Increased risk for clinical onset of myasthenia gravis during the postpartum period

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ABSTRACT

Objective: To study the risk of clinical onset of myasthenia gravis (MG) in pregnancy and during the first 6 months postpartum because an association between pregnancy or the postpartum period and the onset of autoimmune MG is widely assumed but not proven.

Methods: The design was a cross-sectional population-based cohort study of 2 MG cohorts (Norway and the Netherlands) with 1,038 healthy controls from Norway. Data were obtained on 246 women with MG (age at onset 15–45 years). Data on pregnancy, hormonal factors, and clinical symptoms were collected by a previously validated environmental MG questionnaire. Relative risk of MG onset before, during, and after pregnancy was calculated by multinomial logistic regression for Norwegian women reaching 45 years of age, adjusted for the observed distribution of person-years in the corresponding control group.

Results: Of the included women with MG, 13 (11.5%) of the Dutch and 24 (18.0%) of the Norwegian patients had their first myasthenia symptoms during the pregnancy or postpartum period. The postpartum period was confirmed to be significantly associated with the onset of symptoms of MG in Norwegian women with MG (relative risk 5.5, 95% confidence interval 2.6–11.6). The risk was highest after the first childbirth.

Conclusions: Women have a high-risk period for the onset of clinical symptoms of MG in the postpartum period, in particular after the first childbirth. Future studies should aim at elucidating the role of the hormonal-immunological-genetic interaction in the pathogenesis of MG. *Neurology*® 2016;87:2139–2145

GLOSSARY

AChR = acetylcholine receptor; **CI** = confidence interval; **EOMG** = early-onset acetylcholine receptor myasthenia gravis subtype; **HLA** = human leukocyte antigen; **ICD-9** = *International Classification of Diseases, Ninth Revision*; **ICD-10** = *International Classification of Diseases, 10th Revision*; **MG** = myasthenia gravis; **RR** = relative risk.

Autoimmune myasthenia gravis (MG) is hallmarked by fluctuating weakness, fatigability, thymic abnormalities, and antibodies that target proteins at the neuromuscular endplate such as the acetylcholine receptor (AChR) and muscle-specific kinase.¹ The early-onset AChR MG subtype (EOMG) typically starts between 20 and 40 years of age and is characterized by a female preponderance (3:1) and thymus hyperplasia with germinal centers.² EOMG is strongly associated with the haplotype human leukocyte antigen (HLA)-B*08/DRB1*03, but otherwise there are no well-established risk factors.³

Pregnancy has different effects in autoimmune diseases.^{4–6} In patients diagnosed with MG, both pregnancy and the postpartum period are associated with worsening for 30% to 40%. However, there are conflicting data regarding the period in pregnancy or postpartum when the risk of worsening is highest.^{7–10} Sex hormones are suggested as triggers for worsening of symptoms. Estrogens do indeed enhance the immune response in mice models of MG.¹¹ In addition, maternal immunologic adaptation in pregnancy and pregnancy products such as α -fetoprotein are suggested as potential modulators of disease.^{12,13}

Most studies of pregnancy in MG focus on the course and occurrence of neonatal MG,^{7–10} but a few studies have reported the onset of myasthenia in this period.^{14,15} Together with case

Supplemental data
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reports,^{16–18} these reports point to pregnancy and the postpartum period as a risk period for the start of the disease. On the other hand, family planning and fertility are typical issues for this age group, and the association with the peak incidence years of EOMG might be by chance only. To the best of our knowledge, the risk of developing clinically overt MG during pregnancy or shortly thereafter has not been documented compared to controls in an epidemiologic context.

To learn more about the onset of MG during pregnancy and postpartum period, defined as until 6 months after delivery, we designed this case-control study using population data from Norway and the Netherlands.

METHODS Cases. The design was a cross-sectional population-based cohort study of 2 MG cohorts from Norway (nationwide) and the region of south Holland and parts of north Holland (entire regional). Details are provided in a flowchart (figure e-1 at Neurology.org) and were published earlier.^{2,19,20} Patients with MG were identified according to the 9th or 10th version of the ICD codes by the ICD-9 code 358.8 or ICD-10 code G70.0 in the hospitals in the study area. The search was done 20 years back in time in both countries. Medical charts were reviewed to validate inclusion. Patients were included if they were ≥ 16 years of age, lived in the study area, had clinical MG symptoms, and had either AChR or muscle-specific kinase antibodies or diagnostic findings at electrophysiologic tests (such as decremental response on repetitive nerve stimulation or increased jitter on single-fiber electromyography) indicating neuromuscular junction dysfunction. The previously validated environmental MG questionnaire²¹ was mailed to 671 Dutch and 491 Norwegian patients with MG. Nonrespondents were sent a reminder questionnaire after 4 and 8 weeks.

The dataset for the current study was restricted to females with onset of the disease in their reproductive years (15–45 years of age) who were diagnosed between 1950 and 2010 in Norway or between 1952 and 2012 in the Netherlands. The participation rate in this dataset was 119 of 186 (63.9%) in the Netherlands and 138 of 191 (72.2%) in Norway. We excluded 8 patients with thymoma MG (1% in each cohort) because their etiologic mechanisms are considered paraneoplastic, leaving a total of 246 patients with MG for analysis (113 in the Netherlands and 133 in Norway). Age and MG subtype distribution in participants were similar to those of nonparticipants.

Controls. Healthy controls were randomly selected from the National Population Registry in Norway. A total of 2,500 women with the same birth year distribution as the cases were invited by letter to participate in the questionnaire study in the period of September 1, 2012, to October 31, 2012. If no response was obtained, they were reminded once after 6 weeks. A total of 1,038 women (42%) participated in the study.

Data. In the questionnaires, the patients and controls were asked to report data on reproductive health issues such as birth year and number of live-born children, duration of breast-feeding, and other information regarding hormonal status. The questionnaire is available as a supplement to a previous publication.²¹ The questionnaires were scanned into a database with

Cardiff Teleform version 10.4 (Autonomy, Inc, Sunnyvale, CA). The data were controlled for outliers, and all questionnaires were manually inspected. Participants were contacted by telephone or mail to reduce missing data. Data on age at onset, antibody status, and thymus histology were obtained from medical charts. We contacted pathology departments for documentation on thymus histology and the patients' antibody status in the national AChR antibody registry at the Department of Neurology, Haukeland University Hospital. After this, missing data were between 1% and 3% for both cohorts. Data on genotype HLA B*08/DRB1*03:01 or HLA-B*08/DRB1*X for the Norwegian EOMG population were included from a previous HLA study.²²

Definitions. Patients with maternal MG were defined as women who had clinical onset of MG during pregnancy (9 months) or postpartum (6 months). The remaining patients with MG were defined as having nonmaternal MG. For risk calculation, we defined the 4 following groups: (1) onset of MG before any pregnancy, (2) onset in pregnancy, (3) onset in the postpartum period (0–6 months), and (4) onset at least 6 months after pregnancy.

Statistical analysis. To assess risk in pregnancy or the postpartum period relative to other periods of life, a multinomial logistic regression analysis was applied. The primary analysis was performed with only Norwegian patients with MG and healthy Norwegian female controls to make the case and control groups comparable. To limit bias by lost cases after pregnancy, all having a prepregnancy period but not vice versa, only women observed at least until 45 years of age were included in the analysis ($n = 79$). Among the healthy controls, the number of person-years observed before the first pregnancy, in pregnancy, and 6 months postpartum and the time period after 6 months postpartum was calculated (total sum of person-year experience was 18,150). Relative risk (RR) of MG before, during, and after pregnancy was calculated, adjusted for the observed distribution of person-years among the healthy controls, with the prepregnancy group set as the reference level. Because pregnancy is most frequent around the same age as EOMG onset, the analysis was stratified by age groups (15–25, 25–35, and 35–45 years of age) to adjust for potential confounding by age.

For the remaining analyses, both Dutch and Norwegian patients with maternal MG were used ($n = 37$). For the secondary analysis, the pregnancy and postpartum period were further subdivided into 3-month intervals (first, second, and third trimesters of pregnancy, 0–3 months postpartum, and 3–6 months postpartum), again including only women going through the whole observation period. In this analysis, the first trimester was set as reference in the multinomial logistic regression analysis. A linear regression analysis was performed to study the association between breast-feeding and time of onset after birth. For other comparisons, χ^2 and t tests were applied, with a value of $p < 0.05$ considered significant. Statistics were performed with SPSS version 22.0 (IBM SPSS, Armonk, NY) and STATA version 14 (StataCorp, College Station, TX).

Standard protocol approvals, registrations, and patient consents. The study was approved by the regional ethics committee of south Norway, the ethics review committee of the Leiden University Medical Center in the Netherlands, and the Medical Review Ethics Committee of southwest Holland. Written informed consent was obtained from all participants.

RESULTS Background characteristics of the 246 patients with MG, the general population, and the Norwegian healthy controls are presented in tables 1 through 3. Maternal MG was reported by 37 cases:

Table 1 Background characteristics of patients and controls regarding female reproductive health issues

	Patients with MG		General population controls		Healthy controls
	Norwegian (n = 133)	Dutch (n = 113)	Norwegian, 1950–2010	Dutch, 1952–2012	Norwegian (n = 1038)
Onset in pregnancy, mean (SD), n (%)	24 (18)	13 (11.5)			
Age, mean (SD), y	49.7 (15.3)	46.3 (15.5)	—	—	47.8 (17)
Nullipara, n (%)	27 (20.3)	48 (42.5) ^b	—	—	275 (26.4)
Total fertility rate (range)	1.81 (0–6)	1.13 (0–5) ^b	1.9	2.0	1.7 (0–8) ^a
Mother's age at birth of first child, mean (SD), y	24.7 (4.4)	28.0 (4.6) ^b	25.3	27.4	24.8 (4.8)
Mother's age at birth of last child, mean (SD), y	29.0 (5.0)	30.9 (5.0)			30.5 (4.9)

Abbreviation: MG = myasthenia gravis.

^aNo statistical differences were observed between the Norwegian patients with MG and healthy controls.

^bBetween Dutch and Norwegian MG cohort, $p < 0.05$.

24 Norwegian (18%) and 13 Dutch (11.5%) patients with MG ($p = 0.103$). Patients with maternal MG did not differ in clinical features, treatment, or long-term course compared to patients with nonmaternal MG. Another 10 women reported onset in the period of 6 months to 1 year postpartum. Among the patients with maternal MG, 26 reported onset during or after the first pregnancy and 11 in relation to later pregnancies. The estimated risk for maternal MG occurring in relation to later pregnancies was lower than the risk for maternal MG occurring in first pregnancy (RR 0.33, 95% confidence interval [CI] 0.16–0.66, $p = 0.002$), corrected for the observed frequency of first vs later pregnancies among the healthy controls.

A higher frequency of women not having children and a lower total fertility rate were noted in the Dutch patients with MG compared with the Norwegian patients with MG. For this reason, the primary analysis of risk in pregnancy or postpartum compared to risk before any pregnancy included only the Norwegian

patients with MG followed up at least until 45 years of age ($n = 79$, figure 1). Relative to the prepregnancy level, the RR of onset in pregnancy was 0.96 (95% CI 0.28–3.21) before increasing in the period of 0 to 6 months postpartum to 5.52 (95% CI 2.61–11.61). During the following 6 months postpartum, the RR declined back to 1.53 (95% CI 0.81–2.88). RR estimates uncorrected for mothers' age at delivery were only marginally different from the main estimate (RR in pregnancy 0.90, RR 0–6 months postpartum 5.12, and RR after pregnancy 1.22).

Compared to the first trimester, the internal RR in pregnancy and postpartum was 1.0 (95% CI 0.23–4.0) during the second trimester, 0.25 (95% CI 0.03–2.2) during the third trimester, 4.5 (95% CI 1.5–13.3) during the first 3 months postpartum, and 2.5 (95% CI: 0.8–8.0) during 3 to 6 months postpartum (figure 2A).

Linear regression analyses with time of onset after birth as the dependent variable and breast-feeding as the exposure variable revealed that 35% of the variance for time of onset postpartum was explained by the number of months of breast-feeding ($R^2 = 0.35$, $\beta = 0.29$, 95% CI 0.12–0.46, $p < 0.001$, figure 2B).

DISCUSSION In this population-based case-control study including 246 women from 2 MG cohorts, we found that pregnancy preceded the onset of MG in 15% of the cases. The postpartum period was associated with a significant increase in risk for the onset of clinical symptoms.

To the best of our knowledge, there are no reports that disclose the risk of MG onset in pregnancy or postpartum compared to other periods of female reproductive life. Our frequencies of maternal MG are supported by quite similar reported frequencies,

Table 2 Onset in relation to pregnancy

	All	Norwegian cohort (n = 133)	Dutch cohort (n = 113)
Nulliparous, n (%)	75 (30)	27 (20)	48 (43)
Parous, n (%)			
Onset before first pregnancy	51 (21)	34 (26)	17 (15)
Onset in any pregnancy	9 (4)	4 (3)	5 (4)
Onset 0–6 mo postpartum	28 (11)	20 (15)	8 (7)
Parous, onset >6 mo after pregnancy	83 (34)	48 (36)	35 (31)
Onset in first pregnancy	25 (67)	15 (63)	10 (77)
Onset in subsequent pregnancies	12 (32)	9 (38)	3 (23)

Table 3 Clinical characteristics of maternal onset vs nonmaternal onset

	All MG (n = 246)	Maternal MG (n = 37)	Nonmaternal MG (n = 209)	p Value
Age (mean ± SD), y	48.1 (15.5)	51.9 (14.7)	47.4 (15.5)	0.102
Age at onset (mean ± SD), y	27.7 (8.5)	27.5 (8.8)	28.9 (6.5)	0.351
Disease duration (mean ± SD), y ^a	20.4 (14.8)	23.0 (15.0)	19.9 (14.8)	0.244
Serology, n (%)				0.099
AChR antibodies	201 (81.8)	26 (70.3)	175 (83.7)	
MuSK antibodies	6 (2.4)	1 (2.7)	5 (2.4)	
Seronegative ^b	35 (14.2)	8 (21.6)	27 (12.9)	
Missing	4 (1.6)	2 (5.4)	2 (1.0)	
Treatment, n (%)				
Mestinon	169 (68.4)	26 (70.3)	143 (68.1)	0.793
Prednisolone	48 (19.4)	4 (10.8)	44 (21.0)	0.151
Immunosuppressive drugs ^c	42 (17)	4 (10.8)	38 (18.1)	0.348
Ever used IVIG	16 (6.5)	0	16 (7.7)	0.082
Ever used PF	46 (18.7)	6 (16.2)	40 (19.1)	0.674
Clinical symptoms, n (%)				0.252
Remission	48 (19.5)	6 (16.2)	42 (20.0)	
Ocular MG (MGFA I) ^d	10 (4.1)	3 (8.1)	7 (3.3)	
Residual ocular ^e	22 (8.9)	1 (2.7)	21 (10)	
Generalized	166 (67.5)	27 (73.0)	139 (66.5)	
Thymectomized, n (%)	146 (58.7)	28 (75.7)	118 (55.7)	0.073
Histology, n (%)				0.931
Follicular hyperplasia	84 (57.5)	16 (57.1)	68 (57.6)	
Atrophy/normal	34 (23.3)	6 (21.4)	28 (23.7)	
Unknown	28 (19.2)	6 (21.4)	71 (33.8)	
AADs, n (%)	87 (35.2)	16 (43.2)	71 (33.8)	0.472
HLA-B*08/DRB1*X status ^f	65 (58.0)	9 (45)	56 (60.5)	0.218
HLA-B*08/DRB1:0301 ^f	56 (50)	9 (45)	47 (51.1)	0.806

Abbreviations: AAD = associated autoimmune disease; AChR = acetylcholine receptor; HLA = human leukocyte antigen; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle specific kinase; PF = plasmapheresis.

The data are pooled from both the Dutch and Norwegian cohorts.

^aTime since onset.

^bNegative for AChR and MuSK antibodies.

^cInclude azathioprine, mycophenolate mofetil, and cyclosporine A.

^dOcular MG = ocular throughout whole disease course.

^eResidual MG = those with residual ocular symptoms after treatment for generalized disease.

^fSamples available for the Norwegian MG cohort (n = 115).

4% to 13%, in previous epidemiologic reports from different parts of the world.^{15,23,24} The risk of onset was highest after the first childbirth. To the best of our knowledge, increased risk (resulting in live births) vs later pregnancies is not reported in the literature. This may indicate that in women with a certain genetic profile, the first postpartum period is sufficient to develop clinical overt autoimmune MG. A major limitation is the cross-sectional nature of our study, which limits the interpretation of causality. Although the association was strong, it might be that pregnancy or

the postpartum hormonal-immunologic changes merely drive the disease forward rather than causing the disease and that the biological onset occurred earlier in life. To be sure that pregnancy is related to the biological onset of MG, a prospective controlled study with serum samples is needed.

Analogous to our results, there is increased risk of clinical onset of autoimmune thyroiditis and rheumatoid arthritis in the immediate postpartum period.^{5,6} This phenomenon, with increased risk in first-time mothers, is also shown in autoimmune

Figure 1 Increased risk for myasthenia gravis (MG) in the postpartum period

Estimated relative risk (RR) for clinical onset of MG before pregnancy, during pregnancy, 0 to 6 months postpartum, and after pregnancy, corrected for age period and observation time.

thyroid disease.⁶ On the basis of all these associations, one may argue that our findings may represent a universal feature of autoimmunity rather than being MG specific. These disorders share genetic factors with MG, and there is an increased risk of co-occurrence with MG.^{25,26} Focused studies exploring all shared genetic and immunologic pathways are warranted to prove causality and to define the pathomechanisms more narrowly.

Autoimmune worsening in pregnancy has previously been explained by an imbalance in the immune system due to sex hormone exposure.^{12,27} There is

evidence that estrogen enhances cytokine production and immunoglobulin production in patients with MG and animal models of MG.¹¹ This could theoretically also explain onset during pregnancy. Another factor that may contribute to postpartum onset in MG is a drop in α -fetoprotein postpartum.^{13,28} α -Fetoprotein has been reported to very effectively inhibit the binding of AChR antibodies to acetylcholine receptors.¹³ This can explain the lower risk in the third trimester when the α -fetoprotein levels are high and the increased risk in the immediate postpartum period when the levels suddenly drop.²⁸

Figure 2 Myasthenia gravis (MG) in pregnancy and postpartum

(A) Highest risk at 0 to 3 months postpartum. Estimated relative risk of clinical onset of MG in pregnancy and 6 months postpartum in 3-month intervals with 95% confidence intervals (first trimester is reference). (B) Relationship between breast-feeding and postpartum onset of MG. The y-axis shows the percentage of patients who develop MG (columns) or breast-feed (lines). Orange columns represent Dutch women and green columns represent Norwegian women who developed MG in the period indicated in the x-axis. The dotted line represents the declining frequency of breast-feeding after birth among Dutch women, and solid line shows the decline among the Norwegian women.

Other potential mechanisms could be immunologic rebound effect after delivery²⁹ and immunization by fetal antigen.³⁰ The psychological and physiologic stress and related cortisol release from pregnancy and delivery and the associated sleep deprivation could be contributing factors.

There were country-level differences in the timing of onset, possibly associated with breast-feeding. To the best of our knowledge, the role of breast-feeding and its effect on MG disease have not been studied previously. In other autoimmune disorders, breast-feeding is reported to be associated with the clinical onset and course of disease after birth,^{31,32} but with somewhat inconclusive results. The risk of onset postpartum seemed to drop faster in the Netherlands than in Norway. This may be a result of prolonged breast-feeding in Norway, postponing the moment of onset of clinical symptoms of MG. The maternity leave is longer in Norway (9–12 months) than in the Netherlands (3 months). Consequently, according to general population reports, 71% of Norwegian women vs 27% of the Dutch women breast-feed at 6 months, in accordance with our MG cohorts.^{33,34} Hence, we hypothesize that prolonged breast-feeding contributes to the delay of onset of clinical overt MG. However, one cannot exclude that high prolactin exposure is involved in the breakdown of the immune tolerance instead, as hypothesized in rheumatoid arthritis.³⁵ Breast-feeding decreases the estrogen levels and may therefore activate the proinflammatory function of prolactin. An interaction between the prolactin gene and the HLA region has also been suggested³⁶ and could potentially explain a susceptibility in some women for onset and worsening around pregnancy. In our study, however, there was no apparent difference regarding HLA-B*08/DRB1*X between maternal MG and nonmaternal MG.

The strength of the study is the population-based case-control design with a high participation rate and few missing data, ensuring a representative MG sample. Because we conditioned on full observation time, there is no bias due to retrospective design. However, the use of a questionnaire could have introduced selection bias. Cases are more likely to participate than healthy controls, which our participation rates reflect (70% vs 43%). One explanation for the lower participation rate among controls in our study is that, because of ethics regulations, we were allowed to remind them of participation once only, whereas the cases were reminded twice. However, the 42% participation rate is a typical rate for epidemiologic population-based surveys in Norway.³⁷ Moreover, the fact that the reported age of the first child and the number of childbirths were equal to the data gathered from the general Norwegian population supports the representativeness of the controls. We collected the

exposure variables similarly in both controls and cases, and none were informed about the hypothesis of the study. Preferential recall or impaired patient memory may have led to a higher frequency or bias regarding the exact timing of onset. For this reason, we checked the questionnaire data with the medical charts of the patients, which showed good agreement. A previous Norwegian study¹⁴ reported 7 cases with onset in pregnancy in the first pregnancy. These patients with MG were identified through the medical birth registry of Norway, avoiding recall and memory bias. Our results were similar, supporting minimal bias in our study. Another limitation in our study is that we lack information regarding failed pregnancy before first birth among our cases and controls.

The environmental MG questionnaire was made specifically to provide new epidemiologic data on risk factors and should be compared with the population at risk living in the same area. However, because the same frequency of maternal MG is reported in the Netherlands, Norway, and Australia, measured by the same questionnaire²⁴ and we regard our sample to be representative, we believe that our results can be extrapolated to white women in childbearing years.

Women have a high-risk period for the clinical onset of MG in the postpartum period, in particular first-time mothers. Potential hormonal-immunologic-genetic factors contributing to the process have yet to be elucidated.

AUTHOR CONTRIBUTIONS

Dr. Boldingh: designed study, conceptualized study, analysis and interpretation of data, drafted and revised the manuscript. Dr. Maniaol: designed and conceptualized study, analysis and interpretation of data, revised the manuscript. C. Brunborg and H. Weedon-Fekjær: statistical analysis and interpretation, revised the manuscript. Dr. Verschuuren: designed study, analysis and interpretation of data, drafted and revised the manuscript. Dr. C. M. E. Tallaksen: initiated the project, designed study, analysis and interpretation of data, drafted and revised the manuscript.

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DISCLOSURE

M. Boldingh, A. Maniaol, C. Brunborg, and H. Weedon-Fekjær report no disclosures relevant to the manuscript. J. Verschuuren has been involved in the NIH-sponsored thymectomy trial and a FP7-Health-2013-innovation-1 European grant (No. 602420) on MG. The Neurology Department of the Leiden University Medical Centre has received fees and royalties from Alexion, Argen-X, and

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