# Neurological Diseases with Pregnancy

*Essay*

*Submitted for Partial Fulfillment of Master Degree*
*in* ***Neuropsychiatry***

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*2010*

# INTRODUCTION

Almost any medical disorder which can occur in a woman of childbearing age can occur during pregnancy. Most are probably no commoner than would be expected by chance. There are, however, neurological disorders which occur more commonly during pregnancy than at other times, or which demand special treatment at this time (*Guy Sawle, 1998*).

The neurology of pregnancy can be split into two. On one hand, there are women who develop neurological symptoms during pregnancy. On the other hand, there are women having neurological problems such as epilepsy or myasthenia first, and then become pregnant. For these patients, pregnancy may affect the course of the disease, and there may be important issues with respect to investigation, treatment, and prognosis (*Donaldson, 1989*).

A stroke or "brain attack" occurs when the flow of blood to the brain is disrupted either by a blockage (an ischemic stroke) or by bleeding in the brain (a Hemorrhagic stroke). When either of these things happen brain cells begin to die, and brain damage occurs. For young women, stroke is a relatively rare

phenomenon, occurring in fewer than 11 per 100,000 women. Pregnant women, however, have a three to thirteen-fold increase in their risk of developing a stroke (*Davie et al., 2008*). Hormonal changes during pregnancy and the puerperium carry an increased risk of venous thromboembolism (VTE) including cerebral venous and sinus thrombosis *(Ameri, 1992)*.

Reversible posterior leukoencephalopathy (RPLE) may best be understood as one in which cerebral auto-regulation of blood pressure is overwhelmed, usually because of a rapid rise in blood pressure. Vasogenic edema occurs in vulnerable regions. The posterior circulation territory is thought to be most vulnerable because it has a relatively poor ability to auto regulate (*UWO Neurology Residents, 2004*).

Most women of childbearing potential with epilepsy expect to become pregnant. Epilepsy itself is not a contraindication to pregnancy. However, seizure management should be optimized before pregnancy is considered (*Lindhout, 1992*). Freedom from seizures is the ultimate goal in treatment of patients with epilepsy. At the same time, the side effects of antiepileptic drugs (AEDs) should not outweigh the benefits of treatment. With proper management before conception, during pregnancy, and after birth, the vast

majority of pregnancies in women with active epilepsy will have a favorable outcome (*Kälviäinen, 2006*).

Eclampsia is defined as the triad of hypertension, proteinuria, and seizures, in which seizures are the most serious consequence. The symptoms usually emerge during gestation. However, the initial presentation may be involved with postpartum seizures in the absence of previously recognized hypertension or current proteinuria (*Carmel Armon, 2007*).

Symptoms related to sleep are more common in pregnant women than in non pregnant women. Pregnant women are most likely to snore and to have insomnia and daytime sleepiness. A variety of factors may contribute to this increase in symptoms, including weight gain, hormonal changes, nutritional stress, and nocturnal discomfort (*Santiago, 2001*).

The restless leg syndrome is almost certainly the commonest movement disorder in pregnancy (*Golbe, 1994*). It is a sensorimotor disorder characterized by a distressing urge to move the legs and sometimes other parts of the body (*Hening et al., 2007*). Chorea gravidarum (CG) is the term given to chorea occurring during pregnancy. Chorea is an involuntary abnormal movement, characterized by abrupt, brief,

nonrhythmic, nonrepetitive movement of any limb, often associated with nonpatterned facial grimaces (*Wild, 2007*).

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system with onset typically in the second to third decade and is twice as prevalent in females as males. In the past, there has been speculation that pregnancy, together with other stressful life events, adversely affects the risk of relapse or the course of the disease. In fact, pregnancy appears to be associated with a temporary beneficial immune state for patients with MS partly mediated through an effect on T lymphocyte subsets. This effect may have relevance for autoimmune diseases in general (*Mohr et al., 2004*).

Neuromuscular disease in pregnancy is a broad topic and includes focal neuropathies that occur with increased incidence during pregnancy and the puerperium, as well as preexisting inherited neuropathies or myopathies and chronic autoimmune diseases such as myasthenia gravis and chronic inflammatory demyelinating polyneuropathy *(Briemberg, 2007).*

Women with myasthenia gravis (MG) have an increased risk of complications and adverse pregnancy

outcome (*Hoff et al., 2004*). Around a third of women with myasthenia gravis deteriorate neurologically during or after pregnancy. MG frequently affects young women of childbearing age (20-40 y), and pregnancy creates potential risks for both the mother and fetus *(Hoff, 2003)*. Myasthenia has little effect on pregnancy, yet up to 20% of infants born to mothers with myasthenia will have transient neonatal myasthenia *(Ip et al., 1986)*.

# AIM OF THE WORK

TO discuss neurological diseases and its relation to pregnancy, regarding incidence, eitiology, and management.

# Neurology of Pregnancy

Pregnancy affects virtually every organ system. Many of these physiological changes appear to be adaptive and useful to the mother in tolerating the stresses of pregnancy, labor, and delivery. Other changes lack obvious benefits but nonetheless require special consideration in caring for the parturient (*Morgan et al., 2006*).

## Physiological changes during pregnancy

### Some Hormonal Changes during Late Pregnancy and Early Postpartum

Two major forms of estrogen, estrone and 17β-estradiol, are produced in non-pregnant women. Estradiol is more potent and overall more important estrogenic hormone. Estriol, produced by the placenta, is essentially only present during pregnancy, but high levels of both estriol and estradiol are present during the last trimester of pregnancy (*Grow, 2002*). The effects of estrogens are principally mediated by two estrogen-receptor (ER) subtypes, α and β. Estrogenic effects on immune functions are highly dependent on dose and duration of exposure, the target tissue or cell type, and the relative and absolute levels of ERs.

Progesterone is principally produced by the ovary after ovulation but high levels are secreted by the placenta and have a crucial role in maintenance of pregnancy (*Grow, 2002*).

In general, women have stronger immune systems than men, as demonstrated by their enhanced ability to resist infections and by higher basal levels of serum immunoglobulin (IgM) (*Whitacre et al., 1999*). A prevailing hypothesis is that this disparity in immune function may be a major factor underlying the overall higher prevalence of autoimmune illness in women (*Zandman-Goddard et al., 2007*). Part of the difference in immune function may be attributable to sex linked genetic differences (*Bessler et al., 2007*), but evidence suggest that much of the difference is attributable to gender differences in hormone levels. Most attention has been focused on estrogen, progesterone and testosterone, although gender differences also exist in secretion of other hormones (eg, prolactin, growth hormone, cortisol, etc.) (*Whitacre et al., 1999*). Estrogen's effect on T-cell at pregnancy concentrations is expected to be immunosuppressive. Also high estrogen levels increase B-cell antibody production, but at the same time B lymphocytes precursors in the bone marrow are suppressed (*Peeva and Zouali, 2005*). The net effects of estrogens on B-cell dominated

autoimmune disorders might then depend on whether auto-aggressive B-cells are already present when estrogen exposure occurs (*Straub, 2007*).

Human third trimester pregnancy, compared with the early postpartum period, is characterized by a reduction of the monocytic production of the Th1 (T-helper 1) type/proinflammatory cytokines IL (IL)-12 and tumor necrosis factor (TNF), and by an increase of the secretion of cortisol, norepinephrine (NE), and 1,25-dihydroxyvitamin D3. Postpartum, when these hormones return to normal or low normal levels, the removal of their inhibitory effects may induce a rebound of IL-12 and TNF-_ production and a Th1 shift. The changes of Th1 type/proinflammatory cytokine production may provide new understanding of the clinical observations that Th1-related diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS) frequently remit during pregnancy but exacerbate or have their onset in the postpartum period. Some individuals have exaggerated postpartum Th1 type/proinflammatory cytokine rebound, raising the question of the factors that control this phenomenon. These individuals could be at greater than average risk for developing or exacerbating already existing autoimmune diseases (*Elenkov et al., 2001*).

## Haemostatic changes in pregnancy

In normal pregnancy, there is a marked increase in the procoagulant activity in maternal blood characterized by elevation of factors VII, X, VIII, fibrinogen and von Willebrand factor, which is maximal around term. This is associated with an increase in prothrombin fragments (PF1+2) and thrombin–antithrombin complexes. There is a decrease in physiological anticoagulants manifested by a significant reduction in protein S activity and by acquired activated protein C (APC) resistance. The overall fibrinolytic activity is impaired during pregnancy, but returns rapidly to normal following delivery. This is largely due to placental derived plasminogen activator inhibitor type 2 (PAI-2), which is present in substantial quantities during pregnancy. D-dimer, a specific marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses. Overall, there is a 4- to 10-fold increased thrombotic risk throughout gestation and the postpartum period. Disruption of anticoagulant mechanisms may increase pregnancy complications in patients with antiphospholipid antibodies (*Brenner, 2004*).

## Cardiovascular dynamic changes throughout pregnancy

Estrogen has been shown to have numerous effects on the vasculatre. Its beneficial vascular effects include vasodilatation, angiogenesis, microvascular remodeling, and improved vascular reactivity. After cerebral injury, estrogen enhances neurogenesis. In coronary circulation, estrogen improves myocardial blood flow, reduces myointimal proliferation after endothelial injury, and delays the development of coronary artery astherosclerotic plaque. It also improves lipid status by decreasing low density lipoprotein-cholesterol and increasing high density lipoprotein-cholesterol (*Rosendaal et al., 2002*).

The data showed that pulse rate rises throughout pregnancy. Stroke volume and cardiac output rises shortly after conception, the increase over the prepregnancy level being statistically significant by 12 weeks. Thereafter both values falls throughout the rest of pregnancy and were below prepregnancy levels by about term, taking some weeks to regain the prepregnancy value. There are irregular fluctuations in the level of systolic blood pressure; diastolic blood pressure falls during the first 16 weeks and then rises to reach almost the prepregnancy value by term.

Peripheral resistance falls during the first trimester, and then increases markedly throughout the remainder of pregnancy (*Atkins, 1981*).

## Hematological changes

### Red cell volume

Red cell mass increases in a linear fashion during pregnancy by about 20 to 30 percent with maximal effect seen in those taking iron supplements. The rise is due to an increase in the number and size of red cells, which aids the transport of oxygen and carbon dioxide. The increase in red cell volume and red cell production is regulated by an increase in demand for oxygen transport in pregnancy. As the total increase in red cell volume is less than that of the plasma volume, the concentration of red cells in blood falls, hence physiological anemia in pregnancy is noted. These changes are still noticeable at 8 weeks post-partum but would have returned to normal by 4 to 6 months post-partum (*McFadyen, 1994*).

### Other Blood Constituents

The white cell count tends to increase slightly during pregnancy to about 10 to 15.000/ml. the platelet count generally tends to remain unchanged although

there is a downward trend toward the end of pregnancy, hence the term gestational thrombocytopenia. Erythrocytes sedimentation rate rises by fourfold in pregnancy; hence it is not accurate as a diagnostic marker in pregnancy. This rise is due to increased globulin and fibrinogen levels (*Llewellyn-Jones, 1986*).

## Neurologic considerations for all women of childbearing potential

All women of childbearing potential should be receiving folic acid at 0.4 mg/d, the recommendation of the US Centers for Disease Control and Prevention. If neural tube defects occurred in a woman's previous pregnancy, increased antepartum fetal surveillance is required for the current pregnancy. This surveillance should include consultation with a geneticist and targeted fetal ultrasonography to assess the fetal spine and cranium. In addition, preconception supplementation with folic acid at 4 mg/d is recommended; this dosage is higher than that advised for a woman without such a history (*Armon, 2007*).

Vegetarians, particularly strict vegetarians, need to be aware of the risk of vitamin B-12 deficiency and other vitamin deficiencies. Strong consideration should be given to supplementing vitamin intake and checking

levels. Women planning to become pregnant should avoid all alcohol consumption, smoking, and use of illegal drugs (eg, cocaine) before and during the pregnancy because these may have serious deleterious effects on the fetus. Also advisable is to review all medications and supplements the woman is taking with the prescribing provider to assess for possible teratogenicity (*Armon, 2007*).

**Considerations in a woman with any neurologic disease who wishes to become pregnant or who is pregnant**

Any woman with an existing neurologic condition should consult her obstetrician and her neurologist before she becomes pregnant. During this consultation, the patient can be advised about the possible risks associated with her condition during pregnancy and about the possible teratogenic effects of her medications (*Armon, 2007*).

If the woman is already pregnant and if she did not consult her physician in advance, she needs to alert her obstetrician and neurologist. With regard to teratogenicity, her physicians should review her current medications for their teratogenic potential, and those posing a risk should be discontinued if possible. Care should be taken to discontinue medications only when this action makes good clinical sense for the

mother, not solely because they may be associated with congenital anomalies. For example, if antiseizure medications are stopped prematurely, seizure activity may increase during the pregnancy and expose the fetus to several medications at doses higher than those originally used to control the condition (*Armon, 2007*).

At least 2 systems are used to classify the risk associated with specific medications.

The first is the US Federal Drug Administration (FDA) risk categories, as follows:

- Category A - Controlled human studies show no risk
- Category B - No evidence of risk in humans, but no controlled human studies are documented
- Category C - Risk to humans has not been excluded
- Category D - Positive evidence of risk to humans from human and/or animal studies
- Category X - Contraindicated in pregnancy

The second system is the automatic Teratogen Information System (TERIS) (*Friedman et al., 1990; Lo & Friedman, 2002*).

The 2 systems are poorly correlated. According to the TERIS, the teratogenic risk in human pregnancy is