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Mechanism of Autoimmunity in Pregnancy - The Good and the Bad

Lotti Tajouri[1,2], Ekua W. Brenu[1,2],
Donald R. Staines[1,3] and Sonya M. Marshall-Gradisnik[1,2]
[1]*Population Health and Neuroimmunology Unit, Faculty of Health Science and Medicine, Bond University, Robina,*
[2]*Faculty of Health Science and Medicine, Bond University, Robina,*
[3]*Queensland Health, Gold Coast Population Health Unit, Southport, Australia*

1. Introduction

In humans, female's humoral and cellular immunity are actually stronger than men (Nalbandian & Kovats, 2005) and present a higher antibody serum titration than men (Giron-Gonzalez et al., 2000) which could logically and possibly explain their gender predisposition and susceptibility to autoimmunity. Holding an autoimmune disease and becoming pregnant is a serious matter for a woman and knowledge of the course of the condition during pregnancy is essential. Relational variations exist between types of autoimmuny during pregnancy and consequently proper advices from physicians are provided accordingly. In Systemic lupus erythematosus, all advices provided to the patients are meant to dissuade women from getting pregnant while being in a relapse stage of the disease and better wait for the end of the flare pathological course. As for Rheumatoid arthritis and multiple sclerosis, no real dangers are encountered while being pregnant and while the disease symptoms are expressed it still does not present life threatening risks to the gestation. In Myasthenia gravis, during gestation the risks are variable and retrospective studies show increase complications.

Logically, the baby carrying semi-allogenic antigens should prompt an autoimmune reaction from the mother. However a plethora of tolerance measures is put into action by both the mother and the foetus. Pre implantation immunological events are in place to best prepare the nidation of the foetus into the mother endometrium. There is large paucity of published scientific research studies that have attempted to understand the entire pregnancy immune profile due to low power studies, limiting longitudinal samplings and narrow immune component analysis. However, a recent study has shown a Th1 toTh2 shift with increase interleukin 10 synthesis and a decrease responses to pro-inflammatory cytokines such as TNFα, Il-1β and Il-6 during pregnancy (Denney et al., 2011). Immunological adaptations occur early in gestation and are mediated by the uterine epithelium including the fallopian tube secretion of granulocyte macrophage colony stimulating factors (GM-CSF) (Rosendaal, 1975). In addition, the trophoblast that is derived from the fertilized egg secretes GM-CSF to prepare best for the next step of implantation

and formation of the placenta (Burgess et al., 1977). Post implantation, the placenta is formed to accommodate, protect and feed with key nutrients the growing foetus. The placenta is formed of different layers with the basal plate or deciduas basalis, a structure in direct contact with the endometrium, the intermediate layer being the lacunar system and finally the chorionic plate made of two leaflets, the chorionic plate and the amniotic plate. Interestingly, the content of the decidua is composed of different key factors aiming at inducing tolerance and include cells such as maternal Natural killers and regulatory T-cells. Natural killer cells are secreting lots of cytokines with immunoregulation purposes and are non cytotoxic (Chantakru et al., 2002). As for the regulatory T-cells, data showed that human chorionic gonadotropin hormone is responsible for the attraction of such cells in the placenta (Schumacher et al., 2009). It has also been proved that Treg are key determinants in murine pregnancy (Zenclussen et al., 2005) with possibly the mediation of interleukin 10 (Taylor et al., 2006 & Akdis et al., 2001). The relative proportion of immune cells found in the deciduas are as follows, 70% of natural killers (Moffet et al., 2004), 20% of macrophages (Lessin et al., 1988), around 2% of T lymphocytes (Lessin et al., 1988), 1% of dendritic cells (Gardner et al., 2003) and very minute B cell lymphocytes (Veenstra Van Nieuwenhoven et al., 2003). In addition, regulatory proteins decreasing complement action are found in the decidua basalis more precisely on the syncyciotrophoblast T-cells along with cellular membranar Fas ligands and MHC molecules. MHC molecules consist of class III MHC molecules but lack of particular HLAI and HLA II molecules including HLA-A and -B as well as HLA-DP, -DQ and –DR is noticed (Landek-Salgado et al., 2010). Interestingly the placenta is maintaining a tied tolerance status mediated by each of its functional molecular and cellular components playing a major role in this process. Mostly, any activated T-cells that would reach this mother-foetus interface border would be bound to Fas ligand on their Fas receptor condemning them to enter apoptosis (Pongcharoen et al., 2004). This apoptotic process is mediated by Fas pathway through the activation of the death induce signaling complex that ultimately activates the caspase apoptotic cascade. More importantly, regulatory T-cells accumulating in the decidua during pregnancy, dampen any pro-inflammatory that harm the foetus (Tilburgs et al., 2008).

Along with this immunosuppressive function, an immune tolerance is strongly put in place. Transient gestational lowering reactivity is set to prevent potent T-cells from reacting against the semi-allogenic foetus and previously demonstrated in animal studies (Tafuri et al., 1995). Immuno tolerance features that directly play roles on pro-inflammatory immune cells are relying on particular cells called T regulatory cells or Tregs (Kuniyasu et al., 2000). Tregs can be Th4 lymphocytes or T8 lymphocytes and are mostly found to act as immunomodulators in regions of inflammation (Gavin et al., 2002). The action is mediated by contact inhibition of non Treg cells such include subsets of T 4 and T8 lymphocytic cells. Specific markers are differentiating these subsets from regulatory to non regulatory effective T-cells (Teff) and include CD25 markers (α chain of IL-2 receptor) with the so called CD4+ CD25+ and CD8+CD25+ cells. Additional markers are also found in Tregs such as FoxP3+ marker, a repressor activator of activated T-cells such as CD4+CD25+FoxP3+ Treg cells or Cd8+ CD25+ CDFoxP3+ Treg cells. Another Treg marker is CXCR3+ seen in CD8+ CXCR3+ Treg cells. The Treg mediation in tolerance restoration can be undertaken through different mechanisms. Tolerance could be undertaken by contact interaction such as Fas- Fas ligand interaction dictating an apoptotic faith to the Teff cells (Watanabe et al, 2002). The other way Tregs are promoting tolerance to Teff cells is to inhibit Teff cytokine synthesis and

subsequently their Teff cytolytic activation as well as diminishing their proliferation (Duthoit et al., 2005). Teff cells can be CD8+ or CD4+ cells with the latter being classified into two types, TH1 and TH2 both differing in action as pro-inflammatory and anti-inflammatory actions respectively. Briefly, the Th1 activation pathway consists in interferon γ inducing activation of its cell surface receptor on T cells and subsequent intracellular cascade activation. Such cascade leads to the activation of the transcription factor T-bet which function is to bind DNA responsive elements of genes within the nucleus. The main responsive elements controlled and activated belong to the genes interferon γ and IL-12 receptor β2 chain. Upon activation, further expression of these genes is undertaken and IL-12 receptor becomes widely available at higher amounts in the cellular T-cell membranar surface and therefore can be prompted to activation due to the presence of local IL-12 cytokine. IL-12 receptor actiavtion induces a second cascade that is Stat 4 dependent, with the ultimate goal to produce furthermore T-bet transcription factor. Relation between Tregs and pro-inflammatory TH1 and CD8+ T-cells demonstrate an interesting phenomenon that is build around the competition for Interleukin 2 binding. In sites of inflammation, binding of IL-2 by Tregs diminishes the availability of IL-2 to Teffs and therefore limiting their growth, function and even at early stage turning Teffs to be anergic towards antigens (Piccirillo et al., 2001). Briefly, T-cells are activated through the contact of antigen with T-cell receptor under the restriction of MHC class molecules. Such binding activates p56lck tyrosine kinase with subsequent downstream phosphorylation of proteins and activation of phospholipase C. Such phospholipase generates from phosphatidyl inositol diphosphate, two compounds; the diacyl glycerol and inositol tri-phosphate, IP3. The endoplasmic reticulum IP3 receptor is therefore activated with release of calcium in the cytosol. Such Ca2++ induces a membranar activation of the cell membrane calcium release activated calcium channel named CRAC and subsequently increases highly the intracellular Ca2++ concentration. High levels of Ca2++ activate caclineurin, a phosphatase that dephosphorylates the transcriptional factor NFAT (nuclear factor of activated T-cells). Such dephosphorylated NFAT translocates into the nucleus to reach responsive elements of Il-2, AP1 and NFKB enabling their expression and future function. Beside the roles of Tregs as pro-apoptotic cytolytic Teff cells inducers and Teff cells expansion inhibitors, Tregs are capable to modulate the inflammatory 'soup' and pattern observed in inflammation sites. Such action of Tregs is mediated by their synthesis and secretion of both TGFβ and interleukin 10. A higher content of Il-10 is maintained due to Teffs response to TGFβ action and secondly by Il-10 action on dictating Teffs to respond with higher affinity to TGFβ. In addition, the constant increase of progesterone in gestation, which is peaking at the third trimester, is responsible for the activation of particular subsets of T-cells called γδ T-cells. Upon binding to its receptor, progesterone activates γδ T-cells to secrete Il-10 and progesterone induced blocking factor (PIBF) that result in the inhibition of natural killer cells (Barakonyi et al., 1999). In addition, these cells synthesise TGFβ that enhances the mother's T-cell tolerance for the foetus (Mincheva-Nilsson et al., 1992).

2. Autoimmunity and pregnancy

Women are more prevalent to autoimmunity and 3 to 5% will be affected by such disorders. During pregnancy, clinical course of several autoimmune disease are expressed with variable degrees. Some range from higher remission of signs and symptoms while others are

being increased in exacerbations. These influences observed in Pregnancy denote a complex interaction between the pathophysiological course of the disease and the physiological adaptations during pregnancy. Presence of a wide spectrum of auto-antibodies correlates with the parturient pathophysiological course. In some autoimmune diseases, the risk of transient neonatal illness could be observed and can range from low risk as in myasthenia gravis to relatively higher as in Lupus. Self tolerance mechanisms at the cellular and genetic levels are modulated during pregnancy by these autoimmune diseases. Such modulation might reside at different levels and include, allelic variation with the HLA loci and expression, physiological adaptations during pregnancy (hormones) and alteration towards the host immunity or the foetal antigens (paternal HLAs), cytokine profile during pregnancy, HLA from foetus (HLA-G), structural interface integrity between foetus and mother, status of intrinsic and extrinsic controls preventing autoimmunity. We aim in this review at discussing the immunological events that surround pregnancy and autoimmunity especially by focusing on Systemic lupus erythematosus, Rheumatoid arthritis, Myasthenia gravis and Multiple sclerosis.

2.1 Systemic Lupus Erythematosus

2.1.1 Pathophysiology of SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease mainly affecting the connective tissue that consequently demonstrating a plethora of systemic effects mostly observed in individuals of African-Asian origin. A staggering 9:1 ratio females to males is noted with a peak age of onset in young woman between 25 and 35 years of age. More than 98% of SLE patients are positive for the antinuclear auto-antibody (ANA), a marker of the disease. Other auto-antibodies are used to better refine the diagnosis of SLE and include anti cytoplasmic and anti DNA antibodies. The pathology shows a diverse range of symptoms affecting several organs ranging from common cutaneous lesions, serous membrane alteration and intermittent joints debilitations. More precisely, facial malar rashes, arthralagia, polyathritis, pleurisy, pericarditis are experienced along with other symptoms like Raynand's phenomenon and fever. The etiology of this complex disease is unknown but several hypotheses have been raised. Cellular release of antigens from apoptotic and necrotic cells is raised that will trigger macrophage phagocytosis and subsequent antigen presentation, under MHC class II, of such autoantigens to both T and B-cells. Intracellular and extracellular signaling are thought to be dysregulated such as the so called interferon signature, a cytokine profile under scrutiny as links with IRF5 has been shown to be associated with SLE (Graham et al., 2006). CD19 positive B-cells are of high attention in research as several auto-antibodies are pathogenic in the disease such as the anti nuclear antibodies (Madaio et al., 2003).

The genetics of SLE has pinpointed several chromosomal loci with interestingly the 1q23-24 region also called the pentraxin locus, a region harboring some key candidates including the CRP4 allele gene and the PDCD1 gene. A single nucleotide polymorphism in the PDCD1 gene was found to disrupt an intronic enhancer that prevents the gene from further activation with subsequent apoptotic process alterations. Other hypotheses have been investigated such as the possible occupational exposure or environmental effects but with no direct significant links to the disease. An interesting phenomenon though is well documented with the attention on precipitating factors. Such precipitating factors seen in SLE are the intake of oral estrogen contraceptives and hormonal replacement therapies (HRT) (Sanchez-Guerrero et al., 1997). Several studies including a nurse health study for

oral contraceptive use have shown an increase of 1.9 time SLE manifestations compared to non users (Sanchez-Guerrero et al., 1995) and similar effect have been demonstrated with HRT (Cooper et al., 2002). In addition a lot of evidence is showing that the SLE manifestations are correlated with ovarian cycle alterations (Shabanova et al., 2008). A clear link is seen between hormonal changes and SLE therefore higher vigilance is sought for SLE women willing to become pregnant.

2.1.2 Modulation effects of pregnancy in SLE mothers

Pregnancy presents as a life experience where mother's hormonal levels are evolutionally and physiologically adapting to host the baby. Careful monitoring is undertaken as different gestational outcome scenarios are observed, with some being unpredictable, due to recurrence of flares and possible life threatening issues affecting both the mother and the child. Such dangers ranges from intra-uterine growth retardations in 30% of cases (Meyer Oliver, 2003), preterm birth with 25-30% of cases to miscarriages and foetal death. Co-morbidity is most likely to be observed in SLE patients with increase manifestation of the disease in the third trimester of gestation. Lots of evidence show detrimental effects to the kidney such as lupus nephritis, and atheroslcerotic pathophysiological establishments (Roman et al., 2003 and Asanuma et al., 2003) all to which can be further aggravated with other common pregnancy experienced problems like seen with preeclampsia occurrence. Death of the mother can be observed with common SLE risks due to high elevations of pulmonary hypertension. In 37% of SLE pregnant patients, mild increased of pulmonary arterial hypertension can be seen (Johnson et al., 2004). Such monitoring requires the use of several tests, serum antibodies, choice of specific medication, compliance with hydroxychloroquine, as well as the monitoring of SLE disease activity index (SLEDAI) measuring the flaring panel observed in SLE patients. Interestingly, SLE patients would have positive benefits and gains to start their gestation in period of remission before conception. An otherwise preconception with active disease otherwise shows increased flares with particularly renal disease associated problems (Moroni et al., 2002). In addition, lower birth weigths and high number of caesarian deliveries are encountered in proliferative nephritis cohorts. Foetal loss in SLE is a major problem with several studies attempting to link this fatal outcome to molecular triggering factors. The Hughes syndrome is a phospholipid induced pregnancy syndrome commonly named the antiphospholipid syndrome. Such syndrome is part of the coagulopathy diseases and SLE pregnant women are commonly tested for the presence of lupus anticoagulant factor, an anti phospholipid factor named anti-cardiolipin. This immunoglobulin G anti-cardiolipin antibody targets the apoprotein H or beta 2 glycoprotein 1. Such antibody prevents the glycoprotein from undertaking its possible known function as an inhibitor of the intrinsic coagulation cascade, an inhibition required and mediated by the release of complement molecules, C3 and C5 from the liver. As a consequence, SLE mothers with increase anti-ApoH denote a procoagulant pattern with detrimental foetal loss as an outcome. Interestingly, with treatment regimens of aspirin and heparin intakes, levels of live birth rates from SLE pregnant patients is now around 80% (Clark et al., 2007 and Girardi et al., 2004). Several markers for the disease have been found to better classify and understand the pathological course.

Efforts of the research community have helped in the discovery of a series of serum markers for SLE such as adipokine, a cell to cell signaling protein secreted by the adipose tissue (De Sanctis et al., 2009), CD40L or CD154 found in T-cell surface (De Sanctis et al., 2009 b) and

the poly-reactive immunoglobulin M from B-cells (Zhang et al., 2009). All these markers denote an intense cell to cell communication and intense modulatory involvement of the immune system. Both arms of the immunity system are involved in SLE and particular attentions are drawn to further unravel the pathophysiological mechanism in SLE patient's immunity. SLE immune dysregulation involves a role to T-cell activation (Fernandez et al., 2009), B-cell signaling (Liu et al., 2009 and Peng, 2009) along with altered chemokine patterns (Youinou et al., 2009 and Wittmann et al., 2009) with IL-6 playing a role in polyarthritis and joint damage (Fonseca et al., 2009) and as mentioned previously an interferon signature (Finke et al., 2009).

The complex cascade of T-cell activation from the T-cell receptor (TCR) the consequently increase in intracellular content of Ca2++ and NFAT mediated IL-2 Transcriptional activation is an important immune component in SLE. In SLE, such pathway of activation is altered and seems to be associated with the calcium processing. ER calcium content not being an issue, a lot of attention was given to CRAC and studies have shown altered efficiency in this Ca2+ channel. Evidence has also shown that in SLE patients a Ca+ alteration was observed and linked to an upstream mitochondrial dysregulation. Evidence of high membrane hyperpolarisation (MHP) of the inner membrane of the mitochondrial has been pinpointed in SLE T-cells with subsequent ATP decreasing synthesis and failure to regenerate glutathione reduced forms, a anti oxidant molecule. Such dysregulation seems to be as well the cause of the unbalance fate observed in SLE T-cells deaths. Instead of progressing to a program cell death, with the common FAS pathway and death inducing signaling complex cascade, SLE T-cells instead enter necrosis. As both ATP and reduced glutathione pools are low, apoptosis is prevented and as such unbalance of quality cell death tends to develop into two main consequences. First, necrosis is favored and induces inflammation whereas apoptotic bodies do not. Secondly, in SLE, such overall dysregulation of calcium (katsiari et al., 2002), ATP formation (Perl et al., 2004) and low antioxidant capacity profile (Wang et al., 2010) is in favor to auto-reactive T-cells.

A strong correlation has been found between CXCL10 and SLE disease (Kong et al., 2009). CXCL10 is the interferon inducible factor, chemokine (C-X-C motif) ligand 10 also known as IP10 that acts on the receptor CXCR3. Interestingly, the gene coding for such receptor is the unique chemokine receptor found in chromosome X. This is in clear contrast to all other chemokine receptor genes, suggesting unique functions for CXCR3 and the ligand CXCL10 in possibly the role in SLE immunity. In sites of inflammation, a subset of B-cells with high expression of the marker CD19, a co-receptor of the B-cell receptor and known to be implicated in auto-immuniy, shows elevated CXCR3 levels (Nicholas et al., 2007). More challenges are met during pregnancy where placental tissues and the new born semi-allogenic foetal cells are brought together along with SLE (Doria et al., 2008). High consequences were recently tabulated in pregnant women with SLE with approximately 25% of women presenting with disease exacerbations (Lockshin et al., 1989).

2.2 Myasthenia and pregnancy

2.2.1 Pathophysiology of myasthenia gravis

Besides T-cells, breakdown of self tolerance in autoimmune diseases can be associated with humoral B-cell mediated immunity producing pathological auto-antibodies contributing to tissue damage as seen in myasthenia gravis (MG). MG is an autoimmune disease affecting predominantly women with clinical muscle fatigability with patients suffering from degrees

of weakness at various body systems. Under approximately 40 years of age, women are prevalent but after 50 years of age, incidence is then lesser in women than men. (Grob et al., 2008). The disease is categorised into two clinical presentations with on one hand, the ocular MG affecting of the levator and extra ocular palpebrae skeletal muscles with common diplopia and ptosis and in the other hand, generalised MG affecting other skeletal muscles. Interestingly, the disease can occur as relapsing remitting and the onset of symptomatology is varying from acute to subacute. Auto-antibodies target different antigens including the acetylcholine receptor (AchR) and, in most intense disease presentation, target the muscle specific muscle protein named MuSK (Padua et al., 2006). AchR and MusK seropositivity lead to neuromuscular dysfunctions. In the case of anti AChR, the antibodies trigger neutralisation of AChR function (Drachman et al., 1982), as well as antibody dependent complement activation with membrane attack complex formation (Engel et al., 1987) and finally antibody cross link with the ACHR leading to the destruction of AChR. The early onset MG is also associated with the possible occurrence of other autoimmune insults most commonly against the thyroid (Christensen, 1995). In early onset MG, the thymus gland is enlarged and patients present with multiple auto-antibodies. However, late onset MG is not associated with enlarged thymus. Association of HLA markers with individual type of MG onset has been undertaken and data showed that the early onset MG is associated with HLA-B8 and DR3 (Compston et al., 1980) whereas late onset MG is associated with HLA B7 and DR2 (Maggi et al., 1991). Immunologically the thymus is a primary lymphoid organ with a highly responsible function to maturate T-cells. T-cells that were produced in the bone marrow enter the thymus to become thymocytes to undergo a subsequent series of selection. The whole thymus is built to this process with a well vascularised content, clusters of different types of cells including antigen presenting cells such as macrophages, dendritic cells and parenchymal epithelial cells. When maturation of thymocytes is terminated, an efferent drainage successfully drains these cells into mediastinal lymph nodes. This selection is aiming at positively selecting immature T-cells which T-cell receptor would recognise MHC molecules. In the other hand, the negative selection aims at discarding the T-cells that would react to autoantigens presented by APCs. A failure in undertaking the removal of autoimmune T-cells is thought to be the problem occurring in MG disease. Certain T-cells, Th4 or CD4 + were investigated for their possible cell mediated autoimmune dysregulations. Interestingly though, both patients and free of disease normal individuals do have autoimmune T-cells targeting AChR (Schluep et al., 1987). Using experimental autoimmune **myasthenia** gravis (EAMG) animal models with Th1 deficient cells, researchers have shown actually that such animals have susceptibility to autoimmunity (Balasa et al., 1997). In this latter study, the focus was to distinguish between wild type and EAMG interferon gamma knockout mice. Result showed that EAMG knockout mice had no weakness to their muscles and were resistance to MG. However, the level of proliferation of AChR primed lymph nodes was still proliferating as normally observed in wild type mice. As interferon gamma is the primary pro-inflammatory stimulator of TH1 cells with downstream activation of the T-bet transcription factor inducing further interferon gamma transcription, MG autoimmunity induced solely with Th1 cannot be explaining the entire course of the disease. Even other types of autoimmunity such as in multiple sclerosis experimental allergic encephalomyelitis animals, observation of both interferon gamma deficient mice and T-bet knockout mice did not protect these autoimmunity disorders (Ferber et al., 1996). In Balasa et al. study, lymphogenic changes using mice with intact thymus were investigated but researchers focus is also turned into directly thymectomized

animals. The thymic tissue is also harboring regulatory T-cells CD4+ CD25+ cells or Tregs that are anergic to antigen presentation (Crispin et al., 2003). These cells act as suppressors of effective autoimmune T-cells as demonstrated in Tregs deficient animal studies showing increase signs of autoimmunity disorders (Sakaguchi et al., 1995). Particular markers on the surface of Tregs are responsible for the immunological self tolerance function of Treg and include CD80, CD28, CD40 and CTLA4 with the later being a strong negative regulator of T-cell activity. Other subsets of cells called CD4+ CD25+ CD103+ are showing furthermore potentials in self tolerance and suppressive functional features in comparison to CD4+ CD25+ T-cells.

2.2.2 Modulation effects of pregnancy in Myasthenia gravis mothers

T-cells detain estrogen receptors on their membrane and studies have shown a high correlation between estrogens and disease detrimental activity. Interestingly, estrogens induce an expansion of specific Th1 effector cells with subsequent MG autoimmunity and increase of anti AChR antibodies (Delpy et al., 2005). In normal pregnancy, Tregs mediate immune tolerance (Guerin et al., 2009) and data previous data show that in early pregnancy estrogens do act on these CD4+ CD25+ T-cells to mediate indeed immunosuppression and higher immune tolerance. Such effect is relayed by progesterone during the rest of the gestation (Mao et al., 2010). Such positive effect might resign in the difference between CD4+ CD25+ and CD4+ CD25- T-cells. Differential gene expression of these two subsets showed higher expression levels of CTLA4, galactin, CD103, TNFRSF18, TNFRSF4 and the glucocorticoid induced TNF receptor called GITR (McHugh et al., 2002) in CD4+ CD25+ cells. Interestingly, inhibition of GITR abrogates regulatory T-cell activity precipitating autoimmunity. In addition, GITR can be activated by progesterone receptor (Nelson et al., 1999 and Kanamaru et al., 2004) and possibly progesterone acts on Treg cells by upregulating GITR among other effects. Interestingly, in studies experimenting EAMG animals, the treatment of analogs of myasthenogenic peptides notably demonstrated a decrease in lymph node proliferation as well as a decrease of INFγ involving the action of CD8+ Tregs (Ben-David et al., 2007).

Newborn can develop neonatal MG and is observed in around 10 % of mother holding the burden of the disease (Beekman etal., 1997). This acquisition is mediated by the passage from the mother to the foetus of immunoglobulin G anti acetylcholine receptors. In large majority, babies do not pursue the course of neonatal MG and few weeks following their birth, neonatal MG naturally undergo full resolution.

2.3 Rheumatoid arthritis and pregnancy

2.3.1 Pathophysiology of rheumatoid arthritis

Rheumatoid arthritis is a severe chronic inflammatory disease of relatively high prevalence that primarily affects the joints via a systemic autoimmune reaction. While its aetiology remains unknown, many cell populations contribute to the inflammatory response in the synovium, leading to joint erosions, joint deformation and loss of function. Histological features often include proliferation of synovial cells, plasma and lymphoid cell infiltration, neovascularisation, macrophage accumulation and typical palisading structure of the cell lining hyperblasting synovial membranes. One particular hallmark used in diagnosis of RA is the rheumatoid factor (RF) and the particular association with HLA-DR4. Common cytokine abnormalities in RA include an increase in tumor necrosis factor alpha (TNFα) and interleukin-1β (IL-1β) with subsequent induction of metalloproteinases (MMPs) degrading

the synovial matrix (Dayer et al., 2001). Gene expression studies sampling synovial tissue have highlighted the heterogeneous nature of the disease and suggest the existence and contribution of multiple pathogenic pathways (van der Pouw Kraan et al. 2003). As tissue biopsies are invasive, alternative and clinically more practical studies of gene expression changes in peripheral blood mononuclear cells (PBMC) from patients with RA have been reported (Olsen et al., 2004 & Edwards et al., 2007), with a recent study highlighting that 10 differentially regulated transcripts in RA patient PBMC mapped to chromosome region 6p21.3, the major histocompatibility (MHC) locus III (Edwards et al., 2007). In addition to the cellular involvement, Rheumatoid arthritis is an auto-antibody disorder that will ultimately affect the joints. Antibodies like IgM and IgA are known to target the Fc fragments of IgG but in addition targeted citrullinated antigens are found in RA patients but are not exclusive to these patients. The autoimmune attack mainly is associated with elevated amounts of Tumor necrosis factor (Feldmann et al., 1996) and elevation of specific joint cells (found in both cartilage and synovium). The synovium contains macrophage like synovial cells and fibroblast like synovial cells. In RA, the joint macrophage like cells are known to secrete a large panel of pro-inflammatory cytokines whereas the fibroblast like cells are showing invasive the cartilage (Muller-Ladner et al., 1996) and are responsible, at some extent, to joint destruction with osteoclastic activity (Tolboom et al., 2005). Interestingly, inhibiting and preventing osteoclast induce destruction of the joints is not associated cessation of the overall localised pro-inflammatory profile (Cohen et al., 2008). Common therapeutic agents used in treating RA include disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and Tumor Necrosis Factor (TNF) inhibitors which inhibit the pro-inflammatory activity of TNF, identified as a key mediator in the inflammatory response. Despite the improvement of joint function in 60-80% of patients with TNF inhibitors and methotrexate combination therapy, a remaining 20-40% of patients do not respond to this treatment (Baton et al., 2000 & Keystone et al., 2004 & Maini et al., 2004).

2.3.2 Modulation effects of pregnancy in Rheumatoid Arthritis mothers

In pregnancy, RA signs are improved in more than 76% of cases (Pope et al., 1983) but beneficial signs disappear postpartum for approximately 6 to 8 months post delivery. These gestational ameliorations seem to be independent of cortisol rises in pregnancy and independent to administration of different exogenous estrogen levels (Van den Brink et al., 1992). Of note, twenty five percent of RA pregnant women have continuing active arthritis. Interestingly two reports reported that pregnancy decreases by two fold in RA when compared to nulliparous RA women (Spector et al., 1990 & Hazes et al., 1990). During pregnancy, important tolerance occurs in RA. Auto-reactive B cells in RA are somewhat down-regulated since serum levels of alloantibodies remain the same while improvement in the severity is observed (Elenkov et al., 1997). Autoantibodies such as ANA have been reported to decrease in RA pregnancy (Ostensen et al., 1983) as well as the rheumatoic factor, RF (Pope et al., 1983). Interstingly, the disparity between the foetus and the mother seems to be positive for the pregnancy course in RA (Nelson et al, 1993). The impact of the disease on pregnancy and outcomes of RA to gestation seem to show no adverse effects with RA women falling pregnant and giving birth with no life threatening consequences. However, postpartum flares are high and possibly aggravated due to high correlated levels of prolactin postpartum (Zrour et al., 2010). The influence of pregnancy on RA disease is still unknown and no explannations to date are given for the reasons for observing either

remission or none of RA during pregnancy. As for the remissions, attention is dedicated to the maternofetal HLA incompatibility but investigations is generating contrasting reports (Brennan et al., 2000). As for what is possibly occuring in RA and pregancy, a hormonal conditioning mediated by estradiol and progesterone contribute to a shift from TH1 to Th2 immune profile (Ekerfelt et al., 1997) and suppression of both autoreactive T cells and NK cells (Otensen & Villiger, 2002).

2.4 Multiple Sclerosis and pregnancy

2.4.1 Pathophysiology of Multiple Sclerosis

MS is a neurological debilitating disorder that affects particularly Caucasians in their second to fourth decades of their life (Weinshenker BG, 1998). MS was characterised for the first time, by Dr Jean Martin Charcot in 1868 from the hospital "Salpêtrière", in Paris who reported the presence of multiple plaques in the central nervous system (CNS) of a deceased patient. Despite the progress of research in the last 150 years the aetiology of MS remains still unknown.

The disorder is well documented for its neuroinflammatory course and symptoms. The disease has particular hallmarks and is more prevalent in women, and symptoms appear typically between 20 and 40 years of age (Weinshenker BG, 1998). Females account for approximately 60% of MS cases (Weinshenker BG et al., 1994). There are several forms of MS, characterised by the degree of symptomatic debilitation over time: Benign MS (B-MS), Relapsing Remitting MS (RR-MS), Secondary Progressive (SP-MS), Progressive-Relapsing MS (PR-MS), Primary Progressive MS (PP-MS). MS plaques appear as lesions in the normal white matter (NWM) and occasionally in the gray matter (Peterson et al., 2001). Lesions are restricted to the CNS and are not present in the peripheral nervous system (PNS). Plaques are classified into three main types: acute (A), chronic active (CA) and chronic silent (CS) MS lesions. Acute MS lesions are not well-demarcated (oedematous) and are filled with macrophages commonly containing myelin debris. Additionally, these lesions contain hypertrophic astrocytes but no fibrous astrogliosis with an abundance of demyelinated axons. This plaque-type is characterised by the presence of perivascular lymphocytic infiltration and damaged of the blood brain barrier (BBB) (Gay et al., 1991). Chronic active MS lesions, are the second type and do contain a well-demarcated margin. In this case the centre of the plaque is lacking in lymphocyte activity. Instead macrophages reside in a margin which contains the debris of myelin degeneration. These macrophages are microglia in origin. The centre of a CA plaque is astrogliotic, with a generally absence of myelin. However, in this case the centre of CA lesions is characterised by signs of remyelination.

In contrast to both CA and A lesions, CS MS lesions have a highly demarcated margin with a fibrous centre with no inflammatory component. Remyelination can occur in the centre and within the margin. These plaques appear circular and differ from other forms of demyelination (eg. Balo's syndrome). Balo's syndrome, is characterised by alternate rings of degeneration and regeneration (or intact myelin)(Moore et al., 1985). MS also has an autoimmune component, characterised by infiltration in the CNS of activated T-cells that are auto-reactive to myelin white matter proteins. MS is also more prevalent at higher latitudes of the globe (Hernan et al., 1999), suggesting a strong environmental influence; while disease susceptibility has a strong genetic link, as evidenced by numerous twin studies (Mumford et al., 1994). Symptoms include limb weakness, sensory loss, visual alterations and bladder dysfunction, and the appearance of lesions or plaques that are disseminated in

time and space. Multiple sclerosis is an autoimmune disease of the central nervous system, characterized by zones of demyelination and inflammatory plaques.
The genetic of MS has been extensively researched and a major focus in comparison to other autoimmune diseases. Studies appreciating the concordance of twins have shown a six time increase in risk in monozygoting than among dizogotic twins (Sadovnick et al, 1993).

2.4.1.1 The Major Histocompatibility Complex (MHC) and Multiple Sclerosis

The MHC Locus on Chromosome 6p has been linked to the pathogenenesis of MS with the fundamental basis of this association being established as a strong association with HLA-DRB1*15 of the class II gene *HLA-DRB1*(Fogdell et al., 1995). In addition to the problem in exploring possible etiological reasons behind MS, epistatic interaction across alleles are taking place that even are mors of a risky as seen with *HLA-DRB1*08,* on interaction with *HLA-DRB1*15.* A number of genes have been implicated in MS pathophysiology and were discovered throughout both immunological and genetic studies. One of the most consistent findings has been an association of specific major histocompatibility class II haplotypes in MS (Kellar-Wood et al., 1995). The MHC region in 6p21.3, includes MHC I, II and III. As all evidences are supporting an autoimmune basis for MS, the MHC locus is the focus of a lot of research attention as the genes in this locus are involved in antigen presentation. Class I and class II are involved in antigen presentation to CD8 and CD4 lymphocytes respectively. Class I has a region containing HLA loci (HLA A, B, C, E, F, G) known to be altered in normal pregnancy especially at the placental border between the foetus and the mother. Association between MS and molecules on the chromosome 6p21 is variable to the type of population studied. Northern European populations affected with MS do show an association with Class II DR15 and DQ6 phenotypes in (Hillert, 1994). In the other hand, Asians with MS are associated with DPB1 (Ito et al., 1998).
The MHC Class II locus is composed of genes coding for proteins LMP2 (proteasome subunit, beta type, 9) and LMP7 (proteasome subunit, beta type, 7), two protein being integrative of the proteasome complex. Normally, viral proteins or cellular proteins are turned into small peptides by the proteasome. These fragmented petides are then entering the reticulum endoplasmic (RE) binding with new synthesised MHC class I molecules. Both molecules are then deposited to the surface cell where the peptide is then presented to vigilant immune cells. The translocation into the RE is facilitated by the transporter 1, ATP-binding cassette (TAP) 1 and 2 which are coded by genes in the MHC Class II region. Studies attempted to demonstrate a probable association between TAP1 and TAP2 locus polymorphisms but data showed no association with MS (Vandevyver et al., 1994). However, the same study revealed though a differential level of gene expression of these two genes between affected and non-affected tissues. Interestingly, a lot of attention was brought into a region 100kb telomeric to HLA F. This locus harbors the myelin oligodendrocyte glycoprotein (MOG), another potential candidate gene in multiple sclerosis as it plays an important role in myelin sheath maintenance and immunogenicity. Experiments using antisera raised against MOG would activate a downstream signaling pathway resulting in the degradation of microtubules and disruption of myelin basic protein (MBP) (Johns et al., 1999). This pathway is also triggered by antibodies of a marker of myelin-producing cells, the galactolipid galactocerebroside, that was illustrated in glioma cells (Joshi et al., 1992), with possibly engaging a second messenger (most likely Inositol Phosphate 3) activating a voltage Ca^{2+} channel (Joshi et al., 1998) that ultimately results into in an increase of intracellular calcium and microtubule disruption.

In the Class III MHC region, candidate genes possibly implicated in MS pathology include the steroid enzyme 21-hydroxylase gene (CYP21A2) and heat shock proteins (HSP): HSP70-1 and HSP70-2. In addition, MHC class III region contains genes coding for complement molecules of the immune system and interestingly the tumour necrosis factor genes (TNFα and TNFβ). In Multiple sclerosis, TNFα has been shown to be toxic to oligodendrocytes and myelin (Wingerchuk et al., 1997). In MS plaques, TNFβ is present and is at the origin of tissue repair (De Groot et al., 1999). Some studies have investigated TNFα polymorphisms (Wingerchuk et al., 1997) however no association was found with MS except in HLA-DR2+ MS patients compared with HLA-DR2- individuals (Oturai et al., 1999). Studies investigating Caucasians of European descent have shown that class II HLA alleles are more strongly associated with the HLA-DR2 haplotype in MS (Haines et al., 1998).
Noteworthy a predominant immunological hallmark of multiple sclerosis is the important clonal expansion of class I MHC T8 lymphocytes observed in MS (Gay et al., 1997).

2.4.1.2 Immunological mechanism involved in MS

The immune system response is comprised of two immune systems: humoral and cellular. In the case of MS, both systems apply resulting in CNS inflammation coupled with degeneration in myelin sheath. A plethora of cells may be involved in this disorder including microglial cells (macrophages of the CNS), B and T lymphocytes, natural killer cells and peripheral macrophages (Li et al., 1993). Their activities are coupled with the secretion of activating signals such as cytokines and interleukines that upon production affect surrounding cells. It has been reported that auto-reactive T-cells exist in the peripheral blood from both MS affected and healthy individuals (Lindert et al., 1999). In order to reach the CNS, the immune cells have to cross through the BBB but only activated T-cells can penetrate this fence. However, it has been reported that in MS the BBB undergoes a breakdown resulting in facilitated passage of immune cells (McDonald et al., 1992). The activation of T-cells is supposed to be due to a misguided immune response secondary to cross recognition of epitopes shared between a microbial pathogen and a putative antigen in the CNS (Wucherpfennig et al., 1995). These CNS-antigen specific T-cells transmigrate through the endothelial BBB by secreting and expressing adhesion molecules such as selectins and integrins (Monteyne et al., 1997). The T-cells occupy the CNS in regions where further events take place. Furthermore, once they have occupied the CNS, the T-cells stimulate the entry of further immune cells such as peripheral macrophages. Passage of macrophages in the CNS is facilitated by the T-cell induced BBB disruption due to secretion of activated matrix metalloproteases (MMPs). In the cerebrospinal fluid of MS patients, a high gelatinase (MMP9) concentration has been found (Rosenberg et al., 1996). Gelatinase B breaks down the BBB and its inhibition, by serine protease inhibitors, shows a protective effect on the MS animal model, EAE Lewis rats (Brosnan et al., 1980). In the parenchymal of the CNS, T-cells are reactivated with the myelin antigen proximity and secrete a vast group of pro-inflammatory agents such as interferon gamma (INFγ), tumour necrosing factor alpha and beta (TNFα and TNFβ), interleukin 2 (IL-2) (Olsson et al., 1995). IL-2 is an autocrine interleukin triggering a T-cell auto-activation loop process. On both astrocytes and microglial cells, those inflammatory mediators trigger an up-regulation of MHC class II molecules. The increase of MHC class II molecules at the surface of these cells improves the amount of antigen presenting cells. Moreover, microglia as well as T lymphocytes are developing a proliferating process in response of INFγ action (Martino et al., 1995 & Grau et al., 1997). Interestingly, T-bet knockout mice show resistance to autoimmunity (Bettelli et al., 2004).

Activated astrocytes trigger an up-regulation of adhesion molecules at the surface of the BBB (Weiss et al., 1998). Chemo-attractants are produced such as the monocyte chemo-attractant protein 1 (MCP-1) (Van Der Voon et al., 1999) that chemically orientate peripheral phagocytes towards the BBB. The BBB endothelium is thus facilitated for further influx of inflammatory cells such as macrophages. Even macrophages disrupt the BBB with the secretion of neurotoxins (Brosnan et al., 1981). Secondly, activated astrocytes are able to excrete more pro-inflammatory molecules that turn the local CNS microglia (CNS resident macrophages) into ameboid microglia, a more active macrophage state. The activated astrocytes excrete factors such as GM-CSF (granulocyte monocyte-colony stimulating factor) whose role is to induce the proliferation of the ameboid cells.
The local microglia plays an important role in local antigen presentation in the CNS of EAE animals (Bauer et al., 1994) allowing an immune response. The microglia is expressing B7 (Dangond et al., 1997) and vascular cell adhesion molecule (VCAM-1). These two molecules bind CD28 and the very late antigen 4 (VLA4) respectively, on the surface of T-cells (Chabot et al., 1997) and these molecular interactions affect T-cell activation. Complement receptors (CR1 and CR2) are also found and are molecules that allow the binding of complement coated targets to phagocytosis. Complement activation constitutes the major component mechanism of humoral immunity. Contact with complement permits a better activation of the microglia but also the release of TNFα and interleukins (IL-1 and IL-6) (Rajan et al., 1996). Microglia express receptors for Fc fragments of immunoglobulins (Ulvestad et al., 1994) and completes an association action with B-lymphocytes. Those B-lymphocytes, fewer in numbers, can pass the damaged BBB and produce antibodies against myelin proteins (Gerritse et al., 1994). The antibodies are observed, after a lumbo-puncture, in CSF from MS patients appearing as oligoclonal bands in agarose gel electrophoresis. T-cell infiltration in the CNS not only induces microglial activation but also triggers the recruitment of high numbers of macrophages (Hulkower et al., 1993).
Besides inflammation, demyelination is the second most characteristic feature of MS pathology. Both microglia and macrophages are capable of ingesting myelin in EAE animals (Rinner et al., 1995). However, oligodendrocytes do not express MHC calls II molecules so CD4+T-cells cannot have a direct effect. Studies have shown that both complement and immunoglobulins are detected on oligodendrocytes and microglia in MS brain but none of the studies have ever shown the complement system alone (Fabry et al., 1994). Oligodendrocytes are damaged via antibody cell mediated cytotoxicity (ADCC) triggered by microglia, macrophages with the help of T4+, B-cells and complements molecules (Ozawa et al., 1994). The macrophages act as APCs via the major histocompatibility molecule class II. Their activities are indicators of ongoing demyelination activity (Li et al., 1993). Furthermore, the interaction of B-cells with T4 cells (CD40-CD40L) turns the B-lymphocytes into APCs, which in consequence increase the myelinotoxic activity. Antibodies to CD 40 ligand (CD 40L) can prevent the MS like disease in EAE animals (Boon et al., 2001). MBP-specific CD8+ T-cells are detected in MS plaques and have been shown to be cytotoxic in vitro on HLA-A2 not HLA-A3 transfected oligodendrocyte cell lines in the presence of MBP peptide 110-118 (Jurewicz et al., 1998).

2.4.2 Modulation effects of pregnancy in Multiple Sclerosis mothers

A first and remarkable large prospective study was undertaken to monitor MS and pregnancy relation and finally counseling MS pregnant women for their venture into

pregnancy (Confavreux et al, 1998). MS disease does not affect the outcome of pregnancy and interestingly from the first to the successive trimesters of gestation, a decrease in exacerbation rates is observed with at the third trimester a decrease of 87.5% of relapse rates (Confavreux et al., 1998). This gestational decrease in symptomatology is directly observed with a decrease of MS MRI abnormalities in the CNS in MS pregnant women (Van Walderveen et al., 1994). Most interestingly MS patients entering pregnancy even show a reduced MS progressive course and severity in comparison to controls (Runmarker et al., 1995 & Verdru et al., 1994). No differences in rates of caesarians are seen in MS (Mueller et al., 2002). A lot of attention is driven towards obvious gestational steroids such as estrogens and progesterone. Previous studies have shown the autoimmune protection of estrogens which action decrease TNF-α secretion from microglial cells (Dimayuga et al., 2005) and the neurosteroid enhancement effects of progesterone on myelin formation (Jung-Testas et al., 1999). Progesterone has been shown to act on myelination in the peripheral nervous system with marked remyelination following cryo-lesions in mouse sciatic nerves (Koenig et al., 2000). Progesterone acts on its receptor, progesterone receptor (PGR), a receptor localized in Chromosome 11q12, a locus with denotes slight association in MS susceptibility in Australia (Ban et al, 2003). In animals, progesterone shows remarkable actions as a neuro-protector agent (Singh et al., 2008). Activation of the PR by progesterone exerts immunosuppressive roles by directly inhibiting a subunit of NF-κB, a well known intermediate of the pro-inflammatory molecule TNF alpha action (Kalkhoven et al., 1996). In addition, it has been demonstrated that progesterone exerts a protective role on damage brain tissues (Cutler et al., 2007) especially in Traumatic Brain Injuries (TBI) (VanLandingham et al., 2007).

A very interesting study has been undertaken to assess the immunogenic activity occurring in MS pregnancy (Saraste et al., 2007). Natural killer cells and B and T-cells populations with both CD4+ and CD8 + T-cells were all assessed during pregnancy in MS with staggering results showing a decrease from first to third trimester of nearly 40% of NK count in blood of MS patients to then increase by 53% by three months postpartum. In healthy pregnant women a same trend of decrease in NK population is observed (Saraste et al., 2007). This fluctuation of such important innate immunity cellular component is obviously strongly altered by pregnancy and accomplished seen in MS women. Steroids such as progesterone were investigated to establish their roles on NK cells and it has been shown that progesterone induces apoptosis of mature peripheral blood natural killers CD16+ CD56 dim (Arruvito et al., 2008). In Saraste et al. study, an important hallmark demonstrated though a grand difference in CD4+/CD8+ ratios in MS pregnant women versus healthy pregnant women. In From the first to third trimester, MS pregnant women have a CD4+/CD8+ ratio of 1.9 that increase to 2.7 in the third trimester whereas healthy pregnant women showed an inverse trend from 2.4 to 1.6. Authors attempted to give an explanation by seeing such trend as either an increase in T regulatory T-cells or the act that T-cells were prevented from reaching the CNS in pregnancy.

In contrary to gestational time, post partum MS condition is associated with an increase of relapse rate (Bernardi et al., 1991) to resume back to baseline values approximately three months post partum (Roullet et al.,1993). Breast feeding is not affecting the postpartum relapse rate frequency and could be encouraged by the physician except if particular drug treatments are in use (Nelson et al., 1988).

3. Conclusion

The following review was aimed at understanding the interactive relation of the physiological gestational adaptations in coexistence with particular autoimmune diseases. Discussion focused on four diseases that include SLE, MS, MG and RA. Such relation is of no doubt a very complicating process that progressively starts to unravel. Thanks to the overall international research on both the pathogenic mechanism of autoimmunity and enhancement of gestational immunity understanding, new hypothesises and more importantly more insights are found. A powerful physiological protective process occurs in pregnancy, a process strong enough to demonstrate decrease symptomatology in MS, RA and MG pregnancies. In the other hand, SLE pregnancies do not follow such trend and even is showing further aggravation. Mothers are facing a double challenge by undertaking all physiological adaptations of their pregnancy and going through these autoimmune diseases. Steroid hormones play an important role and attempt to orchestrate the foeto-maternal immunological cross communication. In addition regulatory T cells are the direct biological 'diplomats' that taking act on immune-modulating this complex biological enigma.

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