GIVING BIRTH WITH NEUROMUSCULAR DISEASE

A study of pregnancies, deliveries and the newborn in women with Myasthenia gravis and Charcot-Marie-Tooth disease

Jana Midelfart Hoff, M.D
It is better to light a small candle than to curse the darkness.

- Confucius -
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LIST OF PAPERS

This thesis is based on the following four papers. The papers will be referred to by their Roman numerals.


# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>MG</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>CMT</td>
<td>Charcot-Marie-Tooth</td>
</tr>
<tr>
<td>MBRN</td>
<td>Medical Birth Registry of Norway</td>
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<tr>
<td>AMC</td>
<td>Arthrogryposis multiplexa congenita</td>
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<tr>
<td>FADS</td>
<td>Fetal akinesia deformation syndrome</td>
</tr>
<tr>
<td>PROM</td>
<td>Premature rupture of (amniotic) membranes</td>
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<tr>
<td>AChR</td>
<td>Acetylcholine receptor</td>
</tr>
<tr>
<td>MuSK</td>
<td>Muscle specific kinase</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>MCV</td>
<td>Motor conduction velocity</td>
</tr>
<tr>
<td>RyR</td>
<td>Ryanodine receptor</td>
</tr>
<tr>
<td>HSMN</td>
<td>Hereditary sensory motor neuropathies</td>
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MYASTHENIA GRAVIS

Epidemiology of MG

Myasthenia gravis (MG) is a relatively rare neurological disease associated with the loss of acetylcholine receptors (AChR) (Vincent 2002). It is characterized by fluctuating pathological muscle weakness with remissions and exacerbations involving one or several skeletal muscle groups, mainly caused by antibodies to AChR at the neuromuscular junction (Sanders et al. 1996, Vincent et al. 2005). The disease has two peaks; at age 20-40 years and at age 60-80 years. The incidence in men and women is equal (Poulas et al. 2001b), but women dominate the first peak, men the second. The prevalence of MG in the population has been reported to be about 5-15 per 100 000 (Vincent et al. 2001, Poulas et al. 2001a).

Previously, the leading concept was that MG mainly affected young adults. However, recently an increased prevalence of MG in middle-aged and older patients has been reported (Aarli 1999, Evoli 2006). In the United States, over 60% of all patients with MG are now over 50 years (Ciafaloni et al. 2002).

Clinical features of MG

The most characteristic presenting feature of MG is painless, fatigable weakness (Vincent et al. 2001). In a majority of cases, the disease presents with involvement of the ocular and the extraocular muscles, causing diplopia and ptosis (Sanders et al. 1996). The weakness can remain localized to the ocular muscles for many years or spread to other skeletal muscles, thus becoming generalized MG. In generalized MG, especially the muscles in the proximal parts of the limbs are affected (Romi et al. 2005). In addition to
that, there can be an affection of the axial muscular groups such as neck muscles, and facial and bulbar muscles causing difficulties of speech, swallowing and smiling (Vincent et al. 2001). When respiratory muscles are affected, the disease may become life threatening and the patient may need intensive care with mechanical ventilation.

**Diagnosis of MG**

The diagnosis of MG is based on five elements: 1) *Clinical examination*,

2) *Neurophysiology*, 3) *Pharmacology*, 4) *Immunology* and 5) *Thymuspathology*.

1) **Clinical examination**

Fatigable and rapidly fluctuating asymmetric ptosis is a hallmark of MG (Scherer et al. 2005). This can be tested through the ptosis test, where the patient fixates her gaze on a distant object, and is asked to refrain from blinking. The examiner measures the palpebral fissure width at eye level during forward gaze and again during prolonged upward or lateral gaze for 30 seconds (Oosterhuis 1982). A cooling test for the diagnosis of MG is simple, fast, specific and relatively sensitive in differentiating myasthenic from non-myasthenic eyelid ptosis (Golnik et al. 1999). The test is carried through by measuring the difference in palpebral fissures in millimeters before and immediately after a 2 minutes application of ice to the ptotic eyelid. Two or more millimeters of improvement after application is considered as a positive test result (Golnik et al. 1999).

Other commonly weak muscles (see *Clinical features of MG*) may be tested against manual resistance, with a brief rest between repetitions. It is also important to stress that the other parts of the neurological examination should be normal (Scherer et al. 2005). A
history of muscular weakness becoming worse after exercise, with improvement after rest – should always lead the physician to suspect MG.

2) **Neurophysiology**

Repetitive nerve stimulation is the most commonly used electromyographical diagnostic test. Failure of neuromuscular transmission leads to a decremental response to the repetitive stimulation in most patients. It is reported to have a sensitivity of 89% in generalized MG and 68% in ocular MG when performed in multiple and relevant muscles (Ciafaloni *et al.* 2002).

Single fiber EMG is also a frequently used test in the process of diagnosing MG, and is the most sensitive neurophysiological test of neuromuscular transmission (Sanders *et al.* 1996). Increased jitter is showed in almost all patients with MG. The pathophysiology is most prominent in weak muscles, but may also be abnormal in muscles with normal strength. Patients with mild or purely ocular movement may have increased jitter only in facial muscles. A normal test in a weak muscle almost excludes the MG diagnosis, but it is important to bear in mind that also other disorders such as neuropathies and myopathies can give abnormal test results (Sanders *et al.* 1996).

3) **Pharmacology**

The MG diagnosis can be confirmed by testing with an acetylcholine esterase-inhibiting drug (edrofonium). The drug gives an immediate and reproducible improvement of the MG signs after i.v administration in 90% of the MG patients (Romi *et al.* 2005). The response to ordinary per oral treatment with acetylcholine esterase inhibiting drugs with a longer half-life will give diagnostic information as well.
4) **Immunology**

Autoantibodies against the muscle nicotinic acetylcholine receptor (AChR) can be found in the serum of about 80% of the patients with generalized MG and in about 50% of those with ocular MG only (Ciafaloni *et al.* 2002). These antibodies have three effects: (Baets *et al.* 2002):

1) They reduce the number of AChR, by cross-linking the membrane receptors.

2) By binding to the AChR, the antibodies trigger a complement cascade resulting in a focal destruction of the postsynaptic membrane (complement-mediated focal lysis).

3) They inhibit AChR function, by inhibiting ligand binding. Although the presence of AChR antibodies confirms the diagnosis, their absence (seronegativity) does not rule out MG (Ciafaloni *et al.* 2002).

MG without AChR antibodies has a heterogeneous etiology. In some of the seronegative patients, antibodies towards a muscle-specific kinase (MuSK) are detected (Vincent *et al.* 2003). MuSK is a receptor tyrosin kinase, muscle specific and localized to the neuromuscular junction in innervated muscle. The role of MuSK is not clear, but it seems to be essential for the development of the neuromuscular junction during fetal life (Liyanage *et al.* 2002). The proportion of seronegative patients with MuSK seems to vary in different populations (Vincent *et al.* 2005), from around 40% in UK and Italy (Vincent *et al.* 2003, Evoli 2006) to <10% in Norway (Romi *et al.* 2005). There seems to be a distinction in clinical picture between MuSK positive and MuSK negative patients. Patients with MuSK present a more severe clinical status than patients without.
5) Thymus and thymoma

The thymus is hyperplastic in about 70% of MG patients, especially in those with age of onset < 40-50 years (Sanders et al. 1996, Romi et al. 2005). Older patients usually have atrophic thymuses. Thymomas occur in 10-15% of MG patients, while 30-50% of all thymoma patients develop MG (Duwe et al. 2005). MG patients with thymoma have AChR antibodies (Vincent et al. 2004). Thymoma is a neoplasm derived from thymic epithelial cells, characterized by the presence of both immature T-cell precursors and as phenotypically mature thymocytes (Marx et al. 1997). There is reason to believe that autosensitisation takes place inside the thymoma, and that thymoma associated MG is a true paraneoplastic disease. A chest CT scan is the most commonly used screening test for the presence of thymic pathology (Spring et al. 2001). Presence of non-AChR antibodies (titin and ryanodine receptor) will support a diagnosis of thymoma, especially in younger patients (Skeie et al. 2001, Chen et al. 2004).

The association of MG with thymoma is thought to worsen the prognosis of MG, with more severe symptoms (Evoli 2006), and the prognosis seems mainly to depend on the effect of immunosuppressive therapy (Evoli et al. 2002). Thymoma should be considered as a potentially malignant tumor, which requires prolonged follow-up (Evoli et al. 2002).

Pathophysiology of MG

MG is a heterogenous disease, and classified into subgroups (see Table 1). The early-onset MG subgroup is the largest, consisting of about 65% of all MG patients. These patients are predominantly female. They get their disease before or during the fertile
period of life (2nd or 3rd decade) – and many of them have concomitant autoimmune diseases. They have thymus hyperplasia (see above) and have AChR-antibodies.

The late-onset MG subgroup has thymus atrophy as a predominant feature, and usually the concentration of AChR-antibodies is lower than in the early-onset group. However, non-AChR muscle antibodies occur commonly in this group, in contrast to patients with early onset MG.

Table 1. Subgroups of MG and associated antibodies. (M= male, F= female)

<table>
<thead>
<tr>
<th></th>
<th>Early-onset</th>
<th>Late-onset</th>
<th>Thymoma</th>
<th>Ocular</th>
<th>Seronegative*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex ratio</strong></td>
<td>F&gt;M</td>
<td>M&gt;F</td>
<td>M=F</td>
<td>M&gt;F</td>
<td>F&gt;M</td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td>&lt;40 years</td>
<td>&gt;40 years</td>
<td>Any</td>
<td>Any</td>
<td>Most &lt;40</td>
</tr>
<tr>
<td><strong>Thymic pathology</strong></td>
<td>Hyperplasia</td>
<td>Minimal</td>
<td>Thymoma</td>
<td>Minimal</td>
<td>Minimal</td>
</tr>
<tr>
<td><strong>AChR antibody</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>50%</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>MuSK antibody</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>10-40%</td>
</tr>
<tr>
<td><strong>Titin antibody</strong></td>
<td>Negative</td>
<td>Often positive</td>
<td>Usually positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

* See also paragraph “Seronegative MG”

**Seropositive MG**

MG is mainly caused by pathogenic antibodies to the AChR at the post-synaptic site of the neuromuscular junction. The antibodies bind to the extracellular domain of the AChR and cause receptor loss by a combination of mechanisms, including increased degradation of AChR and complement-induced lysis of the postsynaptic membrane (Vincent et al. 2004).

There are two types of muscle AChRs. One subtype that is found in fetal muscle prior to innervation or after denervation, with a subunit composition of $(\alpha 1)\beta 1\gamma \delta$. The other subtype, which is found at mature endplates, has $\varepsilon$ substituted for $\gamma$ subunits (Lindstrom 2000). Antibodies from many MG patients bind fetal AChRs as well or better than maternal AChRs containing $\varepsilon$ subunits (Brueton et al. 2000).

**Seronegative MG**

Ten to twenty percent of patients with generalized MG do not have any detectable AChR antibodies (Lindstrom et al. 1976, Ciafaloni et al. 2002, Evoli 2006). The condition is referred to as seronegative MG, and classified generalized MG (that is: displaying not only ocular symptoms). The diagnosis has been made on electrophysiological, clinical and pharmacological grounds with no AChR-antibodies detected. The term “seronegative MG” is misleading, as these patients have other serum (humoral) factors, which cause their disease (Vincent et al. 2003). Antibodies to the muscle specific kinase (MuSK) have been detected in a proportion of these patients (Hoch et al. 2001).
MuSK is a receptor tyrosine kinase, restricted to the neuromuscular junction after development, co-localised with the AChRs. Concerns have been raised about whether the MuSK antibodies really are pathogenic (Lindstrom 2004). A recent review article points out that these antibodies define a type of MG that can be difficult to diagnose, can be life threatening and may require additional treatments (Vincent et al. 2005). This is probably due to an effect by the antibodies upon the neuromuscular junction, where interference with its function can lead to defects in neuromuscular transmission (Kong et al. 2004). The frequency of patients with seronegative MG who have anti-MuSK antibodies appears to vary remarkably in different studies from 42% in Italy (Evoli 2006) to 25% in UK, Denmark, Netherlands and northern Germany (Vincent 2006) and less than 10% in Norway (Romi et al. 2005).

As for the seronegative patients without MuSK, it seems that they have a milder form of the disease than the MG patients with AChR antibodies (Romi et al. 2005). Thus, presence of AChR antibodies may correlate with a more severe MG.

**Titin and ryanodine receptor antibodies**

Some MG patients, especially those with a thymoma and those with late-onset MG, have antibodies against skeletal muscle antigens in addition to the AChR (Skeie et al. 2003, Takamori et al. 2004)). There are two major antigens for these antibodies (Skeie et al. 2003):

1) The ryanodine receptors (RyR) which are the Ca\(^{2+}\) release channels of the sarcoplasmatic reticulum.
2) Titin, which is a gigantic filamentous muscle protein, essential for muscle structure, function and development.

Ryanodine receptor antibodies are found in about 75% of thymoma MG patients (Skeie et al. 2001). The presence of RyR antibodies in a young MG patient strongly suggests the presence of a thymoma (Skeie et al. 2001). RyR antibodies are also associated with more severe disease and with a less favorable outcome after thymectomy (Romi et al. 2005).

Titin antibodies appear to be highly specific for MG (Chen et al. 2004). They are found in about 95% of MG patients with thymoma, but are also found in late-onset MG patients without a thymoma (Skeie et al. 2003). The presence of titin seems to correlate with a more severe MG, as do RyR antibodies. Thus, it is useful to search for both titin and RyR in a MG patient before assessing the disease prognosis, treatment and follow-up (Skeie et al. 2003, Chen et al. 2004).

Treatment of MG

MG is a heterogeneous disease and thus, not all patients can be treated the same way (Romi et al. 2005). The aims of treatment should be to induce and maintain complete clinical or pharmacological remission with minimal adverse effects (Vincent et al. 2005).

Romi et al (2005) suggested the following pathway to optimal treatment (as shown in the following flow diagram):
MG diagnosis

Pyridostigmine

Thymoma?

+ Thymectomy

- AChR ab+

  Early-onset MG

    Generalized MG

      Thymectomy

    Ocular MG

  Late-onset MG (Titin ab+)

- AChR ab–

MG progression

MG crisis

Immunosuppressive drug treatment

Plasmapheresis

iv-IgG

The depicted strategy illustrates that cholinesterase inhibitors remain the first drug to be given to MG patients. If a thymoma is detected, thymectomy is recommended, which is also the case in early-onset MG with generalized disease. In case of progression of disease, despite of pyridostigmine and often, thymectomy – immunosuppressants such as azathioprine, corticosteroids, cyclosporine and mycophenolate mofetil, used in other autoimmune diseases as well, are recommended. Plasmapheresis and intravenous IgG are reserved for severe exacerbations, before surgery and in cases of myasthenic crisis (Padua et al. 2005).

Myasthenic crisis is a respiratory failure due to MG. In patients with myasthenic crisis who previously have had well-compensated respiratory function, there are usually precipitating events – such as infections, surgery or rapid tapering of immunosuppression (Sanders et al. 1996). Respiratory failure of any cause is a medical emergency and requires prompt intubation and ventilatory support.

**MG, PREGNANCY AND DELIVERY**

**Pregnancy and autoimmune disease**

There is a two-way relationship between pregnancy and autoimmune disease: maternal changes in pregnancy can affect the disease, but the disease can also affect the outcome of pregnancy and the child (Scott et al. 1994).
The main points are that the child is grafted onto the mother, and that immunoglobulin IgG antibodies cross the placenta whereas IgA and IgM do not. Thus a disease mediated by IgG can affect the child in utero or neonatally.

As for autoimmune disease in general, the effect of pregnancy on maternal disease is variable. Until about 15 years ago, the general advice to women with autoimmune rheumatic diseases, especially systemic lupus erythematosus, systemic sclerosis and vasculitis, was to avoid pregnancy, as there was a high risk for both maternal and fetal morbidity (Gordon 2004). However, these risks can be reduced by avoiding pregnancy in active phases of the disease and by continuing appropriate medication in order to avoid disease flares (Gordon 2004).

**The effect of pregnancy on MG**

MG often affects women in the second and third decades of life, overlapping with childbearing years. Pregnancy does not worsen the long-term outcome of MG (Baticchi *et al.* 1999), but the disorder sometimes becomes manifest during pregnancy or postpartum (Vincent *et al.* 2001). The course of the disease is unpredictable during pregnancy. Patients may have disease exacerbations, myasthenic crisis but also partial or complete remission - and the disease course may vary in different pregnancies for the same MG woman (Plauche 1991, Mitchell *et al.* 1992, Tellez-Zenteno *et al.* 2004, Ferrero *et al.* 2005). However, the first trimester and the postpartum period appear to be the most critical periods for MG exacerbations (Baticchi 2002).
The effect of MG upon pregnancy

For women with MG, no increased rate has been found for spontaneous abortions or low gestational weight (Batocchi et al. 1999). One study did show an increase in maternal mortality, morbidity, pregnancy wastage, and premature labor (Plauche 1991) but this could not be confirmed in another study (Batocchi et al. 1999).

To our knowledge, this doctorate thesis includes the first population-based cohort study to compare pregnancies and deliveries in women with MG with an extensive reference group. The material was aggregated through more than 30 years. We were able to link data on each mother's consecutive births, and the linkage showed high consistency in the diagnosis of MG for consecutive births, suggesting no or a very low proportion of false positives in our data set. Thus, the specificity of the diagnosis was high, which prevented dilution of the found effects.

Treatment of MG during pregnancy

Pyridostigmine, the drug of first choice in most MG patients, belongs to class C in the US Food and Drug Administration classification system regarding teratogenicity. This means that it's teratogenic potential remains undetermined. Malformations have been seen in offspring of rats who were given the drug in very high doses (>30 mg/kg per day), but the doses given also produced maternal toxicity (Levine et al. 1991). No epidemiological studies on congenital anomalies have been reported (Briggs et al. 2002).

As for other kinds of treatment, immunosuppressive medications should be discontinued or decreased to a minimum when disease severity allows, so that potential adverse effects on the fetus can be avoided (Stafford et al. 2005). Steroids used in the
first trimester have been linked to increased occurrence in cleft palate, but have been considered safe for the rest of the pregnancy (Lamah et al. 2001, Park-Wyllie et al. 2000).

For many of the other immunosuppressants, they are either definitely contraindicated in pregnancy or in anyone considering conception - such as methotrexate (Lloyd et al. 1999) – or their teratogenic potential remains unclear, such as for azathioprine (Janssen et al. 2000). MG women taking the latter drug have been recommended to delay pregnancy until disease improvement permits discontinuation or dosage reduction (Ferrero et al. 2005).

Plasmapheresis has been carried safely out in MG pregnancies (Batocchi et al. 1999, Djelmis et al. 2002), and is very effective when short-term benefit is critical. However, as complications such as hypovolemia, anaphylaxia and transitory cardiac arrhythmias can occur, careful monitoring is very important (Ferrero et al. 2005).

Treatment with iv IgG is postulated to down-regulate or to have a non-specific suppressive effect on the immune system. In an Italian study this was carried safely out in cases of deteriorating MG during pregnancy (Batocchi et al. 1999). The most important side-effects of intravenous immunoglobulin treatment during pregnancy are probably high viscosity and volume overload (Ferrero et al. 2005).

**Delivery and MG**

Deliveries can be divided into three stages: (Gross 2002):

1) Dilatation of the cervix

2) From full cervix-dilatation to birth
3) Post-partum phase – delivery of placenta, contraction of uterus.

The AChR-antibodies does not affect the function of the uterine smooth muscle, (Stafford et al. 2005) and thus, MG should not affect the first stage or third stage. However, as the second stage involves striated muscle in the expulsive effort, weakness related to MG is highly relevant. Fatiguability in striated muscle can lead to a halt or a prolongation of the delivery process, requiring obstetrical intervention, such as forceps, vacuum or emergency cesarean section. Cholinesterase inhibitors to improve maternal muscle weakness can be given during delivery, preferably parenterally (Stafford et al. 2005).

As for analgesia during birth, epidural anesthesia is considered safer than general anesthesia - both in vaginal and operative delivery. Non-depolarising muscle relaxants may cause a prolonged or exaggerated reaction in MG patients and are better avoided. (Stafford et al. 2005).

**Neonatal MG**

**Symptoms of neonatal MG**

Between 10 to 20% of infants born to women with myasthenia gravis (MG) develop neonatal MG, as a result of IgG antibodies to AChR crossing the placenta (Baticchi 2002). The effect upon the infant is transient, due to the degradation of the maternal antibodies. Approximately 80% of children with neonatal MG develop symptoms during the first 24 h of life, but the condition can develop up to 4 days after birth (Baticchi 2002). The symptoms are usually mild or moderate, including poor sucking and
generalized hypotonia (Papazian 1992). Respiratory support and tube feeding are necessary in rare cases, and it is crucial to observe carefully the newborn of every myasthenic mother for at least 48 hours for signs of weakness of the skeletal muscles, particularly those involved in breathing and swallowing (Baticchi 2002). The condition usually resolves within a few weeks.

**Who gets neonatal MG?**

Why neonatal MG develops in only 10-20% of babies born to MG mothers and why most AChR antibody positive babies do not display signs of MG is still unclear (Batocchi 2002). Most authors do neither find any correlation between the occurrence of neonatal MG and the severity of maternal MG during pregnancy nor between the level of maternal AChR-antibodies and the occurrence and severity of neonatal MG (Batocchi *et al.* 1999, Batocchi 2002, Djelmis *et al.* 2002).

An association between the occurrence of neonatal MG and a high ratio of anti-embryonic AChR has been reported (Vernet–der Garabedian *et al.* 1994). There has also been reported higher anti AChR antibody titers in affected than in asymptomatic newborns (Vernet-der Garabedian *et al.* 1994). The presence of neonatal MG in a sibling seems to be a good predictor for the development of neonatal MG (Morel *et al.* 1988, Ahlsten *et al.* 1992).

**MG and arthrogryposis multiplex congenita (AMC)**

Arthrogryposis multiplex congenita (AMC) is defined as the occurrence of joint contractures of variable etiology that start prenatally (Bonilla-Musoles *et al.* 2002). The common factor causing AMC is the lack of fetal movements, which can result from a
large number of disorders (Gordon 1998). Maternal MG is one of them (Vincent et al. 1995, Polizzi et al. 2000).

AMC can occur either as an isolated phenomenon or as a manifestation of a large number of syndromes (Gordon 1998) AMC can also be a part of the fetal akinesia deformation sequence (FADS) phenotype (Hammond et al. 1995), which is described in the next paragraph.

In children of MG mothers, the severity of AMC is variable, and does not correlate to the severity of the mother’s MG, either at onset time or during the pregnancy (Polizzi et al. 2000). There is, however, a high recurrence rate for giving birth to another child with AMC in these MG mothers. AChR antibody epitope specificity has been suggested as a key factor, where antibodies able to bind to the fetal isoform of AChR are thought to be important (Riemersma et al. 1996), the same mechanism as suggested for neonatal MG.

**The fetal akinesia deformation sequence**

There are various causes of absent fetal movement or akinesia. In general they can be classified into five categories: *Neuropathy, myopathy, restrictive dermopathy, teratogens and intrauterine constraint* (Hammond et al 1995). Although the etiology is heterogenous, the resulting phenotype is often similar, including multiple joint contractures, limb pterygia, pulmonary hypoplasia, short umbilical cord, craniofacial changes, micrognathia, cleft palate, short neck, low-set ears, intrauterine growth retardation and abnormal amniotic fluid volume (Hammond et al. 1995). A less severe phenotype can present only with AMC (Witters et al. 2002). Despite of the heterogeneous etiology, Hall in 1986 (Hall 1986) proposed that newborns with this
phenotype should be referred to as having the fetal akinesia deformation sequence (FADS).

As mentioned above, intrauterine constraint can be one of the causes of FADS (Hammond et al. 1995). One of the causes of intrauterine constraint can be oligohydramnion. In 1965, Edith Potter first reported a fetal phenotype with features including limb abnormalities, large-appearing hands and pulmonary hypoplasia together with oligohydramnion (Potter 1965). It was named Potter’s syndrome, and confirmed that fetal akinesia may occur as a result of deformation from external factors. Potter described oligohydramnion related to fetal renal agenesis. However, it became clear that any condition in which the fetus is exposed to decreased amniotic fluid over a longer time period – which also could be due to undetected prelabour rupture of amniotic membranes (PROM) – would cause identical findings. This observation is now referred to as Potter’s sequence or the oligohydramnion sequence (Hammond et al. 1995).

To distinguish other causes of FADS from the oligohydramnion sequence is difficult (Scott et al. 1995). Even though there seems to be some phenotypical features which are more characteristic for the oligohydramnion sequence (Hammond et al. 1995), it is recommended that detailed evaluation and investigation should be performed in cases of FADS (Christianson et al. 1999). Brueton et al (2000) described six siblings with the FADS phenotype, whose mother was discovered to have asymptomatic MG with AChR antibodies.
CHARCOT-MARIE-TOOTH DISEASE (CMT)

Epidemiology of CMT

CMT constitutes the most commonly inherited form of peripheral neuropathies, the prevalence between 10 and 20/100 000 (Morocutti et al. 2002, Kurihara et al. 2002). CMT belongs to the group of Hereditary Motor and Sensory Neuropathies (HMSN). In addition to CMT 1 and 2 (described in the paragraph below) are the most common forms of HMSN, but the disease group also includes more rare cases of severe demyelinating neuropathies of recessive inheritance with onset in early childhood, referred to as CMT type 3 or Dejerine-Sottas disease (Bosch et al. 1996)

In CMT, gene mutations are postulated to cause disruption of axonal transport, which results in abnormal axonal function (Shy et al. 2002). The name of the disease relates to Charcot and Marie (France) and Tooth (England) who almost at the same time in the 19th century described the clinical features of this inherited motor and sensory neuropathy.

Classification of CMT

The classical subdivision of CMT into CMT1 (demyelinating type) and CMT2 (axonal type) based on electrophysiological and neuropathological criteria, was a cornerstone in the classification of CMT, and is still valid (Pareyson 1999, Pareyson 2004, Carter et al. 2004). Further subdivision, which is based on molecular genetics, is important for correct genetic counseling and prognosis.

CMT1 is the demyelinating form that shows slowing of motor nerve conduction velocities and hypertrophy of peripheral nerves with onion bulb formation and segmental
demyelination (Dyck et al. 1968, Carter 2004). CMT2 is described as the axonal or neuronal form, with normal or only slightly reduced conduction velocities, normal sized nerves and no evidence of segmental demyelination (Dyck et al. 1968, Carter et al. 2004).

It is however, worth noticing that even if demyelination is described as the pathological and physiological hallmark of CMT1, it is the final stage of axonal degeneration/loss that gives the clinical picture with weakness and sensory loss (Shy et al. 2002). Thus, in both groups axonal damage is the end stage, explaining why the clinical phenotype is so similar, regardless of form of CMT (Garcia 1999).

**Clinical features of CMT**

Although the clinical phenotypes of the different types are similar, there is a great variation in age of onset, severity of symptoms and rate of progression. Usually, the patient manifests the disease with distal leg weakness and atrophy. Difficulties in walking, especially on their heels, can be an early sign. Many patients develop the pes cavus deformity as the disease progresses. In most cases the involvement of the lower limbs is followed by hand involvement, but usually not as prominent as in the lower extremities (Garcia 1999).

There have been numerous case reports of respiratory failure in patients with CMT, due to neuropathy of the phrenic and pharyngeal nerves (Gilchrist et al. 1989, Hardie et al. 1990). Vagus nerve dysfunction with vocal fold paresis has also been reported (Sulica et al. 2001). Other less common problems include autonomic failure with dysfunctional anal sphincter and urinary bladder (Stojkovic et al. 2003). Some of these symptoms seem to be related to a specific subset of genes and mutations (Carter et al. 2004). However, it
is also the other way around; that a uniform genetic defect can be related to various phenotypes (Thomas et al. 1997).

**Diagnosis of CMT**

The CMT diagnosis is established through 1) *Clinical examination*, 2) *Electrophysiological examination* and 3) *Genetic testing*.

1) **Clinical examination**

Clinical symptoms usually begin during the first or second decade of life. In CMT2, however, they may be delayed until middle age (Bosch et al. 1996). Inspection reveals pes cavus and hammer toes in nearly 75% of adult patients; mild kyphosis in about 10%. In patients with CMT1, 25% have enlarged hypertrophic peripheral nerves (Bosch et al. 1996). Symmetrical weakness and wasting is found in intrinsic foot, peroneal, and anterior tibial muscles. In CMT1 absent ankle jerks are universal and frequently associated with absent or reduced knee and upper limb reflexes. In CMT2, general areflexia and upper limb involvement occur less frequently (Bosch et al. 1996).

2) **Electrophysiological examination**

In patients with suspected CMT, it is very important to assess the presence, degree and pattern of nerve conduction slowing. In the demyelinating CMT1, the nerve conduction velocities are markedly decreased in a diffuse and homogenous way. By definition, the motor conduction velocity (MCV) is below 38m/s (Pareyson 2004). On the contrary, in the axonal CMT2, MCV is preserved or only mildly decreased (>38m/s) (Kühlenbäumer et al. 2002).
Both in CMT1 and CMT2, electromyographic examination of distal muscles, for instance the anterior tibial muscle, often shows signs of chronic denervation and sometimes, pathological spontaneous discharges (Kühlenbäumer et al. 2002).

3) Genetic testing

Apart from the electrophysiological differentiation between the two forms of CMT, further subdivision is important for correct genetic counseling and prognosis. This is not the subject of this study, but there are two review articles which give a good summary (Shy et al. 2002, Carter et al. 2004).

Treatment of CMT

Although no cures are available for CMT, there are many important treatments available, which can improve the patients’ quality of life and help them maintaining independence (Grandis et al. 2005).

The most common encountered problems for patients are: 1) Weakness and loss of sensation, 2) Pain, 3) Loss of mobility and 4) Impaired breathing, hearing and swallowing (Carter et al. 2004). These symptoms can be addressed as follows (Carter et al. 2004, Grandis et al 2005:).

1) Weakness and loss of sensation

• Can be compensated (partly) through physical therapy with emphasis on the muscles that still function. The general mobility of patients should be improved, joint deformities should be prevented and special training should be developed in order to improve balance and prevent falls.
• Exercise is beneficial, but low impact aerobic exercise should be preferred.
2) **Pain**

- Muscle cramps and pain can be a part of CMT. Depending on whether the pain is neuropathic or arthritic or muscle related, it should be treated accordingly.

3) **Loss of mobility**

- A discrete foot-drop can be compensated by shoes.
- As weakness in ankle dorsiflexion progresses, most CMT patients will require short leg braces or ankle foot orthoses.
- In more severe CMT, equipment such as grab bars, hospital bed etc. should be considered in order to improve quality of life.
- Wheelchair must be considered if gait is very impaired.

4) **Impaired breathing, hearing and swallowing**

- If respiratory failure develops, intermittent positive pressure ventilation by mouth avoids the need for tracheostomy.
- The preferred modality of assisted ventilation in CMT should be bimodal positive airway pressure (Benditt 1998).
- Problems in hearing and swallowing should be managed and evaluated by an otolaryngologist.
CMT, PREGNANCY AND DELIVERY

Despite the frequency of CMT in the population, little is known about pregnancy and delivery in affected women. Mostly there have been case-reports (Reah et al. 1998, Byrne et al. 1992). One study of 21 patients with CMT 1 showed no evidence of a deleterious effect on the course and outcome of pregnancy and labor (Rudnik-Schöneborn et al. 1993). However, the study suggested that whereas pregnancy has no influence on adult-onset CMT, the risk of pregnancy related exacerbation is 50% in patients with early-onset disease.

To some extent, CMT has been considered as a fairly benign disease by neurologists (Shy et al. 2002) and thus, no special emphasis has been put on counseling regarding childbearing. However, in a study of disability and quality of life in CMT type 1 (Pfeiffer et al. 2001), CMT patients were asked whether they would advise against childbearing, if the prospective child would have CMT and the same extent of disability as themselves. The results of this study showed that the extent of disability was determinant for the attitude towards childbearing. Out of 50 patients, 18 patients voted against childbearing. Disability became relevant for the attitude towards childbearing as soon as everyday activities became markedly affected (Rankin score 2 b) (Pfeiffer et al. 2001). These results imply that the effect of CMT on the issue whether to have a child or not, is greater than acknowledged by most neurologists.

The emotional distress of having CMT has been found similar to that of patients with stroke (Pfeiffer et al. 2001). Prenatal diagnostics of CMT is available (Vos et al. 1998), and thus, the fact that many prospective CMT parents worry how CMT may affect
their child must be taken into consideration and addressed by neurologists. Issues such as pregnancy, delivery and taking care of children should be discussed during consultations. In Paper IV, we have examined risks and complications related to pregnancies and deliveries in women with CMT.

TRENDS IN OBSTETRIC CARE – NORWAY AND WORLD WIDE

Since the foundation of Medical Birth Registry of Norway (MBRN) in 1967, new obstetric techniques and routines have altered the way in which pregnancies and labors are managed. More premature children are rescued than before, both due to enhanced prenatal diagnostic tools such as ultrasound and advancements in intensive care. The marked increase in the rate of cesarean sections - both in Norway and world wide - represents a major change in obstetrics in the years 1967-2005 (Curtin et al. 1999).

The increase in cesarean sections

In Norway, the rate of cesarean section was increased from 2% in 1967 to 13.6% of all births in 1998 (Medisinsk fødselsregister. http://www.uib.no/mfr). In 2002, the corresponding number was 15.8% (Annual Report. Medical Birth Registry of Norway. Bergen 2004). Worldwide, the increase in number of cesarean sections is most pronounced in industrialized countries, as in the US where the rate in 2003 was 27.6% (Hamilton et al. 2004). However, there has also been a substantial increase in developed countries such as in Latin America, where an ecological study found the rates in 1999 to
be between 16.8% in Colombia and 40% in Chile (Belizan et al. 1999). Also countries in Asia have high rates; in 2001 27.4% of all births in Hong Kong were cesarean sections (Leung et al. 2001).

There are many explanations for this increase, such as advanced maternal age, the obstetricians’ wish to minimize risks - and a higher birth weight in children, related to the increasing obesity in many populations. The increased relative safety of the procedure and improvement in post-operative care should also be mentioned (Van Roosmalen et al. 1995). In Latin-America, the relation between increased standard of living and cesarean section as well as increased availability of the procedure, has been emphasized (Belizan et al. 1999). Further, there was a change of practice in many countries when a multi-centre study concluded that elective sections were better than planned vaginal births for the term fetus in breech presentation (Hannah et al. 2000). Especially for emergency sections, the technological advances in fetal surveillance during delivery play an important part, as fetal distress is much easier identified.

A Norwegian study from 1999 showed that the two most frequent indications for emergency sections were fetal stress and failure to progress, whereas the most frequent indications for elective cesarean deliveries were previous cesarean section and maternal request (Kolås et al. 2003). There has been a change in attitude among women, who now often see it as their right to choose delivery mode (Showalter et al. 1999).

Centralizing obstetric care

Another trend in Norwegian obstetric care in the period 1967-2004 has been to centralize births to bigger units in order to secure sufficient quality of service. In 1970
there were 150 obstetrical institutions in Norway - the corresponding number in 2001 was 57 (Nilsen et al. 2001). Of the 57 obstetrical institutions in 2001, 24 of them had less than 500 births/ year (Nilsen et al. 2001). This means that there are still many small obstetrical units in Norway, which reflects the topographic and geographical conditions.

A population based study in 1999 showed that the neonatal morbidity was doubled in obstetric units with 100 births a year or less compared to obstetric units with 2000-3000 births/year (Moster et al. 1999). Thus, it remains a challenge to secure the same level of quality in obstetrical practice throughout a sparsely populated country.

**EPIDEMIOLOGICAL REGISTERS - ACCESS, POSSIBILITIES AND LIMITATIONS**

In 2004, there were seven central health registers in Norway. The first one, the Cause of Death Registry, was established as early as in 1951, the second, the Cancer Registry in 1953. The last one, the Prescription-based Medication Registry, came in 2004. Medical Birth Registry of Norway (MBRN) was established in 1967. The fact that some of the registers were established more than 50 years ago, gives a great potential for research. Thus, it is possible to do longitudinal follow-ups of individual patients and to link health-information across generations.

Linking data from the health registries to other registries containing data on social status, level of education and place of birth opens up great possibilities for research. This can be exemplified by a recent study from Norway, where delivery positions in male
newborns, registered in MBRN, were linked to their later scores on an intelligence test at conscription registered in the National Conscript Service (Eide et al. 2005).

However, the individual’s right to privacy must also be protected. In order to obtain access to data in the health registries, one therefore has to go through an extensive application process. This includes acceptance by the regional ethical committee and written consent from patients, in case of identifiable information. It is in accordance with the major principle in biomedical research that the individual’s rights exceed the interests of science and society, as stated in the Oviedo-convention – and also with the Norwegian political administration.

When The Personal Health Data Filing System Act (2002) was discussed in the Norwegian Parliament, it was emphasised that one should be reluctant to establish registries containing all aspects of the individual’s life, and that data should preferably be anonymised or pseudonymised (Myklebust 2004). The Data Inspectorate of Norway, an independent administrative body under the Norwegian Ministry of Labour and Government Administration, has accordingly been very restrictive in giving concessions to the foundation of new health registries. Thus, even though the Norwegian health registers can be utilised for a wide range of purposes, and this utilisation could be expanded through linkage with registries and bio banks, barriers making such research difficult still exist, due to legislation, political as well as administrative routines. This is also the case in the other Scandinavian countries, which also have a long tradition for health registries and related research (Mortensen 2004).
However, every scientist should bear in mind that the use of sensitive information in research is justifiable only when the studies serve widely accepted aims, and are designed and carried out according to the highest standards of quality (Gissler et al. 2004).
AIMS OF STUDY

I. To study the effect of maternal MG upon pregnancy, delivery and the newborn.

II. To study the effect of asymptomatic MG either before diagnosis or in full clinical remission, upon pregnancy, delivery and birth.

III. To identify particular risk factors in women with MG who give birth by studying their obstetrical records, and suggesting ways of optimizing care.

IV. To study the effect of maternal Charcot-Marie-Tooth upon pregnancy, delivery and the newborn
MATERIAL AND METHODS

The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) was established in 1967, and is based on the compulsory notification of all births after 16 weeks of gestation (From 1999: All births after 12 weeks of gestation). The notification form is sent within 9 days after birth or discharge from the institution. The registry contains data on the mother’s demographic variables, the pregnancy, the delivery and the newborn. The registry is placed under the Norwegian Institute of Public Health.

Norway, with its 4.64 million inhabitants (Statistics Norway, 24th of May 2006), is in many ways the ideal country for conducting epidemiological research in medicine. The population is fairly homogenous, and the country has a well-functioning healthcare and social welfare system. Thus, the socio-economic and geographical factors exert less influence on mortality and morbidity than in many other countries.

Every inhabitant of Norway has a personal and unique identification number. It is allocated shortly after birth by Statistics Norway. By using the mother’s identification number which is recorded on the birth registry form, a record link can be established with the National Population Registry (run by Statistics Norway) in order to obtain the infant’s identification number. This procedure ensures complete ascertainment of births.

The birth notification form

The information in the birth notification form is based on three elements:

1) A standard form used during pregnancy by the patient’s physician
2) Oral information given by the woman when admitted to hospital

3) Information from physician and midwife about the actual delivery and the newborn.

Thus, the notification form contains information on the mother’s health before and during pregnancy as well as information about the actual birth and the newborn. The form is co-signed by the attending physician. An unchanged birth notification form was in use from 1967 through 1998 (Appendix 1). A revised and more detailed form has been in use since December 1, 1998 (Appendix 2).

**Obstetrical records**

Mothers with MG were identified through MBRN and asked for consent to collect the full obstetrical records from the hospitals where they had given birth. In case of consent, the hospitals where the women had given birth were asked for copies of the obstetrical records. The content of the records varied, but a partogram was present in all cases. The partogram is the document used by the midwives during labor, describing the different stages, including any difficulties, use of medicine, and interventions. The child’s weight, sex and Apgar score are also noted on the partogram.

**Target group and reference group**

In both Paper I and Paper II, the data material comprised all births registered in MBRN between January 1, 1967 and December 31, 2000. Patients with MG were identified as women in whom the MG diagnosis was noted in the birth notification form. In Paper I, the target group was all births where the mothers had been notified with MG (n= 127 women.) In Paper II, the target group was defined as all births by mothers who in a
previous or later birth had been notified with MG (n= 49 women), but who were not notified with MG at the actual birth. This was possible due to the unique 11-digit personal identification of all inhabitants in Norway, which enabled us to trace each mother’s births consecutively.

The reference group in Paper I was all other births in the same period of time (n= 1,988,865) without a MG diagnosis recorded. In Paper II, all births where the mothers in a previous or later birth had been notified with MG, were in addition excluded from the reference group in Paper I (n= 1,988,816).

In Paper III, 90 women recorded with the diagnosis MG in one or more births between 1967 –2004 were identified through the MBRN. On behalf of the project, MBRN contacted each woman by mail and asked for permission for Dr. Jana Midelfart Hoff to examine their full obstetrical records including records for the newborn and birth protocols. 80 (89%) women replied - 79 women confirmed their MG diagnosis and enclosed a written consent. One woman claimed that she had never had MG. Among the ten who did not reply, one was confirmed dead, and in four cases we were not able to track their current address.

In cases of consent, the hospital(s) where the woman had given birth was identified and the head of the obstetrical department was asked for the following information: The full obstetrical records with special emphasis on any consultations by neurologists, paediatricians and anaesthesiologists, the record for the newborn and the birth protocols. Information was obtained for 135 births by 73 women. In the cases where we did not receive the information, it was either because the record, despite repeated searches, was
not in the archives or because the hospital had outsourced its oldest record material. The protocol of the study was approved by the regional ethical committee.

In Paper IV, the data material from MBRN was extended to include also the years 2001 and 2002. The target group this time was all births by a mother who in at least one birth had the diagnosis CMT. We identified 108 births by 49 CMT mothers. The reference group consisted of all other births (n= 2 102 971).

The Papers I, II and IV were among the first projects to work with data from the new registration form for births in Norway (after 1998). The analytical approach developed has been used for other projects also (Dahl et al. 2005).

**Variables**

The variables studied in Paper I, II and IV were based on the variables which exist in the MBRN. They are defined after consensus in a group consisting of obstetricians as well as neonatologist and epidemiologists. The following variables were studied in Paper I, II and IV:

Descriptive variables:

- Year of birth
- Type of obstetric institution
- Age of mother (completed years)
- Sex of child
- Birth order (parity)
- Birth weight (g)
- Gestational age in completed weeks
• Thymectomy
• MG or CMT

• Outcome variables included:
  • Induction of birth (perforation of amniotic membranes and/or infusion with oxytocin and prostaglandin).
  • Interventions (any intervention, perforation of amniotic membranes, cesarean section, use of vacuum extractor or forceps, manual removal of placenta).
  • Delivery complications (any complications, premature rupture of amniotic membranes (>12 h before onset of labor), functional disorder of birth, injuries in the birth canal, bleeding post partum, obstruction of birth process, complications regarding the umbilical cord). Functional disorder of birth is a collective term that includes the following: Prolonged delivery (>24 h), cervical dystocia, uterine atony and uterine dysfunction.
  • Perinatal mortality (defined as all fetal deaths after 16th week of pregnancy until 1st week post partum).
  • Congenital conditions

In Paper III, data on the course of pregnancy, labor and puerperium as well as the neonatal period were retrieved from the obstetrical records and analysed retrospectively.
We were then able to address the issue of medication at the time of conception and during pregnancy. In the other papers, based on the MBRN notification forms, this was not possible. Before the new notification form was introduced in 1999, medication was only sporadically recorded. However, in the cases in paper I where a severe birth defect was recorded in the child of a MG mother, we were able to retrieve information on medication during pregnancy from the hospital records.

**Hypotheses**

Our aim was to use unique data to evaluate a broad set of associations, which means that our study should be viewed as hypothesis *generating* rather than hypothesis *testing*. This had consequences both for choice of methods and for interpretation of the results. We have discussed this in both papers and thesis (see the *Methodological Considerations* section) and have remarked that findings from such studies should be verified in later studies.

**Statistical testing**

In Paper I, II and IV, cross tables with Pearson $x^2$ test were used for categorical variables to compare the target and the reference groups. Two-sided p-values less than 0.05 were used to indicate statistical significance. Arithmetic means were calculated for each group regarding gestational age, gestational weight, mother’s age and parity, and t-tests were used to compare means. In Paper II, corresponding 95% confidence intervals around the rate-ratio and the two-sided p-values were calculated. In these analyses, the dependent variable was dichotomized (yes/no). In Paper III, cross tables with Pearson $x^2$
test were used to compare different sub groups of the patients with each other. In Paper III, Fisher’s test was used when there were cells with less than 5 observations.

All statistical analyses were performed in SPSS 11.0 (SPSS, Chicago IL).

Stratification, effect modification and confounding

In Paper I, II and IV mother’s age, period of birth, type of obstetrical institution and birth order were considered as potential effect modifiers or confounders. Effect modification was evaluated by stratification. Confounding was evaluated by stratification and secondly by unconditional logistic regression analyses with all variables represented as categorical variables. We also stratified for type of obstetrical institution (university hospital, other) to see if the results varied according to type. In Paper I and II, none of the potential confounders turned out to change the results, and therefore only the crude measures were presented. In Paper IV, the inclusion of period of birth changed the estimates and therefore the results presented in Paper IV were adjusted for period of birth.

In addition to evaluate period of birth as an effect modifier or confounder, we also wanted to look at secular trends in obstetric care and management of MG patients. In Paper I we therefore present results stratified into the following periods of time: 1967-1980, 1981-1990 and 1991-2000.
SUMMARY OF RESULTS AND GENERAL DISCUSSION

In this study, we have examined the pregnancies, the deliveries and conditions regarding the newborn in Norwegian women with MG and CMT. This has been done on the basis of the notification form in the MBRN in three papers (Paper I, II and IV). Although it is the delivery which initiates the completion of the form, the form does not only contain data on the delivery, but also on conditions regarding the pregnancy and on delivery outcome (the child). Thus, it was possible for us to examine all these three aspects.

Increased rate of complications during delivery in MG group

We found that women with MG had an increased risk for complications at delivery compared to women without MG - both when they had the MG diagnosis (40.9% vs. 32.9%, \( p = 0.05 \)) and before receiving the diagnosis or in full clinical remission (protracted labor, 14.3% vs. 6.5%, \( p = 0.03 \)). Particularly, the risk for premature rupture of amniotic membranes (PROM) was three times higher in the MG group compared to the reference group (5.5% vs. 1.7%, \( p = 0.001 \)).

PROM is a complication that facilitates ascending infections (Walkinshaw 1995, Steer \textit{et al.} 1999). Amnionitis comprises a great risk both for mother and child, and is also an important cause of premature birth. We did, however, not find the rate of premature birth increased in our material.

When PROM occurs, the patient is admitted to hospital, confined to bed, and, if necessary, given antibiotics. An increased occurrence of PROM is a feature of other autoimmune diseases as well, such as SLE and inflammatory rheumatic disease (Johnson
et al. 1995, Skomsvoll et al. 1999). The etiology remains unclear, it might be an effect of medication, preferably steroids, or be related to the disease process. Pyridostigmine, drug-of-choice in patients with early-onset myasthenia, has not been associated with a higher occurrence of PROM (Lowe 2001).

Medication was not recorded on MBRN’s notification form until after 1998. However, in paper III we found that an overwhelming majority of the MG women giving birth 1967-2004, who were on medication, used only pyridostigmine at the time of conception and during pregnancy according to the information in the obstetric journal. Only one woman used steroids, and she did not have PROM. No woman used other immunosuppressants. The increased occurrence of PROM in women with MG is therefore not likely to have been caused by steroids.

**Increased rate of intervention during delivery in MG women**

There was a higher rate of interventions during delivery in the MG group than in the reference group. This could either reflect a higher rate of complications making intervention necessary, or alternatively be due to a fear for complications and thus be done because of the MG diagnosis. The rate of cesarean sections in the MG population was higher than in the reference group (17.3 % vs. 8.6%, p= 0.001). When the material was subgrouped into three periods of time (1967-1980, 1981-1991, 1991-2000) in order to adjust for time trends in obstetric care, the higher rate of cesarean section in the MG group was still evident.
Fig. 1  Intervention during delivery 1967-2000 - MG versus reference group (%).

(Tot.interv= Total intervention, C.section= Cesarean section: Forc/vac= Forceps and vacuum.)

The question is whether the higher rate of intervention – cesarean section in particular – represents the fear of the doctors or midwives for complications during vaginal delivery (with possible consequences such as litigation and claims) or the real need of the MG patients. Elective cesarean section was only registered in MBRN after 1988, and so it was not possible to compare the different time periods for this variable. However, in the last period (1991-2000) when the elective sections were recorded, the rate of elective sections was significantly higher in the MG group than in the reference group.

In the time period 1967-2000, as the rate of cesarean sections in MG women rose, there was simultaneously a decrease in use of the emergency procedures forceps and vacuum in this group. This combination of events indicates that the need for emergency
procedures during vaginal delivery was diminished, when more MG women went through elective cesarean section.

There has been a steady rise in the rate of cesarean sections performed in Norway, as well as in the rest of the Western world during the last decades. In 1973, cesarean section was performed in only 2.5% of all Norwegian deliveries. In 2002, the corresponding rate was 15.1%. Even so, the rate is substantially lower in Norway than in most other Western countries (Evans 1995, Mayor 2002) and the United States, where the rate reached 27.6% of all deliveries in 2003 (Hamilton et al. 2004). This difference is probably explained by a restrictive policy among Norway's obstetricians regarding cesarean section.

A relatively low total rate of cesarean section implies that specific risk groups are more likely to have a higher rate than the general population. The high rate of elective cesarean sections in the MG group may have prevented some of the complications related to vaginal delivery. The proportion of elective section was higher in the cases where the mother had been seen by a neurologist during pregnancy (Paper III). Elective caesarean sections are more favorable in MG patients than emergency procedures, particularly because general anesthesia is not well tolerated in MG patients (Eisenkraft et al. 1990). One patient in our study got her MG unmasked (Paper III) when she received general anesthesia during caesarean section, and similar cases have been described previously (Dunsire et al. 2001).

MG women should not automatically be offered elective cesarean section (Ciafaloni et al. 2004). However, in cases of deterioration of disease during pregnancy or extensive fatigue, elective section should be considered. Emergency cesarean sections are
the worst option, and should be sought avoided. By for instance choosing epidural as pain relief during vaginal delivery, the delivery could be comfortably converted to cesarean section if complications should arise.

MG mothers should therefore give birth in obstetric units with proximity to neurological departments and neonatal intensive units. One should be ready to intervene quickly if the delivery is protracted, and the possibility of neonatal MG must be anticipated.

**MG medication in pregnancy**

In Paper III, we found that MG medication had been used before conception in 68 (50 \%) of the 135 pregnancies, and was continued throughout pregnancy in 60 cases (44 \%). Of the MG women using medication, all but one used pyridostigmine only both at the time of conception and during pregnancy (Paper III).

Pyridostigmine belongs to class C in the Food and Drug Administration classification system for teratogenicity, and it’s teratogenic risk is regarded as undetermined. No epidemiological studies on congenital anomalies in humans have been performed (Briggs *et al.* 2002). A Swedish database ([www.janusinfo.se](http://www.janusinfo.se)) on pregnancy and drug safety, reports that 28 births where the mother had used pyridostigmine in early pregnancy, were registered in the Medical Birth Registry of Sweden. Of these 28 children, two were born with birth-defects; one was born with a ventricle-septum-defect, the other with pes calcaneo-valgus (Källen *et al.* 2005). The authors conclude that, based on existing evidence, there is no need to avoid the use of pyridostigmine in pregnancy.
There was no increased rate of severe birth defects in the MG group compared to the reference group (Paper I and Paper II). Six children of MG mothers were diagnosed with severe birth defects; one had Down’s syndrome, one a serious unilateral foot deformity, three had AMC (arthrogryposis multiplex congenita) and one had Potter’s syndrome.

We were able to retrieve information on medication from the hospitals for five cases of the six cases with severe birth defects all mothers had used pyridostigmine during pregnancy. However, based on existing evidence and recommendations (Källen et al. 2005, Ferrero et al. 2005) it is unlikely that these mothers’ use of pyridostigmine caused the birth defects in the offspring. It seems more plausible that the occurrence of AMC and Potter’s syndrome was related to the underlying maternal disease, and not to the medication. This is supported by the fact that two of the children with AMC and the child with Potter’s syndrome had siblings who developed neonatal MG.

**Morbidity and mortality among children of MG mothers**

Six children (including one twinning pair) born by MG mothers had severe anomalies, and four of them died. In addition, another twinning pair died (Paper I and Paper II). Of the six children who died, three children (including one twinning pair) had skeletal anomalies, consistent with the diagnosis of AMC. One child who died was diagnosed with Potter’s syndrome, which is one of the causes of the *fetal akinesia deformation sequence* (FADS). The diagnosis of Potter’s syndrome was made in a postmortem examination, the form with the results from the autopsy was attached to the birth notification form in the MBRN.
The mother of the child with Potters syndrome had previously given birth to a child with neonatal MG, but was in this delivery in complete MG remission. The mother of the twinning pair with AMC, gave later birth to a child with neonatal MG. No skeletal anomalies were found in the other pair of twins that died. Also in this case did the mother’s next child have neonatal MG. Twins do in general have a higher mortality than singletons (Misra et al. 2002), but in view of this mother’s next child developing neonatal MG, one may suspect that an antibody-mediated effect contributed to the deaths also of these twins.

MG is a chronic disease. Even though successful therapy and/or the natural cause of the disease can result in no or very little symptoms, the disease persists as an immunological phenomenon, with AChR antibodies, disease specific T and B-cells and also an increased turn-over of AChR. In accordance with others, we found that the clinical condition of the pregnant MG patient was not a good predictor for whether her child developed neonatal MG or AMC (Baticchi et al. 1999, Brueton et al. 2000, Djelmis et al. 2002).

There has been reported a high recurrence rate of AMC in siblings (Vincent 2000) and a connection between neonatal MG and AMC (Riemersma et al. 1996). Our study indicates that siblings of an affected child – either with neonatal MG or AMC – have an increased risk to develop either neonatal MG or AMC. This is independent of the mother’s clinical state. It is therefore important to discuss previous delivery outcomes with MG patients planning pregnancy.
Identifying risks, optimizing care in MG pregnancies

The incidence of neonatal MG has been found to be between 10 and 21% of all babies born to MG mothers (Plauche 1991, Papazian 1992). In our study, neonatal MG was noted only in 4% of the newborn of MG mothers in the MBRN (Paper I). However, when examining the obstetrical records of MG women, we found that neonatal MG could be suspected in 19% of the cases, based on symptoms such as poor sucking and hypotonia (Paper III). That would be at the same level as described in other studies (Papazian). This indicates that the condition is not fully acknowledged by health personnel at the time of delivery, and that neonatal MG is underdiagnosed in the MBRN.

Newborns with neonatal MG probably had a higher risk for experiencing fetal distress during delivery, as indicated by a higher frequency of stained amniotic fluid, 31% vs. 15%, p= 0.05 (Paper IV). Although Apgar score is a better tool for assessing fetal distress, stained amniotic fluid is still considered as a valid sign of fetal distress (Badawi et al. 1998, 2000, Locatelli et al. 2005) and thus notified in the MBRN.

The reason for the increased risk of fetal distress in children by MG mothers, may be the hypotonia in these children, induced by the AChR-antibodies from the mother, which can prolong the delivery process. Stained amniotic fluid reflects a response of the fetal gastrointestinal tract to acute or chronic hypoxia. Locatelli et al (2005) showed that acidosis in the newborn was more frequent if the amniotic fluid was stained. A feared complication with stained amniotic fluid is the aspiration of meconium in the airways, which may lead to respiratory distress and pneumonia.

The presence of neonatal MG in a previous sibling has been pointed out as a good predictor (Morel et al. 1988, Ahlsten et al. 1992) for the risk of the next child. In our
study, we found a correlation between the occurrence of AMC/Potter’s syndrome and neonatal MG in siblings.

In Paper III, we found that thymectomy in the mother had a protective effect against neonatal MG. The occurrence of neonatal MG was lower in the pregnancies where the mother had been thymectomized than in the pregnancies where she had not. This protective effect has been reported also by others (Djelmis et al. 2002). A probable explanation is that thymectomy causes a lowering of the level of antibodies, both the adult and fetal isoform. Consequently, the transplacental transport of AChR-antibodies is reduced. Thymectomy should be considered in all women with generalized MG with a child wish, especially if they have already given birth to a child with neonatal MG. A further subject for research should be to find out if this applies to AMC as well.

The pregnant woman with a chronic disease imposes a challenge to medicine. The aim should be a careful balance between treating the mother optimally and preventing harm to the child. This can best be achieved through close cooperation between physicians from different branches of medicine. As other authors have pointed out, this should be the case in MG patients as well (Ciafaloni et al. 2004, Ferrero et al. 2005).

In the present study, only in about one-third of the pregnancies did the MG women see a neurologist (Paper III). These cases were characterised by a higher occurrence of previous thymectomy, a higher use of MG medication both prior to and during pregnancy and a higher frequency of elective section. The newborns were more frequently observed at neonate units after birth. No differences were found for complications during pregnancy and birth or for neonatal MG between those who were seen by a neurologist and those who were not. The frequent use of MG medication in this group, both prior to
and during pregnancy, indicates that these patients were more severely affected by their
disease. This finding is supported by the high rate of thymectomy among these patients.
Thus, it seems that only the most affected MG patients were referred to a neurologist
during pregnancy.

To give birth to a healthy child is a fantastic experience, and to have children enriches
your life. Women with MG should not be discouraged from having children, but the
neurologist should seek active cooperation with obstetricians and pediatricians (Ferrero et
al. 2005). Most, if not all, women with MG would probably benefit from being checked
regularly by a neurologist during pregnancy. We have shown that complications during
delivery and neonatal MG can occur even in MG mothers who are asymptomatic. By
raising the awareness of the disease and its effect upon pregnancy and delivery, possible
complications can be acknowledged and prepared for.

The effect of maternal CMT upon pregnancy, delivery and the
newborn

CMT has up till now been regarded as a disease mainly affecting distal extremities with
no significant effect upon pregnancy, delivery and the newborn (Shy et al. 2002). Our
study (Paper IV), in which deliveries by CMT women were compared to those of an
extensive reference group, questions this view. We found an increased frequency both for
maternal (bleeding) and fetal (presentation anomalies) complications. Also the finding of
more frequent use of emergency procedures such as forceps and vacuum (29.6% versus
15.3%, p = 0.002), and a higher rate of emergency sections than in the control group,
indicates that there is a potential risk, which has not been anticipated or fully
acknowledged. In particular, it is interesting that the use of forceps in the CMT group remained relatively high throughout the whole time period (Fig.2), which is in contrast to the general trend in obstetric care at this time (Chamberlain et al. 1999).

Figure 2. The use of forceps - CMT group versus reference group (%)  

In contrast to MG, CMT is a disease that is regularly is inherited by the fetus. In most cases, CMT has a dominant inheritance, which implies that many of the children in our study could be carriers of the gene. This may explain the increased rate of abnormal presentation, which was more likely to occur in the CMT group (9.3% versus 4.5%, p=0.04). A preexisting motor disorder in the fetus increases the likelihood of abnormal presentation (Rayl et al. 1996). Other known risk factors for presentation anomalies such as low birth weight, primiparity and preterm delivery did not occur more frequently in the CMT group.

Although CMT usually is recognized at a later age, muscle weakness, wasting and hypotonia have been described during the first year of life (Wilmshurst et al. 2003). It is therefore possible that patients can display functional motor changes already in utero. As
for future research, it would be tempting to try to track down the children who presented at birth in an abnormal position, to find out if they later developed the disease and how severely they were affected.

In the general population, the most common cause for post partum bleeding is uterine atony (ACOG technical bulletin 1990). The increased rate of bleeding in the CMT group versus the reference group (12.0% versus 5.8%, p=0.02) indicates a CMT mediated effect upon uterine function. This is in accordance with other studies, which show that CMT is not solely a disease of the peripheral sensorimotor nerves, but also can affect the autonomic nervous system (anal sphincter, urinary bladder) (Thomas et al. 1997, Sulica et al. 2001, Stojkovic et al. 2003).

Pregnancy is associated with a physiologic adrenergic nerve degeneration in the uterus, caused by sex steroids (Sporrong et al. 1981). This gestational nerve loss seems to be more widespread when the peripheral nervous system is already damaged (Pollock et al. 1982). Progesterone, one of the most prominent hormones in pregnancy, was instrumental for deterioration of CMT symptoms in an animal model (Sereda et al. 2003). Thus, a CMT-related effect upon uterus might be mediated by the high levels of this hormone.

Women affected by CMT do not have a more severe course of disease than men (Grandis et al. 2005). However, exacerbation of disease during pregnancy has been reported, especially in those with early manifesting CMT, from childhood or youth (Rudnik-Schönenborn et al. 1993). The deterioration of the CMT neuropathy during pregnancy have previously been considered to be transient (Pollock et al. 1982), but a
study from 1993 reported a persisting deterioration in 65% of the women (Rudnik-Schöneborn et al. 1993).

Most people consider having children as adding quality to their lives. CMT patients have been found to score significantly lower when quality of life is measured than the “normal” population (Vinci et al. 2005) or than patients with stroke (Pfeiffer et al. 2001). The results from our study should not discourage any woman with CMT from having children. However, it has been reported that CMT mothers who had experienced deterioration of disease during pregnancy, had a negative attitude towards having (more) children, especially if the pregnancy was unplanned (Rudnik-Schöneborn et al. 1993). Planned pregnancies may therefore be recommended, and it is important to discuss both the possibility of deterioration of disease and complications during delivery with the patient before conception. The need for assistance in caring for the newborn on the basis of the mother’s disability ought to be addressed.
METHODOLOGICAL CONSIDERATIONS

Study design
Paper I, II and IV were designed as retrospective cohort studies, whereas Paper III is a case study.

Internal validity
Internal validity depends on lack of systematic error. Three types of systematic errors will be discussed here: Selection bias, Information bias and Confounding. In addition to that Precision, which is a random error, will be discussed in this section.

Selection bias can affect the result through the way in which the participants in the study were selected. Since the MBRN is a population based health registry with a nearly 100% coverage, this cohort study was most likely not affected by selection bias (Skomsvoll 2003).

Information bias is a systematic affection of the result through a systematically variation of exposure and diagnostical criteria. There are many types of information bias, and information bias may be differential or non-differential. When the misclassification with respect to one axis (either exposure or outcome) depends on the classification of the other axis, then the misclassification is differential. When the misclassification of one axis is independent of the other axis, then the misclassification is non-differential. Whereas non-differential information bias of exposure or outcome always will tend to underestimate the effects under study, differential information bias may either exaggerate or underestimate the effects. One example of differential information bias is the so-called recall bias, where for example in a survey of eating and drinking habits during pregnancy,
a mother who had given birth to a child with malformations would be more careful to recall her habits than a mother with a healthy child.

In our studies (Paper I, Paper II and Paper IV) it may be an issue that mothers may underreport their disease. If an association between an adverse pregnancy outcome and MG/CMT was known, such underreporting could in particular concern women without an adverse outcome. This would lead to inflated risk estimates.

However, this would probably not apply to any significant extent for our studies, as the data on mother’s disease in the MBRN form is registered prior to delivery, at admittance in the hospital.

An important aspect of information bias is misclassification and ascertainment of diagnoses. Paper III reports the specificity (Proportion of negatives correctly identified. Altman 1991) of the MBRN to ascertain a diagnosis of MG. We wrote to all women who had the diagnosis MG (1967-2004) and asked for consent to investigate their obstetrical records. Among the 90 women who were identified, 80 replied. Of the ten who didn’t reply, one was confirmed dead, and in four cases, their current postal address was unknown. Of the 80 women that did reply, 79 confirmed their diagnosis – which gives a high specificity. A high specificity is desirable, as false positives tend to dilute any effects.

In order to obtain high validity of a diagnosis, the sensitivity (Proportion of positives correctly identified. Altman 1991) must also be high. A study of various rheumatic disease diagnoses (rheumatic arthritis, ankylosing spondylitis, systemic lupus erythematosus and psoriatic arthritis) in the MBRN found the sensitivity to be 88.2% (Skomsvoll et al. 2002). Rasmussen et al (Rasmussen et al. 2003) found a high validity of
the Registry diagnosis of an unexplained fetal death, and conclude: “In conclusion, the validity of a diagnosis of unexplained antepartum fetal death based on the Medical Birth Registry of Norway is sufficiently high to justify future large-scale epidemiologic studies based on this database”.

Neither MG nor CMT are common diseases. This could lead to a lower sensitivity, as health personal may not acknowledge – and notify – the diagnosis, especially in mild cases. This could influence the target groups, who would then perhaps mainly include those who are most severely affected, which again would influence risk estimates. However, we have reason to believe that our number of 79 childbearing women in Paper I could well represent the whole target group in the actual period. The prevalence of MG is estimated at about 1 in 10,000 (Robertson et al. 1998, Aiello I et al. 2001, Poulas et al. 2001a). With a Norwegian population of 4.5 million, an equal incidence of MG in male and female patients (Poulas et al. 2001b), an increased incidence above 60 years and a fertility in the MG group assumed to be similar to the general population, our number of 79 childbearing with MG could represent the whole target group in the actual period. The prevalence of MG births in our study was 6.4 in 100,000.

Confounding is defined as a mixing of the effect of the exposure under study on the disease, with that of a third factor. This third factor must be associated with the exposure, and independent of that exposure, be a risk factor for the disease (Hennekens et al. 1987). Confounding can lead to an overestimate or underestimate of the true association between exposure and disease and can even change the direction of the observed effect (Hennekens et al. 1987). Confounding can be managed during analysis – if the appropriate information is available.
The following were in the papers I, II and IV considered to be potential confounders:

- Mother’s age (<25, 25 to 34, 35 + years)
- Birth institution (university hospital, other)
- Birth order

Confounding was adjusted for in stratified analysis and unconditional logistic regression analyses. To avoid assumptions of linear associations, all covariates were represented as indicator variables in the model. In Paper I and Paper II, the adjusted results did not differ from the crude results and so the crude results were presented. In Paper IV the variable “period of birth” was considered to be a confounding factor and thus, adjusted for.

A possible confounding factor not available in our data is the use of medical drugs during pregnancy. Until 1998, the MBRN only sporadically contained data on drugs, which in the case of MG could have influenced pregnancy outcome. As for Paper I, we were able to track down information on drug use in MG mothers who had given birth to children with severe birth defects, but not for the rest. In Paper III, the obstetrical records contained information on medication. This made us able to evaluate the use of medical drugs among pregnant MG women. With respect to drugs specifically related to treatment of MG we could thus consider whether the observed associations seemed to be related to the disease per se or to drugs. However, as for drug use in general, we could not control for possible confounding, as we had no information on drug use in the target population.

*Precision* is defined by the occurrence of random errors: high precision meaning lack of random errors (Rothman *et al.* 1998). “Random” is used to describe unsystematic as
opposed to systematic errors. Within the concept of errors lie both unsystematic measurement errors, sampling errors and normal biological variations. In epidemiological research, the precision is mostly affected by biological variation and sampling errors.

The smaller a study, the more the normal variation in the study population will affect the ability to detect differences between groups. This aspect must be taken into consideration in our study, as both MG and CMT are rare diseases.

Precision evaluation is linked to power calculations. Power calculations can be made in order to decide how many subjects are needed to detect a given statistically significant difference between two groups. In Paper IV, estimates of necessary sample size to obtain an 80% power to detect significant differences in use of intervention between the two groups were calculated in S-Plus (version 6.1 for Windows). The power calculations were based on the observed proportions of intervention (vacuum and cesarean section) in the two groups, a type I error of 5.0% and a two-sided test.

For cesarean section, where the proportion was 9.0% in the reference group and 15.7% in the patient group, 183 CMT patients and a correspondingly higher number of individuals in the reference group would have been necessary to obtain an 80% power to detect a statistically significant difference in the cesarean section rate between the two groups. We had 108 patients in paper IV and thus, the power was not considerably decreased regarding that variable. However, as for vacuum extraction, which was asked about by one of the reviewers, the proportion was 3.9% in the reference group and 5.6% in the patient group. In this case, 1195 CMT patients would have been necessary to detect a statistically significant difference.
Another aspect of precision is *multiple testing*. A large number of significance tests might sometimes be difficult to interpret, because if you perform testing long enough you will inevitably find something “significant”. Given no effect of the actual exposure in studies, one out of 20 tests will in the long run very likely to have a p-value less than 0.05. There exist methods to adjust for multiple testing, for instance the Bonferroni correction (Altman 1991). However, the value of the Bonferroni method is debated, and many epidemiologists claim that it creates more problems than it solves, because it is too conservative and one may miss real differences. (Bland *et al.* 1995, Perneger 1998).

In our study, the use of the Bonferroni correction or similar methods would mean that we had to specify in forehand which and how many tests we would perform. Given the limited amount of knowledge about associations between pregnancy and rare neurologic diseases, and therefore lack of specific hypotheses to test - this was considered not an appropriate method in our study.

What we have done is to describe what tests of significance we have performed, and why – as recommended by Perneger (Perneger 1998). Rather than adjusting the level of significance for the number of comparisons being carried out, the results are presented by their face value. As a general rule, associations found in a study like ours should be verified in later studies.

**Analysis of consecutive deliveries in a mother**

In all papers, we were able to trace each mother’s deliveries consecutively. This enabled us to look at the consistency of the MG/CMT diagnosis, suggesting no or a very low proportion of false positives in our data sets. Furthermore, it was interesting to look
at whether some of the MG/CMT women in the study had a particular great risk for adverse outcome. Were there any particular features of disease that these women had in common? Thus, in Paper I and II, we report cases where a mother gave birth to children with birth defects/neonatal complications in more than one pregnancy and delivery.

In all analyses of birth data where more than one birth to each woman are represented, the problem of dependency for outcomes in the same woman must be acknowledged. However, so far only a limited number of papers using birth registry data have used statistical procedures that account for this dependency, so called “Multiple level analysis” (Goldstein 1995). Such methods will probably be more applied in the future as the procedures become more available in standard program packages.

**External validity**

External validity, or generalisability, refers to whether the results and conclusions in a study could be relevant for other populations than those who are studied. To achieve this quality, the internal validity has to be strong. The present work is based on the data in the MBRN. Norway has a relatively homogenous low-risk, white population. Thus, there is reason to believe that the results should be applicable to all populations of adult white women. However, one must bear in mind that the results probably cannot be directly transferred to countries where the health care system, and especially the treatment of MG prior to and during pregnancy are much different from that in Norway during the study period.
Limitations and advantages

The methodological limitations have been discussed with focus on several aspects, particularly on problems regarding ascertainment of MG and CMT diagnosis and also the lack of drug data as well as other potential confounders that could have influenced the results. We have also discussed the issues of multiple testing and dependency.

It would have been desirable to be able to link disease severity to pregnancy and delivery outcome. However, this information could not be retrieved from the MBRN and not on a regularly basis from the obstetrical records either. To be able to link disease severity to our findings would make it easier to target patients with a special risk for adverse outcome, and should definitely be a point for future research.

One major advantage of this study is the nationwide population based design, which enabled us to get target groups of satisfactory size in such rare diseases as MG and CMT. Furthermore, the data can be reorganized, allowing for analyses of subsequent pregnancy outcomes and recurrence risks. To our knowledge, this is the first study of women with MG and CMT (Papers I, II and IV) using such a study design.
CONCLUSIONS

The present study contributes to the knowledge on outcome in pregnancy and delivery in female patients with an acquired neuromuscular disease, MG, and an inherited neuropathy, CMT.

For MG, the study finds a disease-mediated effect upon pregnancy, delivery and the newborn. Women with MG have a higher rate of complications during delivery, and a higher rate of intervention during delivery than women without MG. The rate of cesarean section was doubled in the MG group. MG is a chronic disease and can affect pregnancy outcome and delivery even if the patient is in clinical remission or even before diagnosis. It seems that the clinical condition of the patient cannot be used as a predictor of complications in MG patients during pregnancy and delivery or for neonatal MG/AMC. Maternal thymectomy seems to have a protective effect on neonatal MG.

Women with CMT seem also to have a disease-mediated effect upon pregnancy and delivery outcome, such as a higher risk for fetal presentation anomalies and for bleeding post partum. Increased use of forceps in these patients, which is an emergency procedure, implies that the increased risk for adverse delivery outcome in CMT mothers is not fully acknowledged. In this study, we did not have access to data on disease severity. A challenge for future research in this field would be to investigate disease severity and to its implications related to our findings.
ERRATA

*Paper III*: Table 1: There has been an omitting error in the text, as well as a false foot-note in table 1. We used the T-test, which is correct for continuous variables, but this is not particularly mentioned in the *Material and methods section*. The foot-note should have read: T-test.

*Paper II*: Table 2: The number for cases where "Induction for birth" was performed was 13. This number is in the table, but incorrect in the text in the *Result* section, where it reads: “*Amongst the 14 induced births...*” All statistics is based on the correct number, 13.

*Paper II*: Table 2: The *confidence intervals* displayed in the Table 2 are the multiplicative inverse ones.

The correct table 2 with correct confidence intervals is displayed on the next page:
Table 2 (Paper II) Corrected version

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Target group</th>
<th>Reference group %</th>
<th>Rate ratio</th>
<th>95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of birth</td>
<td>13 (26.5)</td>
<td>13.4</td>
<td>2</td>
<td>1.2-3.1</td>
<td>0.007</td>
</tr>
<tr>
<td>Total intervention during birth</td>
<td>14 (28.6)</td>
<td>20</td>
<td>1.4</td>
<td>0.02-2.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Caesarian section</td>
<td>7 (14.6)</td>
<td>8.6</td>
<td>1.7</td>
<td>0.8-3.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Vaginal intervention</td>
<td>4 (8.2)</td>
<td>6.3</td>
<td>1.3</td>
<td>0.5-3.3</td>
<td>0.6^a</td>
</tr>
<tr>
<td>Total occurrence of complications</td>
<td>20(40.8)</td>
<td>32.9</td>
<td>1.2</td>
<td>0.9-1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Functional disorder of birth**</td>
<td>7 (14.3)</td>
<td>6.5</td>
<td>2.2</td>
<td>1.1-4.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Premature rupture of amniotic membranes</td>
<td>-</td>
<td>1.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding postpartum</td>
<td>2 (4.2)</td>
<td>5.3</td>
<td>0.8</td>
<td>0.2-3.0</td>
<td>0.7^b</td>
</tr>
<tr>
<td>Umbilical cord</td>
<td>9 (18.4)</td>
<td>12.6</td>
<td>1.5</td>
<td>0.8-2.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (6.1)</td>
<td>1.7</td>
<td>3.6</td>
<td>1.2-11.0</td>
<td>0.02^c</td>
</tr>
</tbody>
</table>

*Pearson chi-square P-value  ** Slow progress in labor/protracted labor

^a) Fishers exact test: p-value= 0.5, ^b) Fishers exact test: p-value= 1.0, ^c) Fishers exact
test: p-value= 0.05.
REFERENCES


