

Obstetric and Neonatal Outcomes in Patients With Maternal Myasthenia Gravis

A Nationwide Cohort Study

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Abstract

Background and Objectives

Muscle weakness, autoantibodies, and medication use in myasthenia gravis (MG) can complicate pregnancy and delivery. Vaginal delivery is encouraged despite increased risk of acute operative delivery. Our aim was to assess childbirth outcomes related to MG in a current, unselected, nationwide birth cohort.

Methods

This cohort study included all singleton births in the Medical Birth Registry of Norway from 1999 to 2022. Maternal MG, defined as MG diagnosis or pyridostigmine use, was identified from current and previous pregnancies. We compared adverse pregnancy, delivery, and neonatal outcomes between MG and non-MG births, with mode of delivery as the main outcome. Odds ratios (ORs) with 95% CIs, adjusted for year of birth, maternal age, parity, civil status, and autoimmune comorbidities, were estimated with logistic regression. In subanalyses, we investigated cesarean section (C-section) rates within Robson-10 subgroups and C-section indications.

Results

There were 134 MG births and 1,351,032 non-MG births. Elective C-section was twice as likely if the mother had MG (adjusted OR [aOR] 1.8, 95% CI 1.1–3.1), but emergency C-section and operative vaginal delivery were not more common. MG increased the risk of induction (aOR 1.5, 1.0–2.3), neuraxial anesthesia (aOR 1.5, 1.1–2.1), episiotomy (aOR 1.8, 1.1–3.0), preterm prelabor rupture of membranes (aOR 2.7, 1.1–6.6), prolonged hospitalization after delivery (aOR 1.8, 1.3–2.7), low birthweight (aOR 2.4, 1.3–4.4), feeding problems (aOR 4.9, 2.5–9.5), and transfer to a neonatal unit (aOR 5.1, 3.6–7.2). Transient neonatal MG (TNMG) was diagnosed in 5 of 134 children (4%). In subanalyses, the crude C-section rate was increased in preterm MG births (50% in MG vs 19% in non-MG) and in MG births after previous C-section (75% in MG vs 47% in non-MG).

Discussion

In this registry-based study, the higher rate of elective interventions suggests a proactive management of MG deliveries. The lower C-section threshold for MG births with relative obstetric indications may be justified, but most vaginal deliveries were uncomplicated. Adverse outcomes were generally not increased in the MG group compared with the general population, although episiotomy and prolonged hospitalizations were more frequent. Notably, 40% of MG-exposed infants had feeding difficulties and hypotonia or required neonatal care, suggesting underdiagnosis of TNMG.

Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that can complicate childbirth.^{1,2} The voluntary muscles affected in generalized MG play a key role in the second

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Supplementary Material

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Glossary

AMC = arthrogryposis multiplex congenita; **aOR** = adjusted OR; **ATC** = Anatomical Therapeutic Chemical; **C-section** = cesarean section; **ICD-8** = International Classification of Diseases, 8th Revision; **ICD-10** = International Classification of Diseases, 10th Revision; **MBRN** = Medical Birth Registry of Norway; **MG** = myasthenia gravis; **OR** = odds ratio; **PPROM** = preterm PROM; **PROM** = prelabor rupture of membrane; **SGA** = small for gestational age; **TNMG** = transient neonatal MG.

stage of labor, thus potentially increasing the risk of operative vaginal delivery and emergency cesarean section (C-section).³ Nevertheless, current guidance articles recommend aiming for spontaneous vaginal delivery in MG births without obstetric indications for C-section.⁴⁻⁶

Surgical stress due to C-section can trigger MG exacerbation,^{1,2} and certain anesthetics can have severe adverse effects in MG.⁷ Neuraxial anesthesia (i.e., epidural or spinal anesthesia) is preferred in MG deliveries while general anesthesia is only recommended if respiration problems are expected, for example, because of impaired bulbar or respiratory function.^{8,9} Early application of epidural anesthesia in vaginal labor could ease instrumental assistance with vacuum or forceps, decrease the need for emergency C-section, and most importantly, reduce the need for general anesthesia if emergency C-section is unavoidable.^{9,10} There is consensus that MG deliveries should be managed in maximum-care hospitals with immediate access to neonatal, obstetric, and neurointensive care.¹¹

A considerable proportion of patients with MG are women of childbearing age.¹² The most common subtype in this population is early-onset MG with thymic hyperplasia and acetylcholine-receptor antibodies.¹³ Owing to MG autoantibodies, which are transferred across the placenta, 3%–30% of children born to mothers with MG express symptoms of transient neonatal MG (TNMG).¹⁴ Symptoms of TNMG often appear after birth with a delay of 1 to 3 days. Thus, all children exposed to maternal MG should be observed for at least 3 days in hospital.¹⁴ Fetal acetylcholine receptor antibody-related disorders are rare but permanent neonatal complications.¹⁵ These include skeletal malformations, such as arthrogryposis multiplex congenita (AMC), appearing as a consequence of reduced fetal movements in utero.¹⁶

Many women with MG worry about giving birth. Among survey participants who did not wish to become pregnant (again), 60% reported that concern about the delivery was a major reason.^{17,18} Although MG is not considered an indication for C-section,⁴⁻⁶ C-section is more common in MG populations.¹⁹⁻²¹ Whether this is related to the condition itself/the neurologic status, or to associated factors, is uncertain. Most previous studies are small single-center case series and inherently subject to selection bias, confounding, and limited power.^{22,23} There are few larger MG pregnancy cohorts and only a couple comparative studies with a prospective design, especially in recent years.^{3,19,21,24-27} The need

for updated evidence is emphasized by rising C-section rates and an aging childbearing population worldwide.^{28,29}

Our aim was to assess the risk of operative delivery and adverse childbirth outcomes in a recent, unselected birth cohort of mothers with MG. Our hypothesis was that there is an increased risk of C-section and operative vaginal delivery with maternal MG, and of other adverse pregnancy, delivery, and neonatal outcomes.

Methods

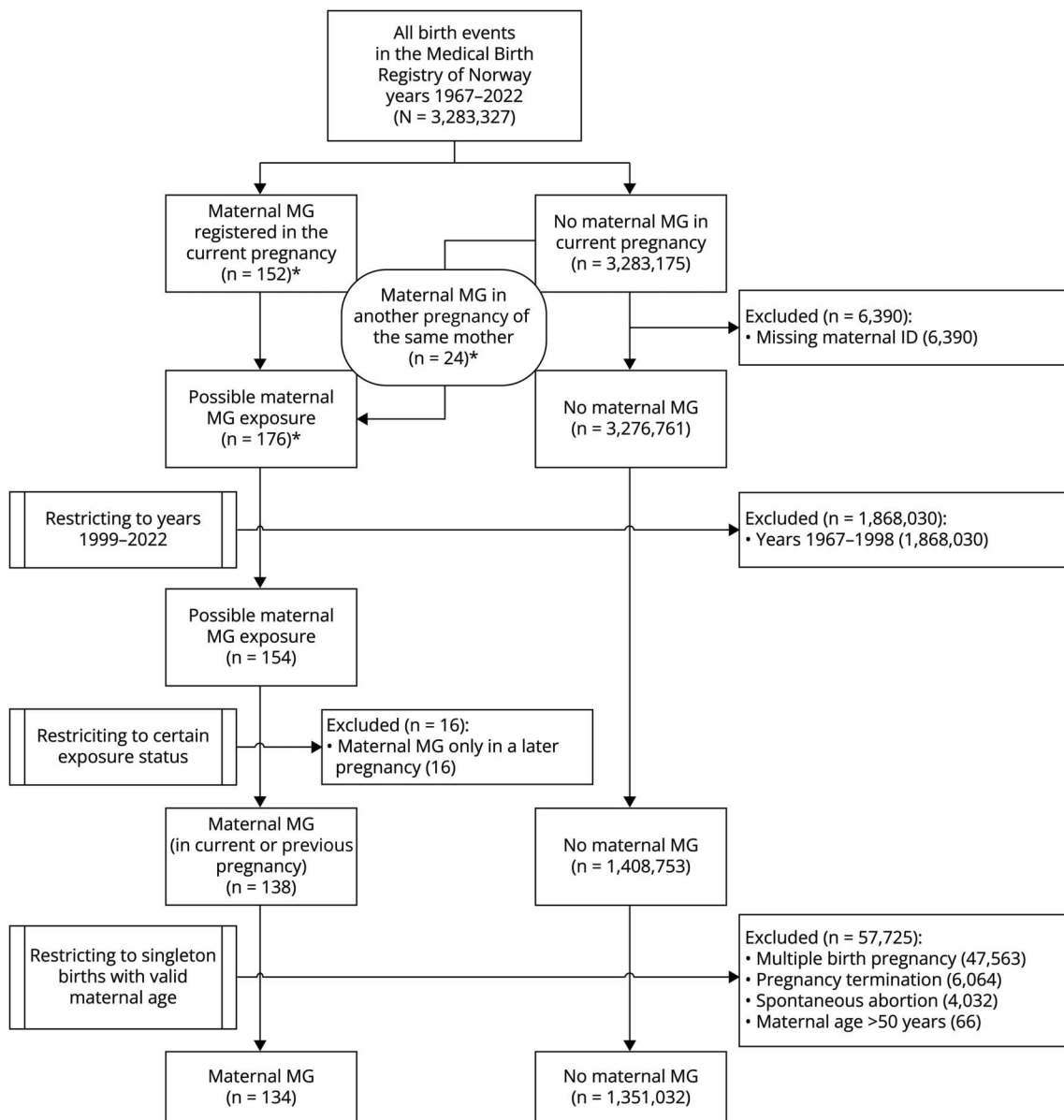
Study Design, Data Sources, and Setting

This was a population-based cohort study based solely on data from the Medical Birth Registry of Norway (MBRN),^{30,31} which is a mandatory health registry covering all pregnancies from gestational week 12 in Norway. We used data on maternal health from the inception of the registry in 1967 to inform about MG and thymectomy status in a previous pregnancy. Variables related to the current pregnancy included birth records starting from 1999. The birth notification form underwent an extensive update in late 1998.

The MBRN obtains information from several sources, linked by the unique personal identification number given to all residents in Norway at birth or immigration. Data on pregnancy course, maternal health, and socioeconomic status are collected by midwives and physicians during regular antenatal visits, offered free-of-charge to all residents of Norway. The mother can only opt out from sharing data on employment, smoking, and alcohol habits. All data are conveyed to the delivery institution, which is responsible for reporting the birth to the MBRN. The delivery institution adds information about the labor and the delivery, the child's and the mother's health after the delivery, and whether the child was transferred to a neonatal care unit. The MBRN receives additional data about the child's health from the neonatal unit after discharge. All congenital conditions diagnosed within 1 year from date of birth are reported to the MBRN since 2001. The MBRN is regularly checked against the National Population Registry and the Cause of Death Registry to update living status and emigration, without any upper age limit.

Study Population and Exposure Definition

We included all singleton births, live-born and stillborn, in the period 1999–2022 (Figure 1). A birth according to the MBRN is defined as gestational age ≥ 22 weeks, or birthweight ≥ 500 g, aligning with the definition by the World Health Organization.³²

Figure 1 Inclusion-Exclusion Flow Diagram of the Total Birth Cohort

*Identification of MG births before 1999 was incomplete.^{20,24} During 1967–1998, some MG diagnoses were recorded on the higher hierarchical level (ICD-8: 733) in addition to free-text specification on the original birth notifications, which we did not have access to. We used only the specific diagnostic code (ICD-10: G70.0, or ICD-8: 733.0 before 1999). We estimate that we captured around 30% of MG births before 1999.^{20,24} When available, information on mother's MG in a previous pregnancy was used to define our study population. MG = myasthenia gravis.

We excluded abortions and multiple birth pregnancies because data protection restrictions prevented us from reporting on small subgroups separately.

We operationally defined maternal MG as either a specific MG diagnosis (ICD-8 code: 733.0 for years 1967–1998, or ICD-10 code: G70.0 for years 1999–2022) or pyridostigmine use during pregnancy (Anatomical Therapeutic Chemical [ATC] code: N07A A02,³³ available since 1999), as it was recorded on the birth notification in the current or a previous pregnancy. Pyridostigmine is rarely used for other indications than MG,³⁴ especially during pregnancy. Only 1 MG birth was

included based on pyridostigmine use only. Maternal MG identified in 1 pregnancy was carried forward to all subsequent pregnancies of the same mother, linked by the mother's ID.

We excluded 16 births with “uncertain maternal MG exposure,” that is, births before the first record of maternal MG. The reference population comprised all singleton births of mothers without MG. We excluded 6,390 births with missing maternal ID number and 66 births with a maternal age registered as older than 50 years (all in the reference population).

Outcomes

Mode of Delivery

The primary outcome was the actual mode of delivery, categorized as C-section or vaginal delivery, elective C-section vs other delivery modes, emergency C-section vs vaginal delivery, and operative vaginal delivery vs all other births not delivered by elective or unspecified C-section.

We defined operative vaginal delivery as vaginal birth where vacuum or forceps was applied. Total use of vacuum/forceps (including instrumentally assisted vaginal deliveries converted into C-section) was included as a secondary outcome.

Secondary outcomes included C-section as the planned mode of delivery, regardless of the actual mode of delivery, and the initiation of the delivery, either prelabor C-section, spontaneous onset, or induction of labor. Prelabor C-sections included, but were not limited to, elective C-sections.

According to the MBRN, C-sections performed within 8 hours of decision making are classified as emergency and after 8 hours as elective. If urgency data are missing, a prelabor C-section that was planned before the delivery is also considered elective. Less than 1% of performed C-sections were unclassifiable.

We explored indications for MG C-sections post hoc using a combination of internal MBRN and ICD-10 codes, whenever available.

Other Outcomes

We included as secondary/exploratory outcomes all other adverse pregnancy, delivery, and neonatal outcomes available to us and of clinical interest. We did not include a statistical correction for multiple comparisons. Composite outcomes were predefined. Most rare secondary outcomes (with 0 or $n < 4$ in the MG group) and subcategories of composite outcomes are reported only in the supplementary material.

We included the following neonatal diagnoses from code strings: TNMG (ICD-10: P94.0), feeding problems (ICD-10: P92), congenital hypotonia (ICD-10: P94.2), AMC (ICD-10: Q74.3), musculoskeletal malformations (ICD-10: Q65–Q79), and major malformations (Q00.0–Q89.9 except Q17.0, Q38.1, Q53, Q65.0–Q65.6, Q82.5, Q86; a previously applied definition³⁵).

Preterm birth was defined as birth before 37 completed gestational weeks. We used the standard definition for low birthweight, that is, $<2,500$ g.³² Small for gestational age (SGA) was defined as a birthweight below the 10th percentile, that is, a sex-adjusted and age-adjusted Z-score <-1.282 . We defined prolonged hospitalization for the mother after the delivery as a longer length of stay than the median value in the whole cohort, that is, >3 days (mean 3.1, SD 1.8, range 0–98 days, skewness 10.9).

Episiotomies and perineal ruptures were counted among vaginal births. Slow progression of labor and the augmentation of contractions were counted among births with spontaneous or induced onset. The following interventions and complications were assessed stratified on the actual mode of delivery (C-section or vaginal): anesthesia, hemorrhage, and hospitalization of the mother.

Covariables

We included the following potential confounders in our main model: year of delivery, parity, mother's age at the time of delivery, mother's civil status, and autoimmune comorbidity. The prespecified autoimmune comorbidity score was based on the number (0–6) of recorded comorbid diseases among 6 common autoimmune diseases known to affect pregnancy: autoimmune thyroiditis (ICD-10: E06.3 or E03.9), inflammatory bowel disease (ICD-10: K50 or K51), systemic lupus erythematosus (ICD-10: M32), diabetes mellitus type 1, asthma, and rheumatoid arthritis (the last 3 included from checkboxes on the birth notification).

In addition to the main model, we ran a simple model including only the year of delivery, parity, and maternal age, and an extended model that also included mother's employment status and smoking status.

We identified use of immunosuppressants during pregnancy (prednisone [ATC-code: H02AB07], prednisolone [H02AB06], azathioprine [L04AX01], cyclosporine [L04AD01], tacrolimus [L04AD02], mycophenolate mofetil [L04AA06], methotrexate [L01BA01], cyclophosphamide [L01AA01], or rituximab [L01FA01]) but did not adjust for medication use because we lacked detailed information on dose, frequency, and timing.

Statistical Analysis

All MG births were compared with all non-MG births. Associations between maternal MG and birth outcomes were estimated by adjusted odds ratios (aORs) with 95% CIs using logistic regression. We present both unadjusted estimates, which describe the total effect of MG, and adjusted estimates, which approximate the “MG-specific risk.” Robust standard errors (Huber-White sandwich estimator) were used to correct for heteroskedasticity due to sibling dependencies. The main model included all selected covariables plus an interaction term of parity and maternal age (the Pearson correlation coefficient was 0.38).

To protect the anonymity of individual participants, we do not disclose nonmissing cell counts between 1 and 3; these are, therefore, reported as <4 . All analyses were performed in Stata version 18.5 for Windows (StataCorp LLC, College Station, TX).

In subanalyses, C-sections were counted within subgroups defined by the Robson-10 classification system (eFigure 1). Robson-10 is suggested as the global standard by the World Health Organization for assessing, monitoring, and comparing C-section rates within and between health care facilities.³⁶ This

tool creates 10 mutually exclusive birth strata with comparable baseline likelihood for C-section using 5 obstetric parameters in the following order: multiple birth pregnancy (not considered in this study), child's presentation at birth (normal cephalic, breech, or transverse), preterm birth <37 weeks (yes or no), previous delivery (yes or no), previous C-section (yes or no), and initiation of delivery (onset either by induction or prelabor C-section, or spontaneous). We report only crude counts and percentages and no tests of association because our study was not powered for subgroup analyses.

Handling of Missing Data

There were no missing values among included covariables in the main model. For the extended model, we performed both complete case analysis (excluding cases with missing values) and an analysis including separate categories for missing employment status and for missing smoking status.

Preterm birth was imputed when the length of gestation was missing (<5% of all cases) and the birthweight was <2,500 g, but ≥ 500 g. This applied to 0 of 2 MG births and 5,913 of 11,899 non-MG births. SGA was missing for 0.5% (2 MG births and 6,680 non-MG births) because of either missing gestational age, missing sex, or missing weight and considered invalid for 0.5% (0 MG births and 6,951 non-MG births) if the Z-score was ± 3 SD from null.

Standard Protocol Approvals, Registrations, and Patient Consents

This project was approved by the Regional Committee for Medical and Health Research Ethics (2018/2188), which waived the requirement for informed consent.

Data Availability

Application for individual-level data should be addressed to the National Service for Health-Data (helsedata.no) maintained by the Norwegian Directorate of eHealth.

Results

Cohort Characteristics

Our final cohort comprised 134 singleton MG births in 85 mothers with MG and 1,351,032 singleton non-MG births in 754,569 mothers without MG (Figure 1).

MG births differed from non-MG births on several important background characteristics (Table 1). Mothers with MG were on average 2 years older when giving birth and had more previous births, partly because we excluded 16 births that occurred before the mother had MG. Mothers with MG more frequently delivered at large hospitals. Assisted reproductive technology treatment was used in 6% ($n = 8/134$) of MG births, but only in 3% of non-MG births.

Among MG births, previous thymectomy was recorded in 17% ($n = 23/134$) and pyridostigmine was used in 37%.

Prednisolone/prednisone and azathioprine were the only immunosuppressants recorded, and either or both drugs were used in 18% ($n = 24/134$) of MG pregnancies. This included prednisolone in monotherapy ($n = 11/134$, 8%), azathioprine in monotherapy ($n = 10/134$, 7%), or the combination of prednisolone plus azathioprine ($n < 4/134$, <3%), with or without concomitant pyridostigmine use. Autoimmune comorbidities were common among mothers with MG, mainly related to autoimmune thyroid disease, asthma, and type 1 diabetes mellitus; 19% vs 8% had at least 1 autoimmune disease other than MG.

Mode of Delivery

The elective C-section rate was doubled in MG births compared with non-MG births, 11% vs 6% (aOR 1.81, 95% CI 1.05–3.12; Table 2). There were no differences in the rates of emergency C-section, 10% for both MG and non-MG births (aOR 0.92, 0.51–1.67), or of operative vaginal delivery, 12% vs 10% (aOR 1.26, 0.71–2.23). No instrumentally assisted MG deliveries were converted to C-section.

Induction of labor was more common in MG (26% vs 18%, aOR 1.53, 1.03–2.27), mainly related to increased prostaglandin use ($n = 22/114$, 19% vs 11%, aOR 1.79, 1.10–2.90; eTable 1).

The most frequently listed indications for MG C-sections were maternal request ($n = 5$) and the general condition/health status of the mother ($n = 4$). Other indications included threatening asphyxia ($n < 4$), prelabor rupture of membranes (PROMs) since >24 hours and failure to induce ($n < 4$), traumatic obstetric history ($n < 4$), and previous C-section ($n < 4$). In 11 cases, no specific indication was listed.

Adverse Pregnancy and Delivery Outcomes

Maternal MG was associated with increased odds of preterm PROM (PPROM; 4% vs 1%, aOR 2.79, 1.14–6.61; Table 3). We did not find an association between maternal MG and hypertensive pregnancy disorders overall, nor with preeclampsia. However, all MG preeclampsia cases ($n = 4/4$) were classified as severe (as opposed to mild or unspecified), whereas severe preeclampsia accounted for only 28% of all non-MG preeclampsia births (eTable 1).

MG was associated with an increased risk of episiotomy (28% vs 20%; aOR 1.60, 1.05–2.44), but no increased risk of severe perineal ruptures. Neuraxial anesthesia was more often applied in MG births compared with non-MG births when the delivery mode was vaginal (44% vs 33%; aOR 1.80, 1.23–2.63). Prolonged hospitalization was more common in mothers with MG, especially after vaginal delivery (35% vs 24%; aOR 1.85, 1.18–2.90).

Neonatal Outcomes

Maternal MG was associated with an increased risk of transferring the child to a neonatal care unit (37% vs 10%; aOR

Table 1 Clinical and Demographic Characteristics of Singleton Births in Norway (1999–2022) of Mothers With and Without MG		
	Maternal MG	No maternal MG
Total number	134	1,351,032
Year of delivery, n (%)		
1999–2003	30 (22.4)	278,585 (20.6)
2004–2008	25 (18.7)	283,504 (21.0)
2009–2013	33 (24.6)	295,852 (21.9)
2014–2018	24 (17.9)	282,627 (20.9)
2019–2022	22 (16.4)	210,464 (15.6)
Mother's age at time of delivery, y, median (IQR)	32.1 (5.8)	30.4 (7.0)
No. of previous deliveries, n (%)		
0	51 (38.1)	565,762 (41.9)
1	51 (38.1)	490,318 (36.3)
2 or more	32 (23.9)	294,952 (21.8)
No. of previous miscarriages/stillbirths, n (%)		
0	91 (67.9)	953,592 (70.6)
1	21 (15.7)	198,559 (14.7)
2 or more	7 (5.2)	79,630 (5.9)
Missing	15 (11.2)	119,251 (8.8)
Previous C-section, n (%)	10 (7.5)	124,227 (9.2)
Place of delivery (size of maternity clinic), n (%)		
1–1,499 deliveries per year	22 (16.4)	424,458 (31.4)
1,500–2,999 deliveries per year	49 (36.6)	352,267 (26.1)
3,000+ deliveries per year	62 (46.3)	562,502 (41.6)
Outside of institution/other/missing	1 (0.7)	11,805 (0.9)
Mother's civil status, n (%)		
Married/cohabitant	124 (92.5)	1,252,649 (92.7)
Other	10 (7.5)	98,383 (7.3)
Mother's employment status, n (%)		
Not employed	26 (19.4)	200,894 (14.9)
Employed, full-time or part-time	73 (54.5)	840,177 (62.2)
Missing	35 (26.1)	309,961 (22.9)
Smoking, n (%)		
No	92 (68.7)	986,481 (73.0)
Yes (before, during, or at the end of pregnancy)	18 (13.4)	181,475 (13.4)
Refused registration	19 (14.2)	163,317 (12.1)
Missing	5 (3.7)	19,759 (1.5)
Obesity (BMI ≥30 kg/m ²) before start of pregnancy, n (%)		
No	45 (33.6)	520,507 (38.5)

Continued

Table 1 Clinical and Demographic Characteristics of Singleton Births in Norway (1999–2022) of Mothers With and Without MG (continued)

	Maternal MG	No maternal MG
Yes	8 (6.0)	76,913 (5.7)
Missing^a	81 (60.4)	753,612 (55.8)
Gestational diabetes, n (%)	4 (3.0)	37,234 (2.8)
Pre-pregnancy hypertension, n (%)	0 (0.0)	7,555 (0.6)
Chronic renal disease (before pregnancy), n (%)	<4 (<3.0)	8,414 (0.6)
Autoimmune comorbidity, as a score, n (%)^b		
0	109 (81.3)	1,244,499 (92.1)
1	25 (18.7)	103,019 (7.6)
2 or more	0 (0.0)	3,514 (0.3)
Thymectomy (before pregnancy), n (%)^c	23 (17.2)	NA
Drug use in current pregnancy, n (%)		
Pyridostigmine	49 (36.8)	0 (0.0)
Prednisolone or prednisone	14 (10.5)	2,301 (0.2)
Azathioprine	12 (9.0)	985 (0.1)
Intravenous immunoglobulin	<4 (<3.0)	90 (0.0)
Assisted reproductive technology, n (%)	8 (6.0)	39,694 (2.9)
Child's presentation at birth, n (%)		
Cephalic, normal	121 (90.3)	1,221,463 (90.4)
Cephalic, abnormal	6 (4.5)	68,936 (5.1)
Breech	6 (4.5)	49,958 (3.7)
Transverse	0 (0.0)	4,220 (0.3)
Missing	1 (0.7)	4,273 (0.3)
Child's sex, n (%)		
Female	64 (47.8)	656,836 (48.6)
Male	70 (52.2)	694,124 (51.4)
Missing/uncertain/not specified	0 (0.0)	72 (0.0)

Abbreviations: ATC = Anatomical Therapeutic Chemical; BMI = body mass index; C-section = cesarean section; IQR = interquartile range; MBRN = Medical Birth Registry of Norway; MG = myasthenia gravis; N = number; NA = not applicable.

^a BMI was not included in the MBRN before 2008 and had a high rate of missing data until 2018 (>50% in 2009 and <10% only from year 2018 onward) with similar missingness patterns for both groups.

^b Number of autoimmune diagnoses other than MG, of 6 preselected disease groups: diabetes mellitus type 1 (tick box), asthma (tick box), rheumatoid arthritis (tick box), autoimmune thyroiditis (ICD-10: E06.3 or E03.9), inflammatory bowel disease (ICD-10: K51 Colitis Ulcerosa or K50 Crohn's disease), systemic lupus erythematosus (ICD-10: M32).

^c Thymectomy was identified in the variable "mother's health before pregnancy," and information on thymectomy was carried forward to all subsequent births from the first record. We used the Norwegian version of the NOMESCO Classification of Surgical Procedures code GEC to define thymectomy for years 1999–2022 and an internal MBRN code (M89) for years 1967–1998.

5.06, 3.57–7.16; Table 4). Among children of mothers with MG, 5 were diagnosed with TNMG (4%), most also transferred to a neonatal unit. Children of mothers with MG had an increased likelihood of unspecified feeding problems (aOR 4.86, 2.48–9.50) and congenital hypotonia (aOR 21.36, 2.98–153.24), issues that could indicate TNMG. All in all,

40% (n = 53/134) of MG-exposed children were either listed with a symptom diagnosis indicative of TNMG, diagnosed with TNMG, or transferred to a neonatal unit. Respiratory treatment was only needed by 3% (n = 4/134) of MG-exposed children, compared with 2% in the reference group (aOR 1.23, 0.45–3.32).

Table 2 Mode of Delivery in Singleton Births of Mothers With and Without MG

	Maternal MG, N (%)	No maternal MG, N (%)	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
C-section planned before the delivery^b	12/134 (9.0)	83,843/1,351,032 (6.2)	1.49 (0.82–2.69)	1.29 (0.72–2.33)
Initiation of delivery				
Prelabor C-section vs other	20/134 (14.9)	95,814/1,351,029 (7.1)	2.30 (1.43–3.70) ^c	1.98 (1.23–3.18) ^c
Induction vs other	35/134 (26.1)	244,239/1,351,029 (18.1)	1.60 (1.09–2.36) ^c	1.53 (1.03–2.27) ^c
Spontaneous vs other	79/134 (59.0)	1,010,976/1,351,029 (74.8)	0.48 (0.34–0.68) ^c	0.53 (0.37–0.74) ^c
C-section, performed				
Total	27/134 (20.1)	205,934/1,351,032 (15.2)	1.40 (0.92–2.14)	1.25 (0.82–1.89)
Elective C-section vs other	15/134 (11.2)	75,658/1,350,443 (5.6)	2.12 (1.24–3.63) ^c	1.81 (1.05–3.12) ^c
Emergency C-section vs vaginal delivery	12/119 (10.1)	129,687/1,274,785 (10.2)	0.99 (0.55–1.80)	0.92 (0.51–1.67)
Unspecified C-section vs other	0/134 (0.0)	589/1,351,032 (<0.1)	NA	NA
Vaginal delivery				
Total	107/134 (79.9)	1,145,098/1,351,032 (84.8)	0.71 (0.47–1.09)	0.80 (0.53–1.21)
Operative vaginal delivery vs non-operative vaginal or emergency C-section	14/119 (11.8)	125,150/1,274,785 (9.8)	1.22 (0.70–2.14)	1.26 (0.71–2.23)

Abbreviations: C-section = cesarean section; MG = myasthenia gravis; NA = not applicable; OR = odds ratio.
^a Adjusted for year of delivery (continuous), parity, maternal age (continuous), civil status, and autoimmune comorbidity (continuous).
^b We assumed “no” for cases with missing (43%).
^c Statistically significant at the 95% level.

Low birthweight was more frequent with maternal MG (8% vs 4%; aOR 2.42, 1.32–4.43). The rate of preterm birth was 8% in MG and 5% in non-MG births, which was not statistically significant (aOR 1.54, 0.83–2.85). Four children of mothers with MG had major congenital malformations (3%). This occurred in 3% of non-MG births. There were no skeletal malformations among MG births (eTable 2).

The simple and extended models gave similar estimates for all main and secondary outcomes (eTable 3).

Subanalyses

Most MG C-sections were performed in full-term nulliparous cephalic births with nonspontaneous onset (29.6% of all MG C-sections and 17.4% of all non-MG C-sections; Figure 2 and eTable 4), mainly driven by higher rates of prelabor C-sections rather than induction failures. Further main contributors to C-section in MG were preterm births (18.5% of MG vs 9.0% of non-MG C-sections) and births after previous C-section (22.2% of MG vs 24.8% of non-MG C-sections).

The crude C-section rate was higher in MG compared with non-MG within 4 Robson-10 subgroups (Figure 3), especially

if the mother had a previous C-section (75% vs 47%) or if the birth was preterm (50% vs 31%).

Discussion

In this nationwide MG birth cohort, elective C-section was twice as likely if the mother had MG. By contrast, the risk of acute operative delivery was similar for mothers with and without MG. The rate of diagnosed TNMG was only 4%, but 37% were transferred to a neonatal care unit and many newborns had symptoms that could signify undiagnosed TNMG. In addition, maternal MG was associated with an increased risk of induction, epidural/spinal anesthesia, episiotomy, PPRM, low birthweight, and prolonged hospitalization of the mother. All associations remained significant in confounder-adjusted analyses.

Most women with MG had uncomplicated nonoperative vaginal deliveries. The C-section rate in our cohort was low compared with other countries, both for MG births (20%)²² and overall (15%).³⁸ In Norway, C-section on maternal request is relatively restricted,³⁹ and C-section is generally not

Table 3 Adverse Pregnancy and Delivery Outcomes in Singleton Births of Mothers With and Without MG

	Maternal MG, N (%)	No maternal MG, N (%)	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Hypertensive disorder in pregnancy^b	8/134 (6.0)	67,061/1,351,032 (5.0)	1.22 (0.60–2.48)	1.16 (0.56–2.39)
Mother had infection during pregnancy	7/134 (5.2)	99,167/1,351,032 (7.3)	0.70 (0.33–1.49)	0.69 (0.32–1.48)
Vaginal bleeding during pregnancy	<4/134 (<3.0)	70,254/1,351,032 (5.2)	NA	0.40 (0.13–1.25)
Oligohydramnios vs other	4/134 (3.0)	41,821/1,351,032 (3.1)	0.96 (0.36–2.61)	0.96 (0.36–2.60)
Polyhydramnios vs other	<4/134 (<3.0)	16,952/1,351,032 (1.3)	NA	1.12 (0.28–4.57)
Prelabor rupture of membranes	19/134 (14.2)	207,226/1,351,032 (15.3)	0.91 (0.56–1.48)	0.89 (0.55–1.44)
Prelabor rupture of membranes >24 h before delivery	8/134 (6.0)	94,156/1,348,235 (7.0)	0.85 (0.41–1.73)	0.83 (0.40–1.69)
Preterm prelabor rupture of membranes	5/134 (3.7)	18,166/1,350,300 (1.3)	2.84 (1.16–6.95) ^e	2.74 (1.14–6.61) ^e
Augmentation of labor vs unaugmented progress of vaginal labor^c	33/114 (28.9)	396,388/1,255,215 (31.6)	0.88 (0.59–1.32)	0.88 (0.58–1.33)
Labor dystocia^c	6/114 (5.3)	99,680/1,255,215 (7.9)	0.64 (0.28–1.47)	0.62 (0.28–1.42)
Episiotomy^d	30/107 (28.0)	223,965/1,145,098 (19.6)	1.60 (1.05–2.44) ^e	1.82 (1.12–2.96) ^e
Perineal rupture, degree III–IV^d	<4/107 (<3.7)	29,790/1,145,098 (2.6)	NA	1.11 (0.34–3.60)
Neuraxial anesthesia (epidural or spinal) vs other or no anesthesia (any delivery mode)	69/134 (51.5)	556,236/1,351,032 (41.2)	1.52 (1.08–2.13) ^e	1.53 (1.09–2.13) ^e
Neuraxial anesthesia vs other or no anesthesia in vaginal delivery	47/107 (43.9)	374,151/1,145,098 (32.7)	1.61 (1.10–2.36) ^e	1.80 (1.23–2.63) ^e
General anesthesia vs other or no anesthesia (any delivery mode)	5/134 (3.7)	38,265/1,351,032 (2.8)	1.33 (0.54–3.25)	1.26 (0.52–3.09)
General anesthesia vs neuraxial anesthesia in C-sections	5/27 (18.5)	28,683/205,934 (13.9)	1.41 (0.53–3.71)	1.56 (0.58–4.18)
Prolonged hospitalization (>3 d vs ≤3 d), total	55/128 (43.0)	396,216/1,321,619 (30.0)	1.76 (1.24–2.50) ^e	1.83 (1.25–2.68) ^e
Prolonged hospitalization after vaginal delivery	35/101 (34.7)	268,185/1,120,913 (23.9)	1.69 (1.12–2.54) ^e	1.85 (1.18–2.90) ^e
Prolonged hospitalization after C-section	20/27 (74.1)	128,031/200,706 (63.8)	1.62 (0.69–3.84)	1.79 (0.65–4.97)

Abbreviations: C-section = cesarean section; MG = myasthenia gravis; NA = not applicable; OR = odds ratio.

^a Adjusted for year of delivery (continuous), parity, maternal age (continuous), civil status, and autoimmune comorbidity (continuous).

^b Any of the following: pregnancy-induced hypertension, preeclampsia, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). Subcategories are given in eTable 1.

^c Among births with spontaneous or induced onset of delivery (not prelabor C-section).

^d Among vaginal births only.

^e Statistically significant at the 95% level.

recommended after only 1 previous C-section.⁴⁰ We found an increased C-section rate in MG if the mother had a previous C-section. This suggests that there is a lower threshold for C-section if the mother has MG.

Preterm C-sections accounted for 19% of all MG C-sections, compared with only 9% in non-MG, although preterm births

were not significantly more common in MG overall (8% vs 5%). The higher preterm C-section rate in MG illustrates that maternal MG is an obstetric risk factor. This is supported by the increased risk of PPROM, low birthweight, and, possibly, severe preeclampsia. This is in agreement with some,^{20,41,42} but not all previous studies.^{25,26} PPROM could be related to the mother's disease because it has been associated with MG

Table 4 Adverse Neonatal Outcomes in Singleton Births of Mothers With and Without MG

	Maternal MG, N (%)	No maternal MG, N (%)	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Preterm birth (<37 wk)	11/134 (8.2)	70,703/1,351,029 (5.2)	1.62 (0.87–3.00)	1.54 (0.83–2.85)
Low birthweight (<2,500 g)	11/134 (8.2)	46,872/1,349,300 (3.5)	2.49 (1.34–4.61) [§]	2.42 (1.32–4.43) [§]
Small for gestational age ^b	16/132 (12.1)	108,401/1,337,401 (8.1)	1.56 (0.93–2.64)	1.58 (0.94–2.67)
Perinatal distress ^c	25/134 (18.7)	298,090/1,348,596 (22.1)	0.81 (0.52–1.25)	0.80 (0.52–1.24)
Stillborn	<4/134 (<3.0)	4,910/1,351,032 (0.4)	NA	1.93 (0.27–13.80)
CPAP treatment or mechanical ventilation	4/134 (3.0)	31,743/1,351,032 (2.3)	1.28 (0.47–3.46)	1.23 (0.45–3.32)
Respiratory distress syndrome	<4/134 (<3.0)	13,990/1,351,032 (1.0)	NA	1.38 (0.34–5.56)
Transferred to neonatal care unit ^d	49/134 (36.6)	132,886/1,351,032 (9.8)	5.28 (3.72–7.51) [§]	5.06 (3.57–7.16) [§]
Treated with systemic antibiotics	<4/134 (<3.0)	39,965/1,351,032 (3.0)	NA	0.72 (0.23–2.27)
Transient neonatal MG	5/134 (3.7)	NA	NA	NA
Congenital hypotonia	<4/134 (<3.0)	442/1,351,032 (0.0)	NA	21.36 (2.98–153.24) [§]
Feeding problems	10/134 (7.5)	21,803/1,351,032 (1.6)	4.92 (2.58–9.37) [§]	4.86 (2.48–9.50) [§]
Icterus, treated	13/134 (9.7)	82,117/1,351,032 (6.1)	1.66 (0.94–2.94)	1.60 (0.90–2.83)
Major congenital malformation ^e	4/134 (3.0)	38,865/1,351,032 (2.9)	1.04 (0.38–2.81)	1.00 (0.37–2.70)
Birth injury ^f	0/134 (0.0)	8,381/1,351,032 (0.6)	NA	NA

Abbreviations: CPAP = continuous positive airway pressure; MG = myasthenia gravis; NA = not applicable; OR = odds ratio

^a Adjusted for year of delivery (continuous), parity, maternal age (continuous), civil status, and autoimmune comorbidity (continuous).

^b Birthweight <10th percentile, sex-adjusted and (gestational) age-adjusted reference values (Z-scores).

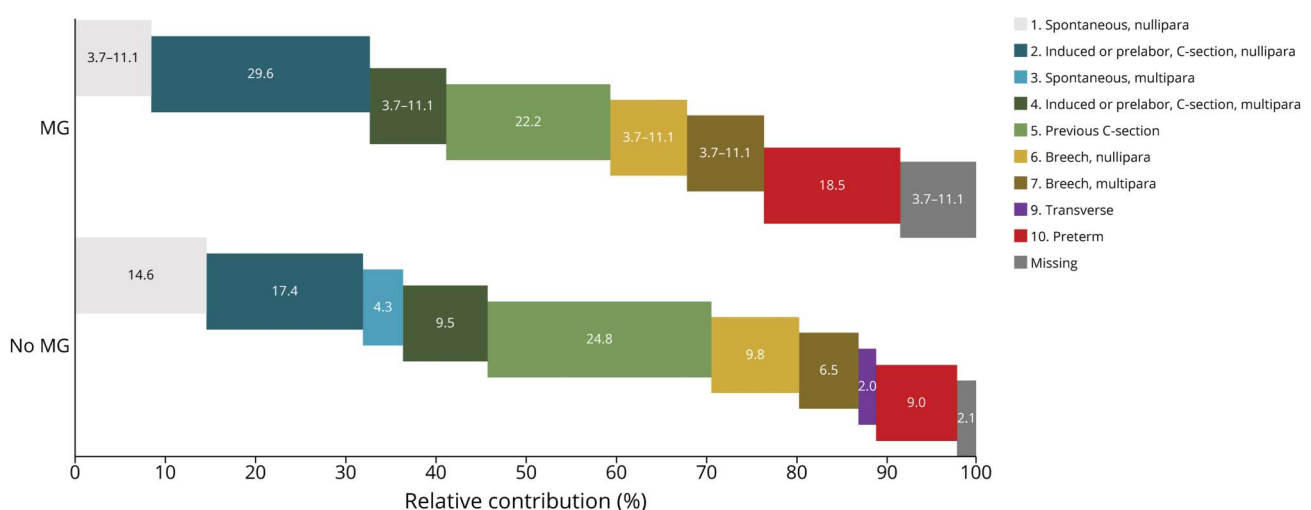
^c Composite variable of: Apgar score³⁷ <7 at 5 minutes, deranged umbilical blood-gas (pH <7), discolored amniotic fluid, or “threatening intrauterine asphyxia” recorded. Subcategories are given in eTable 2.

^d We assumed “no” for cases with missing (4%).

^e Q00.0–Q89.9, except: Q17.0, Q38.1, Q53, Q65.0–Q65.6, Q82.5, Q86 (as previously defined³⁵).

^f Any of the following: facial paresis, intracranial bleeding, plexus injury, fracture of the clavicle, any other fracture.

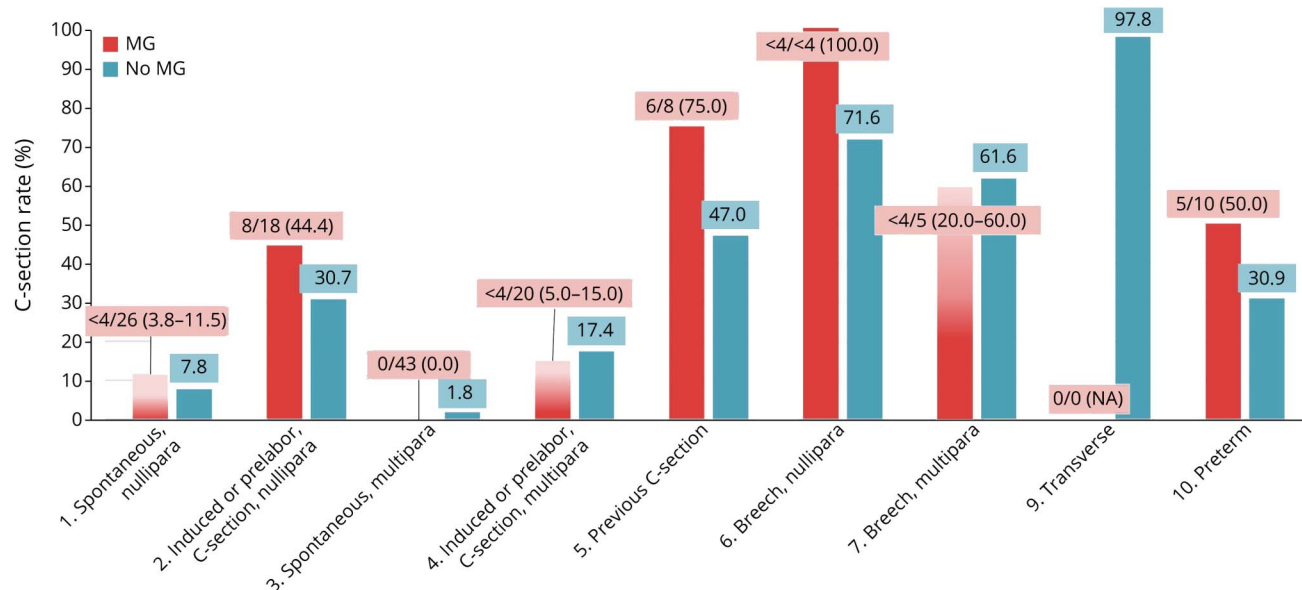
[§] Statistically significant at the 95% level.

Figure 2 Relative Contribution (%) of Each Robson-10 Subgroup to the Overall C-Section Rate

^a Robson-10 categories³⁶ are as follows: (1) No previous deliveries, singleton, normal cephalic, length of gestation ≥37 weeks, spontaneous onset of delivery.

(2) No previous deliveries, singleton, normal cephalic, length of gestation ≥37 weeks, initiation of delivery: induction or C-section. (3) One or more previous deliveries, no previous C-section, singleton, normal cephalic, length of gestation ≥37 weeks, spontaneous onset of delivery. (4) One or more previous deliveries, no previous C-section, singleton, normal cephalic, length of gestation ≥37 weeks, initiation of delivery: induction or C-section. (5) One or more previous deliveries, previous C-section, singleton, normal cephalic, length of gestation ≥37 weeks. (6) No previous deliveries, singleton, breech. (7) One or more previous deliveries, singleton, breech. (8) Multiple birth pregnancy (not included). (9) Singleton, transverse. (10) Singleton, normal cephalic, length of gestation <37 weeks (preterm birth). C-section = cesarean section; MG = myasthenia gravis.

Figure 3 Number of C-Sections by Total Number of Births and the C-Section Rate in Percentage Within Each Robson-10 Subgroup, by MG (in Red) and Non-MG Births (in Blue)



Robson-10 category was missing for <4 MG births. The C-section rate within the missing Robson category was 33.3%–100% in MG births and 36.1% in non-MG births. C-section = cesarean section; MG = myasthenia gravis.

deterioration,⁴³ or to MG medications. The cholinergic effect of pyridostigmine could trigger premature uterine contractions,¹ and in 1 study, PROM was more common in women who used corticosteroids.⁴²

Most MG C-sections were attributed to full-term nulliparous cephalic births with induction or prelabor C-section. This subgroup comprises births with a low baseline likelihood for C-section. C-sections performed on nonobstetric indications, such as at maternal request, typically account for most of the variation observed between different populations within this subgroup.⁴⁴ Mother's MG could also explain the higher C-section rate within this subgroup. On the contrary, obstetric reasons are possible, such as induction failure and severe preeclampsia. One-third of all MG C-sections in our cohort were explicitly performed on maternal request, or because of the mother's "general condition." This stands in contrast to current recommendations, stating that maternal MG in itself is not an indication for C-section and that C-section should be restricted to obstetric indications.^{4–6} Our findings show that elective C-section is often preferred in MG even in the absence of clear obstetric indications. This illustrates that there is a general concern that the mother, because of her MG, has a reduced capacity to achieve a successful vaginal delivery.

Adverse delivery outcomes were not more common in MG, apart from more episiotomies and prolonged hospital stays. This is consistent with other recent studies,^{21,25,26,45} although in stark contrast to many patients' and doctors' perceptions.^{17,46} It is important to note that the rates of acute

operative delivery were not increased in MG and no MG births were converted to C-section after instrumental assistance was applied. Our results reinforce current recommendations^{4–6} and support that vaginal delivery should be encouraged in MG when there are no clear indications for C-section. We consider vaginal delivery with early epidural application as a fair option to planned C-section in unclear cases.

The TNMG rate (4%) was lower than expected,¹⁴ although in line with previous registry-based studies.^{20,21} We suspect that the true TNMG rate was higher because many children were listed with feeding difficulty or hypotonia, symptoms that may indicate TNMG in children of mothers with MG.²¹ In a previous Norwegian MG birth cohort from 1967 to 2004, the TNMG rate was low when solely based on ICD codes but increased to 19% when additional information from hospital records were taken into account.²⁴ We believe that TNMG was both underdiagnosed and under-recognized in our cohort. The similar rates of prematurity, perinatal distress, birth injuries, and treatment with systemic antibiotics indirectly support that undiagnosed TNMG contributed to the increased frequency of transfers, although some children might have been transferred to a neonatal unit because of other reasons or for observation only. The MBRN does not record the reason for transfer. However, undiagnosed TNMG cases were likely mild or moderate because respiratory problems were rare, and no children died in the neonatal period.

There were no skeletal malformations, including no AMC cases in our MG cohort, in contrast to an earlier Norwegian cohort where AMC was observed in 2% of MG births.¹⁶ The

risk may have been reduced because of better disease control for MG mothers in recent years. However, our data set did not capture early pregnancy losses, and we did not include spontaneous and induced abortions, which are incompletely registered in the MBRN.

The strengths of our study included a large cohort and minimal selection bias as we used a nationwide mandatory health register. With the Norwegian ID number and deterministic sibling-linkage forwards and backwards in time, we ensured that all births were included from the first MG diagnosis in the MBRN. The likelihood for a false-positive MG diagnosis in the MBRN is very low. The positive predictive value was 99% in a previous study.²⁴ In that study, 90 individuals with MG were identified in the MBRN and contacted by mail, and 79 of 80 responders confirmed their MG diagnosis. The sensitivity for maternal diagnoses in the MBRN is generally good, being 90% for type 1 diabetes mellitus.⁴⁷ There is excellent agreement between mode of delivery and variables in the MBRN and medical records.^{24,48} We were able to account for a set of relevant confounders, and we took into account obstetric risk factors by stratifying births into Robson-10 subgroups. While Robson-10 subgroupings can indicate the reason for C-section, Robson-10 is not a tool for selecting patients for C-section in the clinic.

Limitations included a lack of clinical information on MG subtype, disease severity, and medication dose and timing. There was incomplete registration of C-section indications. Despite including data from the whole country over a period of almost 25 years, we still lacked power for rare outcomes such as preterm birth, preeclampsia, major malformations, and stillbirth. Our birth cohort might not be generalizable to all MG pregnancies. Spontaneous and induced abortions were not included, and this may be associated with more severe MG. Women with less severe MG could be overrepresented because they are more likely to contribute several births, and we counted births instead of women. Thus, our results might be more representative of women with well-controlled MG. The observed prevalence of MG among mothers in our cohort (11 per 100,000 [85/754,569]) was lower than the overall MG prevalence in women of childbearing age, between 12 and 22 per 100,000, based on a recent study from Nordic countries.⁴⁹ This illustrates that many women with MG remain childless, and they tend to have fewer children than non-MG women. In a previous survey, over 50% of women with MG reported that they had abstained from pregnancy because of MG.¹⁷ MG medication use in pregnancy was lower than expected,^{17,21,24} which could indicate that the women in our study represented a healthier subpopulation of women with MG. On the other hand, medication use may be underreported in the MBRN, especially nonregular medication use and medications discontinued in early pregnancy. A validation study using prescription registry data suggested that the positive predictive value was >80% in the MBRN but sensitivity was below 50%.⁵⁰ The prescription registry captures medications dispensed at pharmacies while MBRN data reflect what the patient reported during prenatal

visits, which may better illustrate actual intake during pregnancy. Our estimates for adverse vaginal delivery outcomes could be biased toward the null, as prelabor C-section represents a competing risk and this was more common in MG. However, the magnitude of this bias should be low, thanks to the low overall C-section rate in our population.

In conclusion, most women with MG can have uncomplicated vaginal deliveries. The risks of emergency C-sections and operative vaginal deliveries are similar to those in the general population. The increased likelihood for planned C-section and induction suggests that MG births are managed proactively in Norway. Contrary to current recommendations, one-third of MG C-sections were performed at the mother's request or because of her medical condition. Adverse neonatal outcomes were generally not increased, except for an increased risk of PPRM and low birthweight. The TNMG rate was lower than expected (4%), respiratory problems were rare, and there were no skeletal malformations. However, we believe that TNMG was under-recognized because 40% of children of mothers with MG had hypotonia and feeding problems or required care in a neonatal unit. This highlights the need to increase awareness and general knowledge of TNMG among health care providers caring for women with MG and their newborns.

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Author Contributions

J.L.V. Lindroos: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M.-H. Bjørk: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J.M. Cohen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. K.C. Danielsson: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. O. Hikmat: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. J.M. Hoff: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. N.E. Gilhus: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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