies. Sinha *et al.*, for example, reported a woman who developed AH during her first pregnancy (at week 32 of gestation), and then experienced a recurrence during her second pregnancy (at week 16) [35].

Perhaps the most compelling evidence of a mechanistic link between pregnancy and increased susceptibility of the pituitary gland to develop hypophysitis comes from a recent case report of ovarian teratoma [37]. Derived from pluripotent germ cells, teratomas can give rise to ectopic tissues (such as teeth, hair, and jawbone) in the organ where they reside. It is exceedingly rare for a teratoma to give rise to anterior pituitary tissue. Schreiber-Facklam and colleagues described a 30-year old woman during the 19th week of pregnancy who developed acute abdominal pain. Ultrasound showed a 4 cm cyst in the left ovary, with normal uterus, placenta, and fetus. The patient underwent emergency laparoscopy to remove the ovarian mass. Histology showed a mature cystic teratoma with an island of adenohypophyseal tissue. Remarkably, this tissue was infiltrated by numerous T and B lymphocytes, faithfully reproducing the histological appearance of AH.

The mechanisms discussed above do not explain why the incidence of AH actually rises during pregnancy. Based on the tolerance mechanisms described above, one would predict suppression or amelioration of AH during pregnancy rather than exacerbation. A possible explanation for the link between pregnancy and AH is molecular mimicry, that is the existence of an autoantigen expressed both in the pituitary gland and the placenta.

O'Dwyer and colleagues first proposed gamma enolase as a candidate for this molecular mimicry. The enzyme catalyzes the interconversion of 2-phosphoglycerate and phosphoenolpyruvate, the penultimate step in glycolysis. This highly conserved protein [38] exists in mammals as a dimer, made by the combination of three different subunits (alpha, beta, and gamma). Enolase 1 or alpha (made of two alpha subunits encoded by human chromosome 1) is expressed in every cell. Enolase 2 or gamma (made of two gamma subunits encoded by chromosome 12) is expressed mainly in the brain including hypothalamus and pituitary, but also in T lymphocytes and pancreatic islets. Enolase 3 or beta (made of two beta subunits encoded by chromosome 17) is expressed mainly in the tongue and skeletal muscle, but also in thyroid, liver, and heart. O'Dwyer and colleagues reported that gamma enolase was expressed also in the placenta, and was recognized by the serum of a patient with peripartum AH [39].

Lupi and colleagues described more recently a peptide (KDLEEGIQTLMGRL) recognized by the serum of AH patients but not controls [40]. This peptide is found in both the pituitary growth hormone (GH1) and the placenta chorionic somatomammotropin hormones (CSH1 and CSH2) [40]. The somatomammotropins, formerly known as placental lactogens, are two nearly identical glycoproteins of 217 amino acids differing only at the third position (proline in CSH1 and alanine in CSH2). It is possible that immune recognition of CSH spreads during pregnancy to GH1, causing the clinical appearance of AH. Notably, CSHs are the hormones that reach the highest concentrations during pregnancy (Figure 1B), providing ample antigenic supply to a primed immune response. More studies need to be performed to confirm that indeed the peptide is recognized specifically by AH patients and is capable of inducing an experimental model of hypophysitis when injected into animals.

Another possible explanation of the link between pregnancy and AH is the transformation in structure and function that occurs in the pituitary during pregnancy (summarized in section 3). These changes may render the pituitary gland more accessible to the immune system or increase

the release of pituitary antigens. Finally, pregnancy and the associated pituitary enlargement can simply unmask a pre-existing but clinically silent disease, working as an enhancing factor.

In summary, the fascinating association of AH and PPAT with pregnancy remains unexplained, but much can be learned through efforts aimed at explaining it.

Take-home messages

- • Pregnancy is associated with a selective and transient state of tolerance, rather than with generalized immune suppression.
- • AH and PPAT presentation is tightly linked with pregnancy.
- • The mechanisms explaining the association between pregnancy and AH or PPAT remain to be elucidated. When identified, they will advance our understanding of disease pathogenesis and likely provide new diagnostic assays or treatments.

Acknowledgments

The work was supported by NIH grant DK080351 to PC, and by the Heideneich-von-Siebold-Stipendium Georg-August-University Göttingen, Germany to AG.

Abbreviations

AH	autoimmune hypophysitis
PPAT	postpartum autoimmune thyroiditis
MHC	major histocompatibility complex
HLA	human leukocyte antigen
hCG	human chorionic gonadotropin
TSH	thyrotropin
CSH	chorionic somatomammotropin hormone

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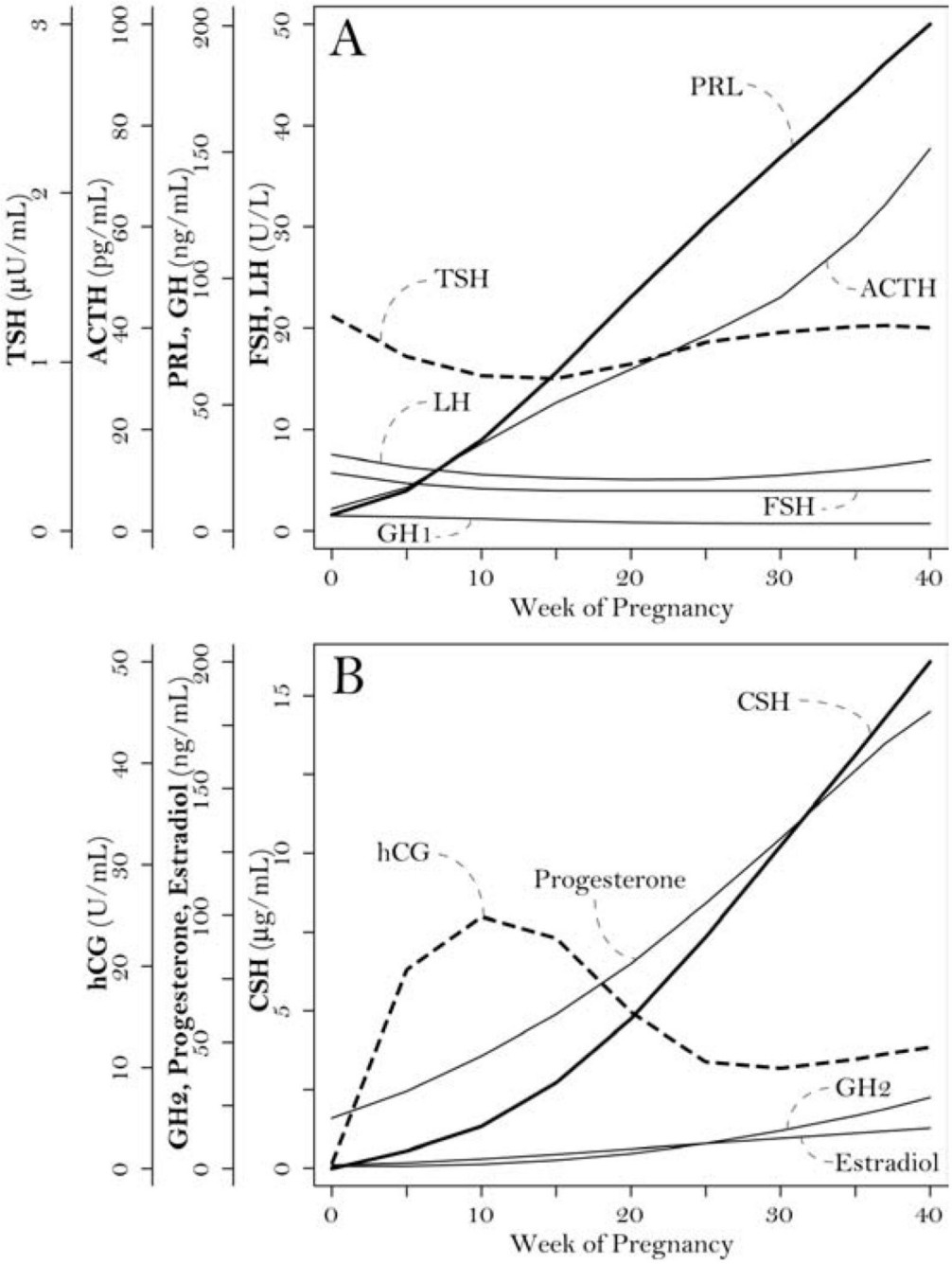

Figure 1.
Serum levels of pituitary (A) and placental (B) hormones during pregnancy.

Table 1

Mechanisms that induce tolerance at the placenta-decidua interface

Syncytiotrophoblast expresses a unique pattern of MHC molecules
Expression HLA-G and release of HLA-G1
Expression of HLA-E
Expression of HLA-C
Lack of HLA-A, HLA-B, HLA-DP, HLA-DQ and HLA-DR
Syncytiotrophoblast expresses high levels of indolamine 2,3-dioxygenase
IDO reduces the local concentration of tryptophan below the level required for T cell activation
Syncytiotrophoblast expresses Fas ligand
Induction of apoptosis on Fas positive T cells
Syncytiotrophoblast expresses regulatory proteins (CD46, CD55, and CD59) that lower complement activity
Decidua is infiltrated by uterine natural killer cells
Decidua is infiltrated by regulatory T cells