Multiple sclerosis and Pregnancy

Pregnancy, delivery and birth outcome in women with

Multiple Sclerosis

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Abstract

This study provides information regarding birth-giving in women with multiple sclerosis (MS).

MS is a common disease in the western world and causes disability in young adults and, like most immune mediated diseases, affects women more commonly than men. The number of births given by women with MS has increased during the last 30 years, and clinicians often encounter these women's concerns about pregnancy-related issues. There are a few studies on the possible effects of MS on the pregnancy and the newborn, but so far no serious adverse effects have been shown. (Mueller et al. 2002;Poser & Poser 1983;Worthington et al. 1994) However, a diagnosis of MS is linked to more frequent operative deliveries. (Davis & Maslow 1992)

We have evaluated the influence of MS on pregnancy, delivery and birth outcome in a large historical cohort. Our study illustrated an overall good outcome for pregnancy and birth in MS women, with no increase in adverse birth effects. However, a diagnosis of MS reduced neonatal birth weight. This was not due to an increased smoking rate among pregnant MS women. MS also increased the duration of the second stage of labor and increased the need for induction and operative intervention during birth. The increased rate of planned caesarean section might be justified, since we found that forceps and vacuum extraction occurred with high frequency despite the increased planned caesarean section rate in MS women compared to the references. Our results indicate that health professionals should discuss potential problems and their possible importance for delivery with each pregnant MS woman.

Introduction

Abbreviations

BMI	Body mass index
CIS	Clinically isolated syndrome
CNS	Central nervous system
CSF	Cerebrospinal fluid
EDSS	Kurtzke's Expanded Disability Status Scale
HLA	Human leucocyte antigen
ICD-8/ ICD-10	International Classification of Diseases version 8 and 10
IFN	Interferon
IL	Interleukin
IVIG	Intravenous immunoglobulin
LBW	Low birth weight (<2500g)
MBRN	Medical Birth Registry of Norway
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NK	Natural killer
PPMS	Primary progressive MS
PRIMS	The Pregnancy in Multiple Sclerosis, a European multicenter, prospective, observational study

PRISMS	Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis Study group
RRMS	Relapsing remitting MS
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
SPMS	Secondary progressive multiple sclerosis
SPSS	Statistical Package for the Social Sciences
UVB	Ultraviolet-B (sunlight radiation 290-315nm)
VER	Visual evoked response

Definitions

Perinatal mortality	All fetal deaths after 16 weeks (12 weeks after 1998) of pregnancy and deaths up to 7 days after birth
Small for gestational age	Birth weight below the 10^{th} percentile at the attained gestational age according to standards for birth weight by gestational age

List of publications

Paper 1 Dahl J, Myhr KM, Daltveit AK, Hoff JM, Gilhus NE. Pregnancy, delivery, and birth outcome in women with multiple sclerosis. Neurology 2005;65:1961-3.

Paper 2 Dahl J, Myhr KM, Daltveit AK, Gilhus NE. Planned vaginal births in women with multiple sclerosis: delivery and birth outcome. Acta Neurol Scand 2006;133(Suppl. 183):1-4.

Paper 3 Dahl J, Myhr KM, Daltveit AK, Gilhus NE. Pregnancy, delivery and birth outcome in different stages of maternal multiple sclerosis. J Neurol 2008.

Paper 4 Dahl J, Myhr KM, Daltveit AK, Skjaerven R, Gilhus NE. Is smoking an extra hazard in pregnant MS women? Findings from a population-based registry in Norway. Eur J Neurol 2007; 14:1113-7.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The disease is one of the common causes of disability in young adults, and affects 1:1000 in the western world, and about 2.5 million people worldwide. (Compston & Coles 2002) In Norway the prevalence seems to be relatively equally distributed (150/100,000), but probably with somewhat fewer patients in the northern parts of the country. (Dahl et al. 2004;Gronlie et al. 2000;Grytten et al. 2006;Torkildsen et al. 2007) The Norwegian MS population is estimated to include about 7000 people, with approximately 300 new cases per year. (Torkildsen et al. 2007)

Clinical subtypes

A relapsing remitting disease (RRMS) affects around 85 % of the patients, characterized by repeated attacks (relapses) of neurological dysfunction followed by remission. (Confavreux & Vukusic 2006) Within 25 years of disease duration the majority (90 %) of patients with RRMS will develop a secondary progressive MS (SPMS), (Weinshenker et al. 1989a) characterized by increasing permanent neurological disability. Some patients that have developed SPMS also keep having distinct relapses superimposed on the progressive course over a variable period of time. A primary progressive form of MS (PPMS) affects 15 % of the patients, with a steady decline in neurological function without remission of symptoms. However, some of the patients in this group have clinical acute relapses superimposed on the steady decline in neurological function. (Confavreux & Vukusic 2006) Despite different clinical patterns and the fact that the disability progression varies greatly, MS is considered to be one distinct disease, but with different clinical phenotypes. (Confavreux & Compston 2006)

Pathophysiology and clinical symptoms

MS is characterised by inflammation, demyelination and primary or secondary axonal degeneration. (Trapp et al. 1998) Oligodendrocytes, responsible for synthesising and maintaining the myelin sheath of axons in the CNS, are the target of the immunologic attack. The attack is dominated by T-cells and activated macrophages or microglia. The inflammation is thought to be mediated by a T-helper cell specific reaction to myelin, but other immune cells are also at play. (McFarland & Martin 2007) On this pathological background two different features are seen in the CNS, the focal demyelinated plaques and the diffuse global brain injury. The demyelinated plaques are characterised by primary demyelination and astrocytic scarring. This pattern dominates early in the relapsing disease course. The diffuse brain injury develops through a slowly progressive accumulation of inflammation resulting in diffuse tissue damage and brain atrophy, which dominates in the later stage of the disease. The process progresses to a state with chronic multifocal sclerotic plaques. (Miller 2004) Although the inflammation has a typical pattern of distribution, all parts of the CNS can be affected and the clinical course is rather unpredictable.

Common clinical symptoms are paresis and spasticity, sensory symptoms including numbness, paresthesias and pain, brainstem and cerebellar symptoms including diplopia, dysarthria and ataxia, as well as visual symptoms (optic neuritis), bladder- and bowel dysfunction and cognitive changes. There is a higher percentage of optic neuritis and diplopia as presenting symptoms in patients with early onset of MS (<30 years) and of motor disturbances in patients with late onset (>39 years). (Weinshenker et al. 1989a) Longitudinal studies on MS cohorts, estimating time from onset to disability milestones, have given valuable knowledge on the natural history of MS. Median time from disease onset to reaching a disability level when one needs a walking-aid is about 20 years. (Confavreux et al. 2003;Myhr et al. 2001) Life expectancy for MS patients is reduced by up to 10 years compared to the general population. (Bronnum-Hansen et al. 2004)

Diagnosis

There is no pathognomonic test for MS, and the patient history is essential for the diagnosis of MS. Due to the inflammatory process, the MS symptoms emerge sub-acute within hours and days, and lasts for >24 hours and up to 4-6 weeks, before full or partial remission. The diagnosis has traditionally been based on clinical features alone with disseminated disease in both time (≥ 2 attacks) and space (≥ 2 lesions in the CNS). However in 1983, the Poser criteria (Poser et al. 1983) included both clinical and paraclinical investigations as it allowed clinical evidence for the disease to be replaced by laboratory abnormalities at the second site within the CNS to diagnose a clinically definite MS. Imaging, electrophysiology (especially visually evoked response, VER) and cerebrospinal fluid (CSF) examinations (oligoclonal IgG bands) were used as supplement when the clinical criteria were not met. In 2001, new extensive criteria for diagnosing MS were developed by an International Panel, the so called McDonald criteria. (McDonald et al. 2001) The main change was inclusion of magnetic resonance imaging (MRI) features for defining dissemination of the disease in both time and space. The McDonald criteria were later reviewed in 2005, (Polman et al. 2005b) focusing on MRI criteria for dissemination in space and time (when a relapsing onset) and in the diagnostic criteria for patients with a slowly progressive syndrome (PPMS) (Table 1 and 2).

A high sensitivity of an early diagnosis of MS, with an acceptable level of specificity is important since early initiation of treatment has been found to prevent the development of disability.(Kappos et al. 2007) Since a high sensitivity of MS to a certain degree goes at the expense of the specificity, evaluating possible differential diagnoses is important. Typical differential diagnoses of MS are acute disseminated encephalomyelitis, infections, and inflammatory disorders such as SLE, sarcoidosis, neuromyelitis optica and malignant disease in young as well as vascular diseases at older onset patients. (Garcia & Blasco 2007)

Table 1 MRI criteria to demonstrate CNS lesions disseminated in space and time suggestive of MS

MRI evidence for dissemination in space - three of the following:

a) ≥ 1 gadolinium-enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium enhancing lesion
b) ≥ 1 infratentorial lesion
c) ≥ 1 juxtacortical lesion
d) ≥ 3 periventricular lesions

NOTE: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion, an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions.

MRI evidence for dissemination in time - one of the following:

a) Detection of gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event
b) Detection of a *new* T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

Table 2 Revised McDonald Diagnostic Criteria for Multiple Sclerosis

Clinical Presentation		Additional Data Needed for MS Diagnosis
Clinical attacks	**Clinical lesions**	
		None
≥ 2	≥ 2	• But paraclinical tests (MRI, CSF) should be done to exclude other diagnoses. If these tests are *negative,* extreme caution needs to be taken before making a diagnosis of MS.
		Dissemination in space, demonstrated by:
≥ 2	1	• MRI *or* • Two or more MRI-detected lesions consistent with MS plus positive CSF *or* • Await further clinical attack implicating a different site
		Dissemination in time, demonstrated by:
1	≥ 2	• MRI *or* • Second clinical attack
1	1	Dissemination in space, demonstrated by:
(monosymptomatic presentation; clinically isolated syndrome - CIS)		• MRI *or* • Two or more MRI-detected lesions consistent with MS plus positive CSF *and*
		• Dissemination in time, demonstrated by: • MRI *or* • Second clinical attack
Insidious neurological progression suggestive of MS (PPMS)		One year of disease progression (retrospectively or prospectively determined) *and* two of the following: a) Positive brain MRI (nine T2 lesions *or* four *or* more T2 lesions with positive VER) b) Positive spinal cord MRI (two focal T2 lesions) c) Positive CSF

Aetiology

MS is regarded as an immune-mediated disorder resulting from complex interactions between multiple genetic and environmental factors. (Kantarci & Wingerchuk 2006) A high monozygotic (25-30 %) versus dizygotic (3-5 %) concordance rate in twin studies reflects the strength of genetic factors relative to environmental factors. (Ebers 2005) MS is 20-40 times more common in first-degree relatives of MS patients than in the general population. (Weinshenker 1996) The search for candidate genes has shown an association between human leukocyte antigen (HLA)-DRB1*1501 (6p21) and MS, confirmed in a large genetic linkage study in families of Northern European descent. (Sawcer et al. 2005) Recently, two new gene associations, with interleukin (IL)7R (5p13) and IL2R (10p15), (Hafler et al. 2007;Lundmark et al. 2007) were identified.

Since the monozygotic twin concordance rate is (only) 25-30 % and the incidence and prevalence varies according to time and geography, environmental factors in the aetiology of MS are likely. The sequence of events that initiates the disease is largely unknown, since it is still not elucidated which antigen is recognised by the immune system or if the local immune response is a primary or secondary event. It seems, however, that the pathological process starts several years before the clinical symptoms emerge, possibly already during childhood. The susceptibility to environmental factors in childhood that can alter the risk of developing MS is supported by migration studies. Migration from low to high incidence areas before the age of 15 increases the risk of MS, compared to migration after the age of 15. (Cabre 2007;Dean & Elian 1997) The correlation of different microbial agents in childhood to later development of MS, have for all investigated viruses been contradictory. (Compston & Confavreux 2006) One strong exception is the Epstein-Barr virus in the herpes virus family. The MS risk is around 10 times greater among individuals who experienced an undiagnosed Epstein-Barr virus infection in childhood, and at least 20-fold greater among individuals who developed mononucleosis, compared to individuals not infected. (Ascherio & Munger 2007a) A

recent investigation on post-mortem MS brains illustrated Epstein-Barr virus markers of infection found in nearly all cases. (Serafini et al. 2007) How the virus is associated with the initiation of MS is not known, but the leading hypothesis is that the immune response to Epstein-Barr virus infection cross-reacts with myelin antigens.

Since the frequency of MS is found to increase with increasing latitude worldwide – even if the difference is starting to diminish, (Ascherio & Munger 2007b) exposure to sunlight (UVB radiation) and a corresponding vitamin D synthesis have been suggested to influence MS risk. Total vitamin D intake at baseline in two large cohorts of US nurses was found inversely associated with the risk of MS. (Munger et al. 2004) In a prospective, nested case-control study among US military personnel, it was found that high circulating levels of vitamin D were associated with lower risk of multiple sclerosis. (Munger et al. 2006) Vitamin D regulates tissue-specific immune responses. (Hayes et al. 2003) However, the underlying mechanisms in the MS pathogenesis are still under investigation.

Another non-infectious environmental factor found associated with MS is smoking. (Ghadirian et al. 2001) In a Norwegian survey of the general population in Hordaland County, the risk of MS was higher among smokers than among never-smokers. (Riise et al. 2003) A positive correlation between smoking and other autoimmune diseases has also been found. (Costenbader & Karlson 2006) The possible mechanisms of the effect of cigarette smoking on MS risk have been little investigated.

Treatment

There is no curative treatment for MS. However, medical treatment strategies for relapses in MS, disease-modifying treatment and symptomatic treatment of common complaints are the three main areas of intervention.

Relapses in MS usually have a subacute onset and appears as either new nervous system deficits or worsening of previous ones lasting for at least 24 hours. (McDonald et al. 2001) Methylprednisolone is recommended to speed up the

recovery from the relapse. Intravenous doses of at least 500-1000 mg daily for 5 days are recommended, (Sellebjerg et al. 2005) with or without tapering. In some cases, oral treatment with dexamethasone 2-4 mg four times daily with tapering is given when intravenous treatment can not be accomplished.

Disease-modifying treatment aims to minimize disease activity in MS to prevent the progression of disability, and is indicated only in MS cases with relapsing disease activity. (Kappos 2004) Since the early 1990s, four major different disease-modifying compounds have become available for MS: interferon-β (IFN-β), glatiramer acetate, natalizumab and mitoxantrone. IFN-β is available in recombinant forms for MS treatment as IFN-β-1b (Betaferon®, Bayer HealthCare Pharmaceuticals), IFN-β-1a (Avonex®, Biogen Idec and Rebif®, Merck Serono). The effects on RRMS of these drugs are a reduction in the annual relapse rate by about 30 %, and a reduction of disability progression. (Jacobs et al. 1996;PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis 1998;The IFNB Multiple Sclerosis Study Group 1995) Similarly as for IFN-β, glatiramer acetate (Copaxone®, Teva Pharmaceutical) has been found to reduce the annual relapse rate by 30 %. (Johnson et al. 1998) These drugs are recommended as first-line treatment in RRMS patients with high disease activity. Initiation of treatment after only one clinical episode (but with clinical silent MRI lesions) is found to reduce the progression of disability, (Kappos et al. 2007) and is indicated in those at high risk of developing clinical definite MS. (Thrower 2007)

While glatiramer acetate is equally potent in MS as for the IFN-β group of drugs, natalizumab (Tysabri®, Biogen Idec and Elan Pharmaceuticals) is found to reduce the annual relapse rate by almost 70 % and the rate of disability progression by 42-54 %. (Polman et al. 2006) Due to the reporting of 2 cases of progressive multifocal leucoencephalopathy in MS patients, (Yousry et al. 2006) the drug is recommended as second-line treatment. Mitoxantrone may be beneficial after treatment failure of the first and second-line treatment.

Symptomatic treatment of common afflictions in MS covers a wide range of drugs. Common symptoms that are amenable to intervention in MS are bladder dysfunction, spasticity, paroxysmal manifestations, neuralgic pain, and depression. Some effects can also be found for medical treatment for sexual dysfunction in the male, bowel dysfunction and fatigue (Micromedex ® Healthcare Series: www.library.ucsf.edu/db/record.html?idrecord=82).

Pregnancy

MS typically affects people between 20-40 years, and with a female preponderance of 2:1. Consequently, the issue of pregnancy is of major concern for many affected women. Questions on oral contraceptives, pregnancy, delivery, breast-feeding and genetic heritage are frequently asked. (Ferrero et al. 2004) Due to the differences in symptoms, disease progression and medical treatment, and social relations, the situation for each MS woman will be different. Issues related to pregnancy inevitably raise anxiety in MS women and their families.

The immune system during pregnancy

The major role of the immune system is to differentiate between self and non-self. Therefore an alteration of the maternal immune system is a prerequisite for a successful pregnancy. On the one hand, the fetus must secure its nutrition through anchorage of the placenta on the uterine wall, and on the other hand, the initiation of an immunologic attack on the fetus must be avoided. Already in the 2nd trimester fetal cells are found in maternal circulation. (van, I et al. 2000) The maternal leucocytes are essential to balance the immune system towards tolerance to fetal cells. Tolerance seems to be antigen-specific since it is induced by the specific presentation of fetal antigens via dendritic cells. (von 2008) This antigen presentation uses general immunological mechanisms to maintain peripheral tolerance to self-antigens during pregnancy. Regulatory T-cells are also important for the development of tolerance, and regulatory T-cells can be induced by the dendritic cells. (Steinman & Nussenzweig 2002)

One classical paradigm has been that pregnancy induces a change in the maternal T-cell activity, with a shift from Th1 (pro-inflammatory cytokine profile) to Th2 (anti-inflammatory cytokine profile) T-helper cell dominance after conception. (Damek & Shuster 1997) Although the Th2 type cytokines appear to contribute to the maintenance of pregnancy by controlling the immune and endocrine systems, (Saito 2000) the picture is more complex. (Chaouat 2007) Regulatory T-cells are found to play an important role in autoimmunity as well as in pregnancy. (Wilczynski et al. 2008) A subpopulation of regulatory T-cells has been found significantly higher in pregnant than non-pregnant women. (Sanchez-Ramon et al. 2005)

Pregnancy is associated with enhanced humoral and reduced cellular immune activity, (Wegmann et al. 1993) and a wide array of cytokines balance humoral and cellular immunity. The delicate immunological balance in pregnancy is modulated by adapted serum levels of corticosteriods, cytokines, hormones (oestrogens, progesterons, prostaglandins) and calcitriol, controlled by the fetus, placenta or the

mother. Oestriol (pregnancy oestrogen) increases during pregnancy and delivery is preceded by a sharp drop in serum levels. Hormones related to pregnancy can directly affect the function of both natural killer (NK) cells and macrophages. (Airas et al. 2007) Finally, there are a broad range of immunoregulatory factors specific for pregnancy, including pregnancy-specific serum proteins and tolerance-promoting signalling molecules. (Airas et al. 2007)

Amelioration of MS during pregnancy

Can some of these immunological changes explain the amelioration seen in MS during pregnancy? In MS and other autoimmune diseases, clinical fluctuations during hormonal changes related to menstrual cycle, pregnancy and treatment with sex hormones have been reported. (Ostensen & Villiger 2007;Voskuhl 2003) Several of the immunologically active substances in the serum of pregnant women have known anti-inflammatory and immunosuppressant effects in human, and may have clinical implications for MS. (Houtchens 2007) In experimental allergic encephalomyelitis models, both oestrogen and progesterone are shown to be suppressive. (Trooster et al. 1993;Trooster et al. 1996) The increased risk of autoimmune disease development and flare-up of already established disease in the postpartum period may be a consequence of a lack of immune modulation by oestrogen. (Jansson & Holmdahl 1998) This theory is supported by the positive effects of oral oestriol on MS disease activity as measured by repeated MRI. (Sicotte et al. 2002) The mechanisms of suppression by the sex hormones are believed to be inhibition of nitric oxide production in microglia, decreasing the rate of pro-inflammatory factors synthesised by activated microglia. (Drew & Chavis 2000) Pregnancy-associated protein alpha-fetoprotein and interleukin-10 are also evaluated with regard to the activity of immune cells, (Houtchens 2007) and interleukin-10 is known to down-regulate cellular immunity. (Saito 2000)

MS pathogenesis is believed to be dominated by Th1 mediated immune responses. (Confavreux et al. 1998;Damek & Shuster 1997) The hypothesis is that Th1 mediated immune responses are counteracted by Th2 cell dominance during pregnancy leading

to an amelioration of the disease activity. The Th2 cell cytokine predominance has been illustrated by cytokine profiles in pregnant women with MS. (Al-Shammri et al. 2004) A return to Th1 cell dominance postpartum may partly explain the increased risk of relapses during the first 3-6 months after delivery. Regulatory T-cells have a regulatory effect on the Th1 and Th2 cells, (van den Broek et al. 2005) and are believed to create a tolerant microenvironment at the fetal-maternal interface. (Zenclussen et al. 2007) Subtypes of this cell are found to prevent auto-reactive T-cells from inducing autoimmune diseases, (Takahashi & Sakaguchi 2003) but the role of regulatory T-cells in relation to pregnancy in MS women is not yet understood. Moreover, a subpopulation of NK-cells, found to be increased during late pregnancy compared to postpartum in MS patients, (Airas et al. 2007) may limit the survival of activated T-cells. (Bielekova et al. 2006) Which of these immunological changes during pregnancy is most important for the disease amelioration during pregnancy is yet to be determined. Still, knowledge in this field will illuminate aspects of the pathogenesis of MS that may suggest new treatment strategies.

MS and reproductive health

Prior to 1970, many studies on the effects of pregnancy on MS showed conflicting results, probably due to methodological weaknesses such as selection and recall bias. (Damek & Shuster 1997) As a result, in earlier periods MS women were to some degree advised against pregnancy and sometimes even recommended abortion, due to the fear that pregnancy could worsen the course of the disease. With the establishment of diagnostic criteria by Schumacher and co-workers in 1965, larger and methodologically sounder studies led to the consensus that MS relapse rate was not increased during the 9 months of pregnancy. (Korn-Lubetzki et al. 1984;Nelson et al. 1988) Several studies during the last decades have reported reduction in relapse rates during pregnancy (Confavreux et al. 1998;Roullet et al. 1993;Sadovnick et al. 1994) and no negative effects of pregnancies on the long term prognosis of MS. (Poser & Poser 1983;Roullet et al. 1993) This has contributed to a shift towards a positive attitude concerning birth-giving in MS women among health professionals and the patients themselves. Availability of disease-modifying therapies and the relatively low risk of transferring MS to offspring (Ebers et al. 1995) should also be reassuring for women who plan to become pregnant.

With the increasing number of pregnancies and births to MS women, there is an increasing need for information on these issues among the women and their families. Obstetricians, midwives and anaesthetists ask for information regarding medication, delivery interventions, caesarean section and anaesthetics in pregnant MS women. (Ferrero et al. 2004;Ferrero et al. 2006)

Pregnancy and its effect on MS

Short term effects

Both retrospective (Salemi et al. 2004) and prospective (Confavreux et al. 1998) studies have illustrated a significant decrease in numbers of relapses in the third trimester of pregnancy with a succeeding increase in the first months after delivery. The Pregnancy in Multiple Sclerosis (PRIMS) study, (Confavreux et al. 1998) was a large prospective, multicenter study, where 269 pregnancies among 254 MS women were followed up until 24 months after delivery. The study illustrated a maximal reduction of the relapse rate with 70 % in the third trimester followed by a 70 % increase in the first three months postpartum, as compared to the pre-pregnancy relapse rate. In sum, the relapse rate during the pregnancy plus the first 3 months postpartum was equal to the pre-pregnancy relapse rate. These findings were partially confirmed by two smaller prospective studies. (Sadovnick et al. 1994;Worthington et al. 1994) It has also been shown that the relapses tend to be milder during pregnancy, (Roullet et al. 1993) and more severe in the postpartum period. (Worthington et al. 1994) The changes in disease activity during pregnancy have additionally been illustrated on repeated MRI examinations by reduction in the number of active lesions during the second half of pregnancy followed by an increase during the first months postpartum. (Paavilainen et al. 2007;van Walderveen et al. 1994) Unfortunately, studies on the effect of pregnancy on disease progression in women with primary progressive MS are lacking. Also due to lack of studies there is uncertainty whether permanent symptoms like fatigue, bowel and bladder disturbances and ambulatory problems of MS women can be aggravated during pregnancy. However, pregnancy and childbirth have been found not to influence the characteristics of urinary disorders in MS women. (Durufle et al. 2006)

In the high-risk period of relapses the first 3 months postpartum, 28 % of the MS women in the PRIMS study experienced a relapse. (Confavreux et al. 1998) The clinical factors found to predict a postpartum relapse were relapse experienced during the pre-pregnancy year and during pregnancy. (Vukusic et al. 2004) In a smaller study, the women's past history of relapses was found as the best indicator for the clinical course of MS in pregnancy and after delivery. (Sadovnick et al. 1994) Breast-

feeding did not influence the risk of postpartum relapses. (Achiron et al. 2004;Nelson et al. 1988)

Long term effects

It has been debated whether pregnancy affects MS disease progression in the long run. (Bennett 2005) Pregnancy and childbirth did not influence disability in a prospective study of 32 pregnancies in a population of 125 MS women, (Roullet et al. 1993) and in another smaller prospective study where the MS women were followed up for 3 years postpartum. (Worthington et al. 1994) Similarly, no acceleration in the development of disability postpartum was found in the PRIMS study. (Confavreux et al. 1998;Vukusic et al. 2004) In a retrospective population-based Canadian survey of term pregnancies in a population of 185 MS women, no association between long-term disability and worsening of the disease during pregnancy and the postpartum was detected. (Weinshenker et al. 1989b) The timing of birth relative to onset of MS has been shown not to affect the long-term disability. (Thompson et al. 1986;Weinshenker et al. 1989b) This was contradicted in another study that reported a decreased risk for a progressive course in women who were pregnant after MS onset compared to before. (Runmarker & Andersen 1995) But the authors commented that the results could have been influenced by selection bias, since MS patients with a high disease activity and frequent relapses might have tended to avoid pregnancies.

Postpartum follow-up

Postpartum MS relapse can prevent maternal care-giving, due to hospitalization and separation, and can lead to unsatisfactory mother-child bonding. In a German study, (Poser & Poser 1983) it was found that up to 30 % of the MS mothers were prevented from giving their newborn adequate care due to their MS. A population-based cohort study showed that women with MS twice as often as control women were hospitalized within the first three months after delivery.(Mueller et al. 2002)

Fatigue can be very pronounced in MS, and increase the need for help in the family. Domestic help, supplementary feeding instead of mother's milk, separate bedrooms mother-child should be assessed individually. A major challenge in a family in which the mother has MS is to raise the question of the family's needs, and to secure that relief efforts can be introduced early when necessary. More studies are needed to better identify those MS women with a high risk for postpartum relapses.

MS effect on pregnancy, delivery and birth outcome

There are few large-scale studies on the effect of MS on pregnancy, delivery and birth outcome. Prospective data from the PRIMS study showed no effect of MS on the risk of miscarriage, stillbirth and congenital malformations. (Confavreux et al. 1998) This has been supported in other studies on pregnant MS populations. (Achiron et al. 2004;Sadovnick et al. 1994) A population-based cohort study of 198 MS women reported that maternal anaemia was increased compared to non-MS controls, but there was no increase in pregnancy or delivery complications. (Mueller et al. 2002) Nor was any increase in low birth weight (LBW), preterm births or malformations detected. A prospective study of 15 pregnant MS women reported few pregnancy and birth complications, and normal distribution of birth weight and head circumference in newborns. (Worthington et al. 1994)

MS and anaesthetics and operative intervention

Reliable data on the relapse risk in MS women having anaesthesia and operative interventions during birth is scarce. Epidural anaesthesia during labor is considered safe for women with MS, (Achiron et al. 2004;Confavreux et al. 1998) and is preferred to spinal anaesthesia due to presumed neurotoxic effects to demyelinised spinal neurons with a potential postoperative worsening of the disease. This preference is not supported by robust studies. However, a study of 32 pregnancies indicated increased risk of relapses in MS women who received higher concentrations

of local anaesthetic agents. (Bader et al. 1988) A high concentration of local anaesthetic in the CSF has been found also in the spinal cord after spinal technique was used in dogs. (Cohen 1968) Epidural anaesthesia did not influence the risk of postpartum relapse in the MS mother. (Vukusic et al. 2004) But a recent questionnaire study among UK obstetric anaesthetists revealed a lower threshold for administering a general anaesthesia to MS women than to healthy women. (Drake et al. 2006) However, the majority preferred regional anaesthesia for labor and caesarean section.

The criteria for operative intervention during birth in MS mothers are in principle exactly the same as for healthy non-MS women. MS-related motor symptoms such as spasms, decreased muscle tone or control in lower abdomen and extremities may however affect the birth process. Fatigue can increase exhaustion and make the use of forceps necessary. (Davis & Maslow 1992) Vacuum extraction during delivery has been reported increased among MS women. (Mueller et al. 2002) Mental symptoms related to MS, such as fatigue, can influence the decision regarding caesarean section and other operative interventions during birth. Surgical procedures in general have been reported not to affect the relapse rate in MS women. (Sibley et al. 1991) The rate of complications after a caesarean section is found to be 21.4 % in a Norwegian cohort of 2751 caesarean sections representing the general population, and the complication rate was higher for patients who received general anaesthesia compared with regional anaesthesia, and the risk of complications increased the further labor had progressed. (Hager et al. 2004) Antibiotics are recommended for all patients with emergency caesarean delivery in Norway, which is supported by a Cochrane review. (Smaill & Hofmeyr 2002)

MS, smoking and pregnancy

Although a limited response rate (50 %), smoking frequency among MS patients has not been found increased compared to reference populations. (Friend et al. 2006;Turner et al. 2007) The smoking rate was high (40 %) in a Norwegian MS

population, (Nortvedt et al. 2005) but the smoking rate has not been examined in the birth-giving part of the MS population. Possible effect of passive smoking was recently shown in a study of 129 cases of childhood MS reporting that their parents were more frequently smokers compared to a large group of matched controls. (Mikaeloff et al. 2007) Among those with RRMS the risk of developing SPMS is higher in smokers than in non-smokers. (Hernan et al. 2005)

The smoking rate in pregnancy has been decreasing during the last decades in the Nordic countries, (Ericson et al. 1991;Eriksson et al. 1996) and the smoking rate at the end of pregnancy was as low as 10.4 % in Norway during 2004 (www.fhi.no/eway/default.aspx?). Birth weight is reduced by a mean of 200g if the mother smokes during pregnancy. (Haug et al. 2000) The correlation between smoking and birth weight exists irrespective of other causes for reduced birth weight, (Haug et al. 2000;Kramer et al. 1990) and a dose-response relationship has been found. (Kallen 2001) Smoking during pregnancy increases the rate of being small for gestational age (SGA) infants, preterm birth and perinatal death. (Kallen 2001;Raatikainen et al. 2007) Stopping smoking during pregnancy reduces the reduction of birth weight, since the effect of smoking on birth weight is strong close to term. (Ananth & Platt 2004) In addition, smoking can represent an extra hazard to pregnant MS women.

MS and medication during pregnancy

Conception often occurs unplanned while women are receiving disease-modifying therapy or symptomatic medication. IFNβ taken by MS patients has generally been recommended discontinued before conceiving, or at least when pregnancy is suspected or confirmed. The large size of the IFN molecules may inhibit transferral across the placental barrier, as suggested from analysis of women treated with IFNα. (Pons et al. 1995) Limited data on pregnancy outcomes in women exposed to IFNβ have shown a slightly increased rate of miscarriages (Sandberg-Wollheim et al. 2005) and a slight reduction in birth weight. (Boskovic et al. 2005) A recent retrospective

study of 34 pregnant MS women exposed to disease-modifying therapy during pregnancy showed no effect on pregnancy outcomes. (De, V et al. 2007) The numbers of women exposed to IFNβ during conception or later in pregnancy are too small to provide reliable data, and discontinuation of IFNβ is still recommended. Since there is no evidence of teratogenicity or birth defects related to IFNβ therapy, induced abortion is not indicated. IFNβ can in exceptional cases be continued in pregnancy after a clinical consideration has shown that treatment is essential for that woman.

Glatiramer acetate used in pregnancy has not been shown to increase the risk of fetal malformations. However, some adverse drug reactions related to pregnancy have been reported, like spontaneous abortions. (Tremlett & Oger 2008) Since there are no reliable data so far, this drug is not recommended in pregnancy. Pregnant women on this drug should continue using it only if regarded as absolutely essential.

Natalizumab has not been studied in pregnant women, and is contraindicated during pregnancy. Mitoxantrone is not recommended during pregnancy due to its strong immunosuppressant activity, teratogenicity in rats and the lack of data on security. Methotrexate and cyclophosphamide are not recommended used during pregnancy due to teratogenicity. Intravenous immunoglobulin (IVIG) can be used safely during pregnancy. (Achiron et al. 2004)

Prednisone is not recommended in the first trimester due to the increased risk of oral cleft. (Park-Wyllie et al. 2000) Acute relapses in MS women during pregnancy can be treated with methylprednisolone and prednisone in the second and third trimesters, and short-term high-dose regimes on methylprednisolone is preferable in the same manner as for non-pregnant women. (Sellebjerg et al. 2005) Due to adverse effects of glucocorticoids, like gestational diabetes, hypertension, oedema and premature rupture of membranes, tapered courses should be avoided during pregnancy. (Ferrero et al. 2006)

Fatigue, bladder and bowel dysfunction, spasticity, movement problems and pain can be aggravated during pregnancy. The majority of medications indicated for these problems are contraindicated during pregnancy, (Schwendimann & Alekseeva 2007) according to the U.S. Food and Drug Administration (www.fda.gov/). MS women have a higher risk for urinary tract infections during pregnancy. Chronic infections in MS patients can be treated with drugs like nitrofurantoin or ampicillin.

MS, breast-feeding and medication

Breast-feeding rates in Norway have increased from a bottom level in the late 1960s, when 30 % breastfed for 3 months or more, (Liestol et al. 1988) to 1991, when more than 95 % were breast-feeding their baby when discharged from the maternity clinic. (Heiberg & Helsing 1995) Breast-feeding does not influence postpartum relapse frequency or severity. (Confavreux et al. 1998;Vukusic et al. 2004) Thus, breast-feeding can be encouraged in MS women. A recent multicentre study on IVIG post partum in 163 MS women revealed that 85 % breastfed, and two thirds of them for 3 months or more. (Haas & Hommes 2007) The MS mother's ability to nurse or care for the baby can depend on the disease activity postpartum and the level of disability. Stress related to the maternal sleep deprivation during the postpartum period can be alleviated by somebody else feeding the baby with pumped breast milk at night time.

If the MS mother needs medication in the postpartum nursing period, there will be concern about whether the drugs or metabolites pass into the breast milk. According to Norwegian guidelines (www.relis.no), medium dose methylprednisolone can be given when medication is required for postpartum relapses, due to low transmission across placenta in doses 80mg or less per day and a half life of maximum 4 hours. (Hale 2006) With higher doses, corticosteroids will secrete into the breast milk and can cause growth suppression and reduced bone density in the baby due to interference with endogenous corticosteroid production. IFNα is not excreted in human breast milk at clinically relevant levels, (Kumar et al. 2000) but it is not known to what extent IFNβ is absorbed in the baby, and IFNβ therapy is therefore not

recommended during breast-feeding. It is not clarified whether glatiramer acetate passes into the breast milk. A survey study of women neurologists' practice illustrated that nearly 86 % did not prescribe disease-modifying medication to MS patients during breast-feeding, and if it was used, glatiramer acetate was the most frequent drug. (Coyle et al. 2004) Mitoxantrone and cyclophosphamide are found in breast milk and should not be used during breast-feeding. If a disease-modifying drug is indicated, and the mother has a strong wish to continue breast-feeding, IVIG therapy is reported to reduce the attack rate without adverse effects on the baby, (Achiron et al. 2004;Haas & Hommes 2007) and is thus regarded as safe during breast-feeding.

General trends in obstetric care

Important developments in obstetric care in Norway since the foundation of the Medical Birth Registry of Norway (MBRN) in 1967 have been the progress in obstetric techniques and routines for antenatal, intra-partum and postnatal care. Especially the enhanced in utero monitoring has resulted in more premature children being rescued. Increased operative intervention and especially more planned caesarean sections represent a major change during these years.

There has been a world-wide increase in the rate of caesarean section during the last decades. (Black et al. 2005;Menacker et al. 2006) In Norway, this rate has increased gradually from 2 % in 1967, to 13.6 % in 1998 and 16.3 % in 2006 (www.fhi.no/eway/default.aspx?). Several explanations have been suggested for this increase, such as technological tools enhancing early intrauterine diagnosis, preference for caesarean section with term breech presentation, (Hannah et al. 2000), increase in maternal age, increased proportion of nullipara and plural births, as well as previous caesarean section. A Norwegian prospective survey for the years 1998-9 illustrated that emergency caesarean sections account for 64.3 % of all caesarean sections. (Kolas et al. 2003) The repeat caesarean section rate was as high as 50 % in this study, and the most frequent indications for planned caesarean section were

previous caesarean section and maternal request. In comparison, the repeat caesarean section rate was almost 90 % in the US in 2004. (Menacker et al. 2006)

The attitude among women towards their right to choose delivery mode has been changing. (Bettes et al. 2007) However, the range of personal reasons for requesting caesarean section varies between countries and social classes. (McCourt et al. 2007) The increase in caesarean section rate has been found not to lower perinatal mortality. (Eckerlund & Gerdtham 1999) Compared with planned vaginal birth, planned caesarean delivery increased the transfer rate to the neonatal intensive care unit from 5.2 % to 9.8 %. (Kolas et al. 2006)

More premature children are rescued due to improved antenatal care, prenatal diagnostic tools and premature intensive care units. Increased maternal age, plural births and the rate of extremely premature children can alter the frequencies of neonatal conditions and further the morbidity. The quality of the obstetric care can be measured as the rate of perinatal mortality. The rate of perinatal mortality (among foetuses ≥500g which corresponds to the birth weight at 22 weeks of gestation) in Norway has decreased from 2.2 % in 1967, to 1.2 % in 1980 and 0.4 % in 2005 (www.fhi.no/eway/default.aspx?). Recent numbers show similar perinatal mortality rates in all Scandinavian countries (Health statistics in the Nordic countries 2005. Copenhagen: NOMESCO 80:2005).

Small obstetric units are located in scarcely populated regions of Norway. However, during the last 20 years obstetric care in Norway has been centralized, (Nilsen et al. 2001) and this has also been reported in Finland. (Viisainen et al. 1999) The very small units (<100 births per year) have doubled neonatal morbidity compared to the units with 2001-3000 births per year, also after accounting for differences in selection to small and large units. (Moster et al. 1999) The experience, expertise, and equipment of larger institutions can reduce the risk of neonatal death to a minimum both for low-risk and high-risk deliveries.

Aims of the study

The objective of this thesis was to explore whether birth-giving is affected by multiple sclerosis, by four papers analysing the following:

I. The effect of maternal MS upon pregnancy, delivery and the newborn, including MBRN data during 1967-2002 (Paper I).

II. The effect of maternal MS upon pregnancy, delivery and the newborn: an analysis of planned vaginal deliveries, including MBRN data during 1988-2002 (Paper II).

III. The effect of maternal MS upon pregnancy, delivery and birth outcome by comparing births before onset of MS, births between onset and diagnosis of MS and births after MS diagnosis. A coupled data file from the MS Registry and the MBRN during 1967-2002 was included (Paper III).

IV. The effect of smoking as a possible risk factor for the lower birth weight of the neonates in MS births. Smoking habits and social factors in pregnant MS women versus references were analysed for MBRN data during 1998-2005 (Paper IV).

Materials and Methods

The studies in this thesis are population-based historical cohort studies, utilizing the data of two registries: the Medical Birth Registry of Norway and the Norwegian MS Registry.

The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) was established in 1967 by the Directorate for Health and Social Affairs. It is a complete, nationwide registry based on the compulsory notification of all births after 16 weeks of gestation (12 weeks from December 1, 1998). It is one of seven health registries in Norway. From 2002 the registry has been run by the Norwegian Institute of Public Health. A standardized notification form (Appendix 1) was principally unchanged from 1967 to 1998. A new and revised notification form has been used since December 1, 1998 (Appendix 2). The form is filled in by the physician and midwife assisting during the delivery and based on information from:

1) A standard form used during pregnancy by the woman's physician
2) Information given by the woman when admitted to hospital
3) Information from the physician and midwife about the actual delivery and the newborn.

The registry contains comprehensive data on demographics, maternal health, and previous reproductive history, complications during pregnancy and delivery and pregnancy outcome. The newborns are examined medically by a physician, usually a paediatrician, before discharge from the hospital, and all neonatal diagnoses recorded are based on these examinations. The attending midwife is responsible for completion of the notification form and the attending physician is a co-signer. Complete ascertainment of the MBRN is accomplished through record linkage to

Statistics Norway. Linkage to other patient or health registries is possible since every inhabitant of Norway has a unique personal identification number, allocated shortly after birth. Using the mother's identification number, linkage to the National Population Registry, run by Statistics Norway, can yield the identification number of the newborn.

The MBRN is a valuable resource for information on the effect of maternal disease on pregnancy, delivery and birth outcome. Data have been collected and evaluated for other patient groups. Births by women with myasthenia gravis, (Hoff et al. 2003) connective tissue disease and inflammatory rheumatic disease, (Skomsvoll et al. 2000) and polio, (Veiby et al. 2007) have been investigated with an epidemiological approach due to the advantageous nationwide MBRN.

Linkage of data from the MBRN and from other registries requires approval from the Regional Committee for Medical Research Ethics, the Data Inspectorate, and the Directorate of Health and Social Affairs.

The Norwegian MS Registry

The Norwegian MS Registry was established in 1998 and financed through a grant from the Social and Health Department. The Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital runs and harbours the MS Registry, which registers demographic, clinical and treatment variables on (preferably all) MS patients in Norway (Appendix 3). The year of onset and diagnosis of MS is recorded. The MS onset is defined as the year when the first MS related symptom occurred, with the neurologist interpreting the patient history. The MS diagnosis is set according to McDonald criteria. (McDonald et al. 2001;Polman et al. 2005a) The validation of the reported year of onset and year of diagnosis has not been done systematically in the MS Registry. The patient history, symptoms and clinical signs, and the results of the paraclinical investigations may be evaluated in each case.

The registration is based on written informed consent, given to the local neurologist. (Myhr et al. 2006) The first patient was registered in 2001, and the registry included 3087 patients per May 2005. Given a prevalence of MS of 150 per 100,000, (Grytten et al. 2006), this accounted for almost 50 % of all MS patients in Norway. Linkage to the National Population Registry enabled us to exclude those patients that were dead (64 patients). The 3023 MS patients alive who were the source population for Paper III, had a relapsing remitting MS rate of 86.7 %, mean age at onset of 33.1 years and included 67 % women, indicating that this was a representative MS population. (Celius & Vandvik 2001;Dahl et al. 2004;Grytten et al. 2006) Written informed consent from the patients was necessary to link the MS Registry to the MBRN. Information was sent to all 3023 patients, followed by a reminder to those patients (901) that had not responded to our approach. The collection was then closed, and 2560 patients, 1755 women, had consented to record linkage. A total of 463 patients had for various reasons not answered or not answered yes (6 had wrong addresses, 1 claimed wrong diagnosis, 11 refused and the rest had recently died or did not answer for other reasons). The proportion of women was 68.6 % in the consenting versus 59.7 % in the non-consenting group.

Of the 1755 consenting women, 1371 were registered with a total of 2783 births in the MBRN. Linkage of the MBRN and the MS Registry gave unique access to a large material of women with MS that had gone through pregnancy and birth at different stages of their disease.

MS and reference groups

In Paper I all births registered in MBRN from January 1, 1967 to December 31, 2002 were included. Among these 2,103,079 births, a diagnosis of MS coded as 340 (International Classification of Diseases (ICD)-8) or G35 (ICD-10) was noted in 461 mothers with 590 births. In 45 (9.8 %) of the MS mothers, the MS diagnosis was missing on one or more of the consecutive births (n=59). Since MS is a chronic

disorder with persistent immune mediated lesions in the central nervous system, we included these births in the MS group. These 59 births did not differ from the 590 MS coded births regarding complications during delivery, rate of operative delivery and neonate's characteristics. Thus, the study population consisted of 649 births. The reference group consisted of all remaining 2,102,430 births. Plural births were not excluded from any analyses other than the calculation of SGA.

In Paper II, we wanted to evaluate the delivery and birth outcome among women who were planned to have a vaginal delivery, which were women who underwent a vaginal delivery or an emergency caesarean delivery. From 1988, caesarean delivery was classified as planned or not, and we therefore included MBRN births during January 1, 1988 to December 31, 2002. A total of 449 MS births were compared to 815,060 reference births.

In Paper III the database was generated by the linkage of MBRN (January 1, 1967 to December 31, 2002) and the MS Registry. The births were categorized to pre MS, that was birth prior to year of MS onset; early MS, that was birth between the year of onset (included) and the year of diagnosis; and manifest MS, that was birth from the year of diagnosis (included) and later. If only the year of either onset or diagnosis was known (n=54), the birth was placed in the group with the assumed highest risk (later MS stage), to yield bias towards zero. If neither the year of onset nor the year of diagnosis was recorded exactly in the MS Registry, all births from that woman were excluded from the study (n=10). This led to a total of 1910 pre MS births, 555 early MS births and 308 manifest MS births in 1368 women. The mean age of MS onset for all included MS mothers was 33.3 years. Only the MS diagnosis from the MS Registry was used in Paper III, in contrast to the other Papers which used the MS diagnosis noted in the MBRN. The non-MS reference births in Paper III included all births during the same time period with no MS registered in the MS Registry and consisted of 2,100,281 births. The non-MS reference births included 441 births where MS was recorded in the MBRN (but not in the MS Registry). Since this accounted for only 0.02 % of the total, they were not excluded from the non-MS references. For

some birth weight analyses the groups early and manifest MS were grouped together (n=863) as births after onset of MS, and compared to pre MS births (n=1910).

The majority of the MS women (86.4 %) had births in only one of the three categories, and only 0.4 % of the mothers had births in all three categories. Of all births one year or more after the MS diagnosis, 74.7 % was recorded in MBRN with a diagnosis of maternal MS, and the accordance increased the longer since the MS diagnosis.

In Paper IV, data on smoking from December 1998 to October 2005 was collected. Such information has been registered in the MBRN from December 1, 1998. Linkage to Statistics Norway generated information on the mother's highest attained educational level by December 2004, as well as employment status. A total of 372,128 births were registered, and in 250 of them the mother was registered with MS. All the non-MS births were included in the reference group. Since this database did not contain maternal serial numbers, we could not link births by the same mother.

Information on smoking, included in the standard birth registration form used from December 1, 1998, was given by the birth-giving mother on her admittance to hospital. Smoking was registered as no smoking or daily smoking, recorded both for the beginning and for the end of the pregnancy. Those who reported smoking only occasionally at the end of the pregnancy (1.4 %) were grouped as non-smokers. Since 97 % of those who reported daily smoking at the end of the pregnancy also reported daily smoking at the beginning, we defined this group as smokers during the entire pregnancy. Twenty-seven births in the MS group were reported as daily smokers at the end of the pregnancy. They constituted the target group in the analyses on adverse birth outcome to evaluate if smoking was an extra hazard for women with MS. Smokers at the beginning of the pregnancy but not at the end (n=15) were classified as non-smokers for the analyses of birth outcome.

For the analysis of smoking rate, the cases that lacked information on smoking both at the beginning and at the end of the pregnancy were excluded. The frequency of

totally missing smoking information was equal in the MS and the reference groups (14.0 %) and amounted to 35 births in the MS group and 52,203 in the reference group.

Variables and classification

The variables in Paper I-IV were generally based on the variables which exist in the MBRN. The variables have been defined after consensus in a group consisting of obstetricians, epidemiologists and neonatologists. The following variables were studied:

Descriptive variables:

- Year of birth
- Age of mother (completed years)
- Marital status
- Maternal diseases before or during pregnancy (MS, inflammatory arthritis, urinary tract infections, hypertension, haemorrhage, anaemia, diabetes mellitus, rubella, epilepsy, thyroid condition)
- Type of obstetric institution (university hospital or not)
- Birth order (parity), mean parity of all births

Outcome variables:

- Birth weight (g), length (cm) and head circumference (cm)
- Sex of the neonate
- Gestational age in days and completed weeks
- Preterm birth (less than 37 weeks of gestation)

- Pregnancy complications (any complication and preeclampsia defined as increased blood pressure after 20 weeks of gestation with proteinuria, oedema or both)

- Complications during delivery included slow progression of the second stage of labor (defined as a duration of more than 60 minutes, or more than 75 minutes with epidural anaesthetics) (Bergsjoe et al. 1993), postpartum haemorrhage and presentation anomalies.

- Induction of delivery (perforation of amniotic membranes and/or infusion with oxytocin and prostaglandin) any time during delivery

- Operative interventions (use of a vacuum extractor, forceps or caesarean section)

- Outcome variables regarding the neonate were Apgar scores (at 1 and 5 minutes), stillbirth, perinatal mortality (all fetal deaths after 16 weeks (12 weeks since 1998) of pregnancy and deaths up to 7 days after birth) and birth defects (further classified as severe or not, based on ICD-8 until December 1998 and thereafter ICD-10).

- Small for gestational age (SGA) was defined as birth weight below the tenth percentile at the attained gestational age. We used a standard for birth weight by gestational age based on MBRN data, which exclude stillbirths, plural births, neonates with birth defects and births by caesarean section. (Skjaerven et al. 2000) The standard was applied on all singleton births with attained gestational age 28 to 44 weeks and term births (37 or more weeks).

- High birth weight was defined as 4500 grams or more independent of gestational age. Low birth weight (LBW) was defined as below 2500 grams (in births ≥28 weeks of gestation).

From 1988, caesarean section was classified as planned or not. From 1999, mother's medication during pregnancy as well as smoking habits was registered.

Additional variables after linkage of MBRN and the MS Registry (Paper III)

- Year of MS onset
- Year of MS diagnosis
- Initial course of MS (RRMS or PPMS)
- Duration of MS from onset to time of giving birth, and from MS diagnosis to time of giving birth (in years)

Additional variables in the database with information on smoking (Paper IV)

- Smoking: no smoking and daily smoking, at the beginning and at the end of the pregnancy. Only daily smokers at the end of pregnancy were grouped as smokers, and 97 % in this group also smoked daily at the beginning of the pregnancy.
- Ever smoking (those who smoked to some degree at the beginning or at the end of pregnancy)
- Maternal cohabiting status
- Highest attained education in years (high educational level with education for 13 years or more, or low level with less than 13 years)
- Employment status (full-time, part-time or not working)
- Miscarriages (less than 24 weeks gestation) in earlier pregnancies

Statistics

For statistical analysis we used the Statistical Package for the Social Sciences (SPSS, Chicago IL) for Windows version 13.0 and 14.0. Pearson chi-square tests were used to compare categorical variables. Fisher's exact test was used for tables with expected cell frequency lower than 5. Arithmetic means were calculated for neonatal anthropometrics and gestational age. Means of continuous variables for two groups were compared by Student's *t*-test. Means of continuous variables for the three groups in Paper IV were compared in a one-way ANOVA test. The power to detect a given difference in mean birth weight between two groups was estimated in the adjusted linear regression model (Papers III and IV). The power to detect a given difference between the MS and reference smokers in the categorical variables listed in Table 2, Paper III was calculated in S-Plus (Insightful, Seattle). All tests were two-sided, and a statistical significance level of 0.05 was used.

Stratification, effect modification and confounding

Confounding represents a confusion of effects, where an apparent effect of the exposure is distorted by a confounder. A confounder must be associated with the exposure, it must be a risk factor for the outcome, and it must not be an intermediate step in the causal pathway between the exposure and the outcome. A confounder can be attempted managed during analysis. Possible effect modifiers or confounders such as time period, mother's parity, mother's age, and educational level, were considered by stratification and secondly by linear regression or unconditional logistic regression analysis. In some analyses (Paper III) gestational age and caesarean section were also evaluated as confounders. Statistical testing of effect modification was evaluated by including an interaction term in the logistic regression model (Paper IV).

To detect possible changes over time due to trends in obstetric care, management of MS patients and MS diagnostic criteria, the material was subdivided into three time periods: 1967 to 1980; 1981 to 1990 and 1991 to 2002. Data of operative intervention were presented in strata according to these periods in Paper I. For the association MS and operative intervention in Paper III, time period was divided into 6 categories,

since time period was a very strong confounder for the association between MS and operative interventions. This was due to the skewed representation of births at the different stages of MS in the different time periods, illustrated in table 1 in Paper III.

Due to the higher ascertainment of cases with a recent diagnosis of MS in the MS Registry (see Methodological considerations), as well as an increasing number of births to MS women throughout the period, the group of manifest MS births was overrepresented in the last time period compared to pre MS births (Paper III). The increasing number of MS births throughout the examined time period was a major finding also in Papers I and II. As a consequence, time period was a strong confounder for nearly all our studied variables and especially for caesarean section due to the changing attitudes to caesarean section among pregnant women and obstetricians during these years. (Black et al. 2005) There were also effects of time period on birth weight, possibly due to changes in mothers' lifestyle. (Skjaerven et al. 2000)

Births were stratified by parity (first, second and third or more). Mean parity was similar in the MS and the reference group (Papers I and II). However, in the analysis of birth weight and smoking in Paper IV, it was necessary to adjust for parity. Maternal age is a confounder for many birth outcomes. This variable was stratified in completed years at birth-giving (less than 25, 25 to 29, 30 to 34 and 35 years or more). Since the MS group as expected had a higher mean age at the time of giving birth, and high maternal age in itself can account for differences in the neonates' anthropometrics, maternal age was typically included as a categorical covariate in the multivariate models.

The highest attained educational level for the mother was only available in the database used for Paper IV. Educational level was a strong confounder for the association between smoking in pregnancy and MS. This association was further complicated by the declining smoking rates during the period 1998-2005. Data on the highest attained educational level was imported from Statistics Norway by January 2005, and our database contained births from the period December 1998 to October

2005. We could expect an effect of the difference in mean maternal age between the MS and the reference group for comparison of educational level. The groups were made comparable for educational level by excluding births by mothers <25 years of age.

Age of gestation was stratified as less than 37 weeks (preterm births), 37 to 42 weeks (term births) and 43 weeks or more. In Paper III, the effect of MS on birth weight was adjusted for gestational age. This was done in order to evaluate whether the decrease in mean birth weight in term births observed among MS mothers could be due to the increased use of obstetric intervention in the MS group, such as use of caesarean section. An alternative to adjustment for gestational age might have been to adjust directly for caesarean delivery. However, since conditions leading to LBW can by themselves cause caesarean section, we found it not justified to include caesarean section as a confounder for the association MS and birth weight. Reduced birth weight in the manifest MS group compared to the pre MS group remained also after inclusion of gestational age (in weeks) in the multivariable model. In Paper II, the planned caesarean sections were excluded for all analyses. In these analyses, no difference in gestational age was observed between the MS group and the references. Since the indications for planned caesarean section can be different in MS and non-MS births due to the patients' and health professionals' attitudes, such an exclusion of planned caesarean section can imply selection bias. This is commented on in Methodological considerations.

Low age of MS onset could be associated with a more advanced disease at the time of pregnancy and delivery. Therefore, age of MS onset was considered as a possible confounder (Paper III). Our study design included grouping of births in three different stages of MS. The pre MS group (giving birth before any MS symptom) would naturally have a significantly higher mean age of MS onset compared with the other two groups, giving birth after MS debut (early MS, manifest MS) illustrated in Table 1, Paper III. However, since adjustment for age of onset did not change the association between manifest MS and birth weight, we did not include age of MS

onset in our final analysis. In a larger dataset of MS cases, one could have included a stepwise duration of the disease from MS onset to the year of birth to see if there is a trend for duration of MS regarding negative birth outcome in this patient group.

Medication during pregnancy was not registered in MBRN until 1999, but would have been interesting to evaluate as a possible confounder. However, since MS specific disease-modifying therapy including cortisone-like drugs were not reported used in pregnancy during the period 1999-2005 in the MS group (all Papers), we can discount any effect of such treatment for our studied associations.

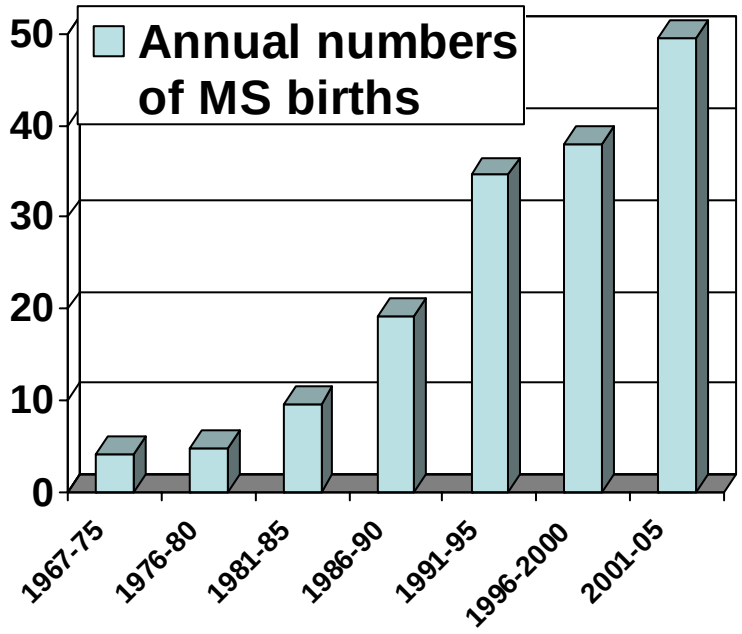
Ethical approval

The study was approved by the Regional Committee for Medical Research Ethics Review in West-Norway, the Directorate of Health and Social Affairs in Norway as well as by the Data Inspectorate of Norway.

Summary of results and general discussion

1. Increasing numbers of MS births (Paper I)

The number of births by MS mothers increased markedly during the studied period 1967-2005. (Figure 1)



In the same time period, the annual number of non-MS births was relatively stable and varied between 50,278 (1983) and 68,901 (1969) (Paper I). The incidence rate of MS in Hordaland county increased from 1953 and onwards for both men and women, (Grytten et al. 2006) but was relatively stable since the early 1980s, illustrated in several studies. (Dahl et al. 2004;Grytten et al. 2006;Midgard et al. 1996) Improved case finding and diagnostic procedures as well as real changes in risk factors might have contributed to the increased incidence rates. (Grytten et al. 2006;Marrie et al. 2005) Improved diagnostic procedures, including the use of MRI, CSF and electrophysiological examinations, improved treatment options, as well as improvement of the general health care and neurologic services have given a shorter onset-diagnosis interval. (Grytten et al. 2006) This shortening of the time interval from clinical MS onset to the diagnosis of MS may also have contributed to the increase in registered MS births seen in our data. The patients also have stronger

demands to be informed of their diagnosis and possible treatment options by their neurologist. Thus, it is reasonable to assume that more women gave birth between MS onset and diagnosis during the earlier years covered by our study, and hence are not reported in the MBRN to have MS. However, this was not supported by our data in Paper III.

The increasing numbers of births for the whole MS group over time (Paper I) was not accompanied by a simultaneous increase in parity for these women. This suggests a real increase in the proportion of women with MS who give birth. The last 10 years with new disease-modifying treatment and the reassuring findings in several studies showing no risk of pregnancy in MS women (Roullet et al. 1993;Weinshenker et al. 1989b;Worthington et al. 1994) have probably had a substantial, positive impact on MS women's preferences related to pregnancy and birth-giving. These factors have led to a change both in patients' and physicians' attitudes. The increased numbers of MS births is a background characteristic for interpreting our data. Thus time period was regarded as a strong confounder for many of our studied variables along with changes in obstetric trends.

2. Reduced birth weight in MS births (Paper I-IV)

Women with MS had a higher frequency of neonates being SGA (13.5 % versus 11.3 % among references, P=0.003 adjusted for mother's age and time period) (Paper I). The association MS and SGA was even stronger when we compared term births in MS to references (OR 1.61, 95 % CI 1.26-2.05, P<0.001 adjusted for mother's age and time period) (Paper I). Reduced mean birth weight (-96g) and length (-0.5cm) for the MS neonates (Table in Errata), was in line with this finding. We applied the SGA definition that uses data from the MBRN (Skjaerven et al. 2000) to our dataset, and excluded plural births, but not infants with malformations, still births and births with caesarean section. SGA is associated with caesarean section since conditions that give rise to restricted fetal growth, like preeclampsia and congenital malformations, also

can be indications for a caesarean section. SGA by itself may also be an indication for caesarean section. But despite the increase in SGA births in the MS group, no negative clinical impact in terms of increased mortality for the MS newborns was found.

Since caesarean section may be a result of inadequate fetal growth, we found it not appropriate to adjust for caesarean section in the analysis of the association MS and birth weight. Instead we excluded births with planned caesarean sections in Paper II. However, although equal mean gestational age of the newborns in the MS (281 days) and the reference group (282 days) for the planned vaginal deliveries, we found that both length (-0.3cm, P=0.04 adjusted for mother's age) and weight (-108g, P<0.001) was reduced in the MS group (Paper II). A possible limitation in this analysis was that selection for planned caesarean section might have been different in MS and non-MS women and thus give rise to selection bias. This problem could arise if the threshold was lower for this operative intervention in MS mothers than in healthy mothers.

Our results in Paper III indicated that the reduced birth weight in MS was linked to manifest disease only. Mean birth weight was 3509g, 3511g and 3428g in the pre MS group, the early MS group and the manifest MS group, respectively. Neonates born after the MS diagnosis of their mother had 89g (95 % CI 21-157) lower birth weight among term births compared to those born before onset of MS (pre MS) (P = 0.046, adjusted for gestation in weeks, mother's age and time period). Naturally none of the pre MS and early MS births were reported in the MBRN as MS births, in contrast to the manifest MS where the majority of the births (74.7 %) were recorded with MS in the MBRN. The mothers in the manifest MS group were consequently known by the health professionals to have this disease. This may have resulted in a different handling of the birth in the manifest MS group compared to previous births in the same women. Women with manifest MS had an increased rate of caesarean section (17.2 %) compared to the pre (7.8 %) and early MS (10.5 %) births (Paper III), although this was not significant when adjusted for the time period (P=0.68). Our

multivariate analysis showed that the reduced gestational age, most likely related to the increased rate of caesarean section did not fully explain the lower birth weight in the manifest MS group. High numbers of MS births were required to find this modest difference in weight. This might explain why previous studies have failed to detect the reduction in birth weight. (Confavreux et al. 1998;Worthington et al. 1994)

A reduction in both birth weight and length in the MS group, in contrast to a normal head circumference, indicates that fetal nutrition might have been insufficient during pregnancy. Factors that may affect the well-being of the fetus, like infections, malformations and chromosomal abnormalities, (Cunningham et al. 2001) were not found to be increased in our material. Additional possible explanations for reduced fetal growth include maternal disease (co-morbidity), but only inflammatory arthritis and urinary tract infection were more frequent in the MS group, and the rate of preeclampsia was even lower in the MS group than in the reference group (unpublished data, Paper I).

Fetal growth is influenced by maternal factors like body weight, nutrition and smoking. We found the same effect of smoking on birth weight in MS and the reference group (Paper IV). However, low numbers cause uncertainty of this finding. Regarding low maternal body weight, previous studies of body composition among MS patients diverge. (Ghadirian et al. 1998;Lambert et al. 2002;Nortvedt et al. 2005;Slawta et al. 2003) A reduction in body weight could be due to changed metabolism after MS onset or muscle atrophy as a result of reduced mobility. This is influenced by duration of the disease. In our study, the mean maternal age (at giving birth) was 29.5 years and MS duration from the year of diagnosis to birth was only 4.5 years in the manifest MS group (Paper III), making a reduced maternal body mass index less likely.

The reduced birth weight of neonates of MS women could also be linked to aspects of neurological dysfunction. Bowel, bladder and sexual dysfunction are frequent and may be early manifestations of MS. (Crayton et al. 2004;Nortvedt et al. 2007) Pregnant MS women had increased frequency of urinary tract infection (Paper I).

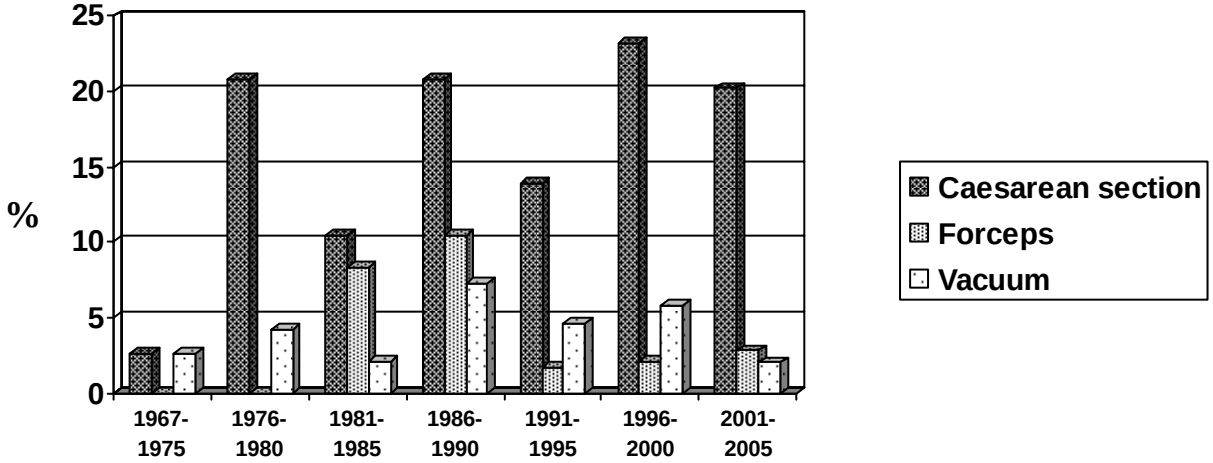
This indicated affection of pelvic organs, which may have caused suboptimal intrauterine conditions and influenced fetal growth. However, other signs of uterine insufficiency like an increased rate of preterm birth were not found in the MS group.

Thus, reduced weight in the MS group could have been due to a combination of several factors. Based on our available data, we cannot define the contribution from nutrition, body composition or neurological dysfunction. One major limitation is that clinical data like pre-pregnancy disability and body mass index (BMI) measurements of the birth-giving mothers were not available. However, comparing all term births after onset for PPMS versus RRMS, showed that the PPMS group (22 births) had 279g (95 % CI 62-496) lower mean birth weight than the RRMS group (664 births) (P=0.001, adjusted for mother's age, time period and gestation in weeks) (unpublished data, Paper III). Despite rather small numbers this indicated an association between MS neurological deficiency in the mother and reduced birth weight of the neonate.

3. Increased rate of operative interventions (Paper I-III)

In MS births, the mothers had a higher rate of operative interventions (caesarean section, forceps, and vacuum extraction) during delivery compared to the reference births (OR 2.54; 95 % CI 1.29-1.84, P<0.001) (Paper I).

The yearly rate of operative interventions for each five year interval in the MS births is illustrated (Figure 2).



Except for the 2.6 % rate in the early years 1967-75, the caesarean section rate has been fluctuating between 10-23 %. During 1991-2002, the mean rate of caesarean section was 18.5 % in the MS group versus 13.2 % in the references (P=0.001). The increased rate of total operative interventions in the MS births compared to the references included an increased rate of forceps use during 1981-1990 (15.3 % in the MS group versus 7.4 % in the references, P<0.001), and an increase in caesarean section rate in all time periods (Paper I). Data since 1988 illustrated that at least in this time period the increase in caesarean section was due to a high number of planned procedures, 9.5 % in the MS group versus 4.6 % among references had a planned caesarean section, P<0.001, while the rate of emergency caesarean section was equal (9.3 % in the MS group versus 8.5 % among references) (unpublished numbers Paper I). The increase in operative interventions could reflect both a higher rate of complications making operative intervention necessary, and fear of complications due to MS in the birth-giving mother. A common indication for a planned caesarean section in Norway is previous section, (Kolas et al. 2003) which will contribute to maintaining a high caesarean section rate in the MS group. The practice of caesarean section has been rather restrictive in Norway, with a rate of 13.5 % in 2000 versus 15-22 % in similar countries. (Martin et al. 2001;Mayor 2002;Odlind et al. 2003) This restrictive attitude among the obstetricians in Norway has kept the rate low in the general population, which makes it easier to find an increased rate in specific risk groups.

We were not able to identify increases in obstetric complications that could account for the increase in caesarean section in the MS group. The complication rate in the MS group could possibly have been higher if the rate of caesarean section had been held at the same level as for the reference population. This was supported by our finding of an affected birth process in planned vaginal MS births with an increase in the need for induction (P=0.05), and a slower progression of the second stage of labor (P=0.06) and more frequent use of forceps (P=0.04) (Paper II). Induction of birth included induction both as an initial procedure and also to enhance the labor process, and includes the use of prostaglandin, oxytocin and amniotomy. Since slow

progression of the second stage of labor was strongly correlated to induction of birth, induction was also included as a covariate for the association slow progression of second stage of labor and MS. This did not change the association of slow progression of second stage of labor and MS (P=0.08) (Paper II). The second stage of labor is a physically demanding phase of labor, and symptoms like fatigue, pareses, spasms and sensory disturbances that affect extremities and lower abdomen and pelvis may interfere in the labor process and increase the need for intervention in this patient group. Maternal exhaustion requiring forceps delivery has been suggested to be more frequent in mothers with MS. (Davis & Maslow 1992) In contrast to a previous report, (Mueller et al. 2002) we did not find an increase in the use of a vacuum extractor, however, regional differences in obstetric practice may account for diverse findings. The importance of MS-related symptoms for the decision regarding operative intervention was supported by the high proportion of planned caesarean section.

The rate of total birth complications and operative interventions did not differ between the pre MS, early MS and manifest MS groups (Paper III). This could illustrate that the MS women during their whole birth careers have an increased rate of operative intervention. Of the 1368 MS women, 982 had 2 or more births, and 5.7 % of these women had two or more caesarean sections (unpublished data from Paper III).

To what degree the MS diagnosis plays a role when diagnosing complications during pregnancy and birth is not known. However, Mueller et al. (Mueller et al. 2002) compared non-MS and MS births and their data supported a heightened degree of monitoring during the antenatal care in MS cases. The recording of our studied variables in the MBRN had very few missing values both in the reference and the MS groups, indicating that recording was reasonably independent of maternal diagnosis.

Our data cannot be used to define the need for operative intervention in MS patients, or to establish recommendations for such intervention in MS. But as the increase in

caesarean section over time did not result in a reduction in the use of forceps and vacuum extractor (Paper I and II), our results indicate that both complications and need for operative assistance might have been increased if the caesarean section rate had been held low in the MS group.

4. Maternal diseases (Paper I-II)

Unlike other immune-mediated disorders such as rheumatic disease (Skomsvoll et al. 2000) and hypothyroidism (Leung et al. 1993) we have found that MS was associated with a reduced risk of preeclampsia. The rate of preeclampsia was 1.7 % in MS versus 3.6 % in the reference group (P=0.01 adjusted for time period) (unpublished data, Paper I). As preeclampsia may develop late in pregnancy, the higher rate of planned caesarean section in the MS group could have prevented some cases of very late preeclampsia. However, adjustment for planned caesarean section did not change the difference in preeclampsia rate. The frequency of preeclampsia in the MS group and the reference group were 1.4 % versus 3.2 % in term births and 5.9 % versus 9.2 % in preterm births. Having MS probably leads to a closer follow-up during pregnancy and birth, (Mueller et al. 2002) indicating that the lower frequency of preeclampsia in our study was true. How this finding relates to MS is unknown.

Urinary tract infection was increased in MS mothers during pregnancy (4.0 % versus 2.4 % among the references, P=0.001 adjusted for mother's age, Paper I). This condition predisposes for pyelonefritis that can lead to other pregnancy and delivery complications like preeclampsia, premature delivery, LBW and fetal mortality. (Le et al. 2004) Some of these complications can lead to an increased rate of operative intervention during birth. This was illustrated by the association of urinary tract infection to emergency caesarean section in our data (Paper II).

There was an increase of inflammatory arthritis (rheumatoid arthritis and ankylosing spondylitis) in our MS group (P=0.018 adjusted for mother's age and time period, Paper I). However, the numbers were too small (inflammatory arthritis reported in six

births by four different mothers) to relate this to birth outcome (birth weight in particular). Co-morbidity has not been supported in the literature. (Somers et al. 2006)

5. Medication in pregnant MS women

Use of medication during pregnancy was reported for 21 % both in the MS and the reference group (unpublished data, Paper IV). None of 250 MS mothers giving births used any kind of immunomodulatory drugs including corticosteroids during the pregnancy (unpublished data, Paper IV). Medication before pregnancy is not recorded in the MBRN.

The frequency of folic acid supplement before pregnancy registered in the MBRN was higher in the MS group than in the reference group (unpublished data, Paper IV). This can be due to a higher motivation among pregnant MS women to follow up recommendations (Tell et al. 1998) regarding health, or a more determined recommendation from doctor, midwife or others. As many as 32 % of the MS women reported the use of folic acid supplement during pregnancy despite an assumed underreporting of vitamin supplements in the MBRN (Annual Report 2003/4 MBRN).

Data on folic acid supplement were not included in Paper IV, but were as follows: (Table 1)

Folic acid supplement	MS, % (n)	References, %	P-value
- before pregnancy	14.4 (36/250)	9.8	0.02
- during pregnancy	32.0 (80/250)	28.7	0.26

6. Smoking in pregnant MS women (Paper IV)

Our study on smoking among pregnant MS women (Paper IV) showed that smoking did not seem to explain the lower birth weight in the MS newborns. We found no difference in the smoking rate 1998-2005 during pregnancy between the MS group (10.8 %) and the reference group (11.4 %) (P=0.78). The daily number of cigarettes among smokers during pregnancy was slightly lower in the MS group (mean 5.7±4.1) compared to the references (7.4±4.6) (P = 0.07). We found that smoking affected birth weight similarly in the MS and the reference groups (P-value for the interaction MS and smoke on birth weight was 0.72). The difference in mean birth weight between smokers and non smokers was found to be 291g in the MS group (P=0.10) versus 197g in the reference group (P<0.001) (Table 2, Paper IV), the latter difference being in accordance with previous data. (Haug et al. 2000) There was no difference in the rate of SGA, LBW and preterm births between smoking MS and references. However, our group of pregnant MS smokers was rather small (n=27).

A reduction in the smoking rate during 1998-2005 was seen for both groups (29.4 % during 1998-9 to 7.7 % in 2004-5 in the MS group versus 19.1 % to 9.7 % in the references, respectively. Figure 1, Paper IV). The reduction was more pronounced among pregnant MS women (P=0.03 for the interaction MS and time period, adjusted for education). The smoking rate among pregnant women in Norway over the years 1987-1994 fell from 34 % to 22 %. (Eriksson et al. 1996) Our data illustrate that the smoking rate in pregnancy has continued to fall. In Finland the smoking frequency was unchanged and 15 % in the period 1987-1997. (Jaakkola et al. 2001) This has also been the case in England (1992-1997) with a smoking frequency of 25 %. (Owen et al. 1998) Other countries have experienced a fall in smoking rates. In the US smoking rates among pregnant white women have been falling from 18 % in 1990-94 to 14.2 % in 1995-1999. (Ananth et al. 2005) In Sweden smoking in early pregnancy decreased from 30 % in 1973 to 12 % in 2000. (Odlind et al. 2003)

The reason for the stronger fall in smoking rate in the MS group is uncertain. The MS population could to a larger extent have been influenced by the information on the hazards of smoking, and especially during pregnancy. A national campaign against smoking during pregnancy was introduced in 1989, and the study illustrating birth weight reduction in smoking versus non smoking mothers in a large Norwegian survey (Haug et al. 2000) got a lot of publicity in 2000. Women with chronic diseases where environmental factors play a role in the pathogenesis, like MS, could possibly be more receptive to health information than healthy women. Slightly more MS patients, however not significant, stopped smoking during pregnancy. Higher maternal age and higher educational level as seen in the MS group should increase the chance of giving up smoking during pregnancy. (Kleinman & Kopstein 1987;Lindqvist & Aberg 2001). Cigarette smoking is an increasingly negative factor for birth weight through pregnancy. (Ohmi et al. 2002) The negative effect of smoking on birth weight is partly caused by impaired placental blood flow. (Larsen et al. 2002) Stopping or reducing smoking to less than five cigarettes per day has been found to protect against growth retardation, LBW and low Apgar score (Raatikainen et al. 2007). Elimination of smoking in pregnancy has been estimated to reduce the number of SGA cases by 12 %. (Rasmussen & Irgens 2006)

The smoking information was collected through an interview of the birth-giving mother when admitted to hospital. There is no reason to believe that MS women report their smoking habits differently compared to the reference group, also confirmed by the same frequency of births missing this information (14 %) in both groups. All of the smoking MS mothers reported the number of cigarettes per day. The groups excluded due to missing smoking information were similar in the MS and reference group concerning education level. Preterm birth could be one cause of missing smoking information. Data from the MBRN illustrates a 116 % higher occurrence of still births in women with missing smoking information than in non-smokers. (www.fhi.no/eway/default.aspx?) However, since the number of missing cases in both the MS and the reference group was equal, we do not believe that our results are biased regarding the comparisons of smoking effect in the two groups.

7. Adverse birth outcomes (Papers I-IV)

Paper I illustrated that there was no increased rate of perinatal mortality and birth defects in the MS group compared to the references. We found no difference between the births in different stages of maternal MS (Paper III). However, the number of births in the MS group was too low to observe minor differences for infrequent complications. The rate of still birth in Norway was 0.9 % in 2002, the perinatal mortality after 22 weeks of gestation was 0.6 % and the rate of total birth defects was 4.6 % (Annual Report 2001/2 MBRN). The power to detect a doubling in the rate of still births in our MS group with 649 births was 51 %. With 1280 births the power would have been 80 %. Hence, unless we assume a marked increase in the risk, we have low power in all our four studies to detect differences in these adverse birth outcomes. Regarding more frequent adverse outcomes, preterm birth was found nearly significantly increased in the MS group (7.9 % versus 6.2 % in the references, P=0.07) (Paper I). However, after excluding planned caesarean sections (Paper II) there was no longer any such difference (P=0.25). There was no increase in the rate of LBW in the MS newborns (Paper I). Thus, our data supports previous studies that did not find any adverse birth outcomes in MS women. (Achiron et al. 2004;Confavreux et al. 1998;Sadovnick et al. 1994)

8. Recommended obstetric strategy for pregnant MS mothers

Our data illustrate the overall safety regarding birth-giving in MS women. The reduced birth weight in the MS group did not seem to have any negative effect on the general health of the newborn. We do not have any reasons to recommend more operative interventions in the MS group.

Births by MS women are affected by a reduction in mean birth weight and an increase of SGA, in addition to an increased rate of induction of birth, second stage of labour and forceps assistance in planned vaginal births. The two latter findings might justify the increased rate of planned caesarean section. However, since we lack

clinical data on the mother we cannot link our results on delivery and birth to MS severity. Several MS-related symptoms and findings like fatigue and muscular extremity, abdominal and perineal weakness and spasticity may cause the slow progression of the second stage of labor and increase the need for operative assistance. One should be aware that urinary tract infection in this patient group increases the risk of operative delivery. Prior to the birth, a clinical assessment of all MS women should be made bearing in mind symptoms and signs that can influence the birth such as fatigue, paresis, spasticity and urinary tract infection. However, present recommendations for pregnancy and obstetric strategies for MS mothers do not differ much from those for healthy women.

Methodological considerations

Study design

All studies presented in this thesis were designed as historical cohort studies. To evaluate the internal validity and precision in our studies, we have addressed systematic and random error in the MBRN and the MS Registry. Internal validity depends on lack of systemic error (selection bias, information bias and confounding). Selection bias comes about when the association between exposure and outcome differs for those who participate and those who do not participate in the study. Information bias can occur if there are errors in measurement or classification of the participants in the study. Confounding is discussed under Statistics.

MBRN

Selection bias

For most purposes, we have used the entire birth cohorts in the MBRN during the specified time period and made comparisons between the MS group and all other births. Due to the record linkage with Statistics Norway, the ascertainment of births in Norway in the MBRN is close to 100 %. This registry is population based and we can assume a negligible selection bias in those studies where MBRN was the only source of information (Papers I and IV). In Paper II, we excluded women with planned caesarean section from the analyses. This was done in order to evaluate whether MS women who were selected to a vaginal delivery had a risk of complications during delivery or operative delivery that differed from women without MS selected to a vaginal delivery. Even if MS women in this study had an equal or higher risk of complications during delivery or operative delivery compared to women without MS, differences between the two studied groups may not necessarily imply that such differences exist between the MS and the reference

populations in general. However, our goal in Paper II was not to describe risks in the overall MS population, but to describe risks among those MS patients selected for a vaginal delivery.

Information bias

Any misclassification or reduced ascertainment of the MS diagnosis in the MBRN will weaken the internal validity of the study. Ascertainment of the MS diagnosis in the MBRN will depend on diagnostics of MS in general, to what extent her diagnosis is recorded in her antenatal record, and to what extent a mother with MS informs about the disease when asked during delivery. As discussed in the introduction of this thesis, the MS diagnostic criteria have changed during the years 1967-2002. The Poser criteria (1983) which included CSF examination, and even more importantly the McDonald criteria (2001) which additionally included MRI of the brain, both allowed an earlier diagnosis. This has resulted in a shortening of the time interval between MS onset and MS diagnosis. (Grytten et al. 2006;Marrie et al. 2005) This allows more of the women's births to take place after the MS diagnosis. Whether or not maternal diagnoses are recorded, will not depend on birth outcome, since maternal diagnoses in general are reported prior to delivery (from the mother or the standard form filled in during pregnancy by the patient's physician), at admittance to the hospital. Since the neurological record does not follow the pregnant women, the information on the MS diagnosis is exclusively dependent on information from the mother, the attending physician or the midwife.

In our historical cohort, 461 MS women (Paper I) gave birth during a 36 year period, with MS mothers representing 0.04 % of all the mothers. The incidence of MS in Norway has gradually increased, but has remained stable on around 8 per 100,000 during the last 20-25 years, (Celius & Vandvik 2001;Dahl et al. 2004;Gronning et al. 1991;Grytten et al. 2006) of which 2/3 will be women. MS prevalence in Hordaland County January 1 2003 for women aged 18-45 years was 152/100,000. (Grytten et al. 2006)

Validation of the MS diagnosis as given in the MBRN has not been done. In our Paper III, linking of the MS women from the MS Registry to the MBRN revealed that 75 % of the 308 births during the first year after the diagnosis MS, were confirmed reported with the diagnosis MS in MBRN (the MS registry is considered the "goldstandard" with a high positive predictive value of the MS diagnosis). For each year after the diagnosis, the frequency of MS mothers that had their MS diagnosis (from the MS Registry) recorded also in the MBRN, increased. Five years after the MS diagnosis 84 % of the births were noted as MS in the MBRN. The MS group in the MBRN may possibly be constituted by the more affected cases since a smaller proportion of those with recent MS diagnosis are missed in the MBRN. An increasing load of symptoms and disability of MS increase the possibility for the mother to inform about the diagnosis or the diagnosis to be evident to the attending midwife or doctor. This may lead to an over-estimation of the effects of MS (using the MS diagnoses recorded in the MBRN) in our study.

A high number of false positive MS births in our material would have diluted any effects. A sensitivity of 88.2 % for rheumatic disease (Skomsvoll et al. 2002) and a positive predictive value of 98.8 % for myasthenia gravis (Hoff et al. 2007) have been reported in the MBRN. Linking consecutive births showed that the MS diagnosis was highly consistent (Paper I). In only 9.8 % of the 461 MS mothers the information on MS diagnosis was missing, after MS was first noted in one, two or three consecutive births. Although some of these cases may represent false-positive cases, part of this may be due to clinical remission. MS is a well-defined and specific disease, well known to both doctors, midwifes and patients. In addition, MS is a type of disease that usually influences family planning. All these factors increase the MS sensitivity and specificity in MBRN. In all Papers, a few MS births were probably included in the (non-MS) reference group (false negatives). But since the reference group is large, the false negatives will have hardly any dilutive effect on the risk estimates.

Smoking information in MBRN

We assume that women with a chronic disease like MS give accurate smoking information to the MBRN to the same degree as the reference group. The smoking information was collected at admission to hospital, and therefore before an eventually complicated birth with a negative birth outcome. The recall bias is considered low. This direct interview could, however, have resulted in under-reporting either by denial of smoking or by refusing to give information. Giving information on smoking habits was optional for the women. Fourteen percent of all birth-giving mothers chose not to give smoking information, equal in the MS and the reference group, suggesting that MS women did not have a different attitude to reporting smoking habits. Since the same proportion of births lack smoking information in the MS and the reference group, excluding these from the analysis of smoking frequency and birth weight will probably not give biased results regarding the comparisons between MS and non-MS. Of the 250 MS women included, only 27 smoked at the end of the pregnancy. This group is treated as if they smoked during the entire pregnancy.

Norwegian MS Registry

Selection bias

Ascertainment of MS cases in the MS Registry at the time of linkage between the two registries was estimated to only about 50 % (May 2005). Since the neurologists tended to report recently diagnosed cases, the Registry had a predominance of newly compared to formerly diagnosed cases. The reporting is done mostly by the treating neurologist, so we would suspect a slightly higher proportion of patients with immunotherapy and frequent follow-ups included, which means those with more active disease. Expanded disability status scale (EDSS) score is not registered. Immunomodulatory treatment was not used by any of the MS women during pregnancy. The reporting to the MS registry was geographically skewed since some hospitals had reported only a minority of their patients. However, this should not bias our results.

The proportion of MS subtype, mean age at onset and gender proportions indicate that the MS registry population is a representative population of MS patients. Female:male ratio in the MS Registry in 2005 was 2.1:1 and the frequency of RRMS was 84 %, similar to what is found in Norwegian epidemiological studies and in other Western populations. The patients must consent to register, and one could speculate that factors like social status, education and MS severity would influence the patients' willingness to register.

Eighty-six percent of the women in the MS Registry gave a positive written response to our approach. The consenting versus the non-consenting women were comparable for frequency of RRMS (89.8 % versus 88.5 %) and mean age at MS diagnosis (32.6±9.8 versus 32.1±9.0). In Paper III, the records of all the female patients in the MS registry were linked to the MBRN. Due to the start of registration in the MBRN, MS women who gave birth prior to 1967 were not included. 1371 of the 1755 consenting women had births registered in the time period 1967-2002. With a mean maternal age for giving birth between 26.2 years in 1967 and 29.4 years in 2002 and MS onset most commonly between the ages of 20 and 40 years, the majority of births occur prior to the MS diagnosis. This was illustrated in our study comparing births in different stages of MS.

Information bias

The definition of MS onset was the year when their first MS related symptom occurred, with the neurologist interpreting the patient history. Validation of MS diagnosis given in the MS Registry has not been done. However, specificity is considered high – only neurologists report to the registry, using the McDonald criteria. (McDonald et al. 2001;Myhr et al. 2006). From the start of registrations in 2001 and until 2005 (the whole period that is relevant for our study) the same criteria for MS have been used. In 1960-70, before disease-modifying treatment was introduced, some avoidance to give the women the MS diagnosis could have lead to women not knowing that they had the diagnosis even if they fulfilled the diagnostic

criteria. If such cases were included in our study, this could have lead to underestimation of the MS effects.

A certain misclassification of MS has been revealed in autopsy studies, and according to data from the Danish Multiple Sclerosis Registry the diagnosis definite MS was in a clinical and pathoanatomical study correct in 94 % of the cases. (Engell 1988) The comparison of the validity of MS from the Danish to the Norwegian MS Registry can not automatically be done due to different ways of classifying the diagnosis according to the different criteria. (Fangerau et al. 2004) Compared to the Danish Multiple Sclerosis Registry (duration of 40 years) with a completeness of the Registry estimated to be high, probably about 90 %, (Koch-Henriksen & Hyllested 1988) completeness of the Norwegian MS Registry (duration 4 years) is still not satisfying.

The categorization of births in Paper III was: births before year of debut; births in the year of debut or later, but before the year of diagnosis; birth in the year of diagnosis or later. A MS flare-up postpartum can be both first symptom and precipitate the MS diagnosis. This may lead to a wrong categorization. By categorizing births in the group with the assumed highest risk, we minimized the risk of overestimating any association.

The period from MS onset to MS diagnosis has become shorter in recent years. (Grytten et al. 2006;Marrie et al. 2005) Since our historical cohort comprises births from 1967, we could assume that there will be a relatively larger population of birth-giving MS mothers who gave birth between onset and diagnosis in the first part of the period, but fewer women in the last years. This was not supported in our data (Table I, Paper III). Particular for this group (early MS) was that they have MS but without the women or the obstetrician being aware of the developing neurological disease during pregnancy and birth. From an immunological point of view, it might be more correct to compare before and after the clinical onset of MS only. This was done for birth weight analyses.

Precision

High precision implies lack of random errors. For our epidemiological research this includes especially sampling errors. The smaller the study group and the rarer the studied outcomes are, the more the normal variation in the study population will affect the ability to detect differences between groups. Power analyses can yield information on the strength of the data to find measured differences as significant. Power-estimations for the associations between smoking and pregnancy outcomes according to MS status are implemented since birth defects and perinatal mortality are low frequency unfavorable birth outcomes. The power was 30 % to detect a perinatal mortality rate among MS smokers of 3.7 % versus 1.0 % among reference smokers as different. For 5-min Apgar <7 and preterm birth the power to detect a difference of the observed magnitude was 17.9 % and 6.8 % respectively. We also presented power to detect a difference of the observed magnitude in models of birth weight analysis (Papers III and IV).

External validity

External validity implies an evaluation of to what degree the results and conclusions obtained from our data are valid also for other MS populations. The external validity is strongly dependent on the internal validity. Our results would have had higher validity if the MS Registry had an ascertainment close to 100 %. Due to the extensive time period examined, the selection of MS women who give birth will differ due to changing attitudes towards birth-giving in MS women. This selection may also differ between countries, partly due to social welfare benefits. An advantage of conducting an epidemiological study like this in Norway is the relatively homogenous population both genetically and socially. We have examined a large group of MS patients, and a large and unselected reference group, which is important for the high external validity. Thus, there is reason to believe that the results should be applicable to all populations of white women in countries with similar health care system and treatment of MS prior to and during pregnancy.

Multiple testing

The issue of how MS affects pregnancy, delivery and birth outcome is studied on an open basis, evaluating many different possible associations. Therefore our study (especially Papers I and II) can be viewed as explorative and hypothesis generating rather than hypothesis testing. Both the choice of methods and the interpretation of results must be viewed in this context. A broad range of possible associations between MS and pregnancy, delivery and birth outcome risks exists. With a 5 % significance level and given no effect of the exposure studied, one out of 20 studied associations will fall out positive in the long run. Statistical methods, like Bonferroni correction, (Altman 1991) to adjust for multiple testing can be valuable if one has a pre-defined set of associations. Such statistical corrections have been implemented in studies of candidate gene regions in MS patients. (Datta et al. 2007) The value of adjusting for multiple testing is debated, and one objection is that it is too conservative and one may miss real differences. (Bland & Altman 1995;Perneger 1998) In that case the null hypothesis is maintained even if the alternative hypothesis is correct (type II error). Due to the explorative design of the study, we have not adjusted for multiple testing. If we had a situation with a large number of significant associations the method for correction would more likely be used. In our study only a few significant associations were found and the findings were associated with each other, like an increased rate of SGA together with a decrease in birth weight and length. The most important task for our study was to investigate the risk of complications during pregnancy and birth for the MS women, and identify potential risk factors. Associations found need to be verified in future studies.

Assumption of independence

The statistical methods that we have used are based on the assumption of independence between the observations. In the analyses of birth data where women may give birth more than once, the data cannot be regarded as independent. While so far only a limited number of studies that use birth registry data have used statistical procedures that account for such dependency, the use of such methods will probably

be more common as more statistical program packages develop and implement the necessary procedures. In general, not accounting for dependent data will result in standard errors estimated too small, leading to confidence intervals that are too narrow and p-values that are too small. However, to the degree that birth data are stratified for birth order, data will not be dependent. Parity was not a significant confounder for the association MS and caesarean section.

Limitations and advantages

The MS Registry will be of greater importance as the ascertainment increases in coming years. However, the lack of clinical data is the one major disadvantage with both MBRN and the MS Registry. Clinical neurological data at the time of pregnancy could have been obtained through a clinical prospective study, or retrieved from hospital records. One indirect measurement of disease activity would be disease activity measured on MRI in birth-giving MS women. In this way MRI could be applied to compare pregnancy, delivery and birth outcome to CNS inflammation. Studies where disease severity can be linked to delivery and birth outcome can reveal if there is any subgroup of MS women at special risk. Thus, the correlation between MS disability and the pregnancy, delivery and birth outcome is a major challenge for further studies.

Effects of the exposure of disease-modifying drugs used during pregnancy on the pregnancy, delivery and newborn could not be undertaken in our study due to the lack of mothers taking such drugs. In the future, there will possibly be some pregnancies where the MS mother has used disease-modifying drugs, and effects of this exposure can be evaluated comparing with MS birth without such exposure.

The main advantage of our study is the nationwide population based design that enables us to find target groups of satisfactory size. Large size target groups are important especially for infrequent outcomes. Also, data used in the study are

retrieved from two registries with well defined procedures for collection and recording of the information.

Conclusions

The results of our epidemiological study underline the overall safety and the good outcome of pregnancy and delivery in MS women.

Still, our study demonstrates an impact of MS on pregnancy, delivery and the newborn. We found that mothers with MS have an increased risk of operative delivery and especially planned caesarean section. Delivery was affected in the subgroup of MS mothers with planned vaginal births. MS affected the neonate prenatally with a reduced birth weight but without resulting birth defects or increased mortality. Our study of births in the different stages of MS suggests that manifest MS in birth-giving mothers seems to affect birth weight, and this might indicate a relation to the neurological dysfunction in this patient group rather than genetic or constitutional factors. Smoking did not seem to explain the lower birth weight found for the neonates of MS mothers.

A clinical assessment should be made prior to birth bearing in mind symptoms that can protract or complicate the birth for the MS woman such as fatigue, paresis, spasticity and chronic urinary tract infection.

Errata

Table 3 in Paper I presents means of the neonates' characteristics retrieved from the adjusted analyses. The correct table below includes observed means and adjusted differences in mean.

Table 3 *Characteristics of the neonates*

	MS	Controls	Difference in mean	Adjusted difference in mean	*p* Value
Sex, % boys	49.0	51.4			0.22
Mean gestational age, days	277.5	280.4	2.9	1.8	0.018*
Preterm (<37 weeks of gestation), %	7.9	6.2			0.07
Mean length, cm	49.6	50.1	0.5	0.4	0.003†
Mean birth-weight, g	3391	3487	96	123	<0.001*
Mean head circumference, cm	35.1	35.2	0.1	0.07	0.39*
Low birth-weight (<2500g), %	4.9	5.2			0.76
High birth-weight (≥4500g), %	2.3	3.5			0.014*
Small for gestational age, %‡	13.5	11.3			0.003*

**p* Adjusted for mother's age and time period.† *p* Adjusted for time period. ‡Singleton births at gestational age 28 to 44 weeks for the years 1967 to 2002, according to the standards for gestational age in single births for the years 1987 to 1998 in Norway.

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