The German Multiple Sclerosis and Pregnancy Registry: rationale, objective, design, and first results

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Abstract

Objectives: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) predominantly affect women of reproductive age. During the last few decades many disease-modifying therapies (DMTs) have been approved. It is therefore important to provide epidemiological structures for the collection of safety information on exposed pregnancies. Data on disease activity after withdrawal of DMTs are in high demand especially as severe relapses have been described after ceasing highly effective DMTs. Although breastfeeding is recommended, it is still unclear if the early reintroduction, especially of highly effective DMTs, has a beneficial effect on postpartum relapse risk or a combination of both, however safety data are lacking.

Methods: The German MS and Pregnancy Registry (DMSKW) is a nationwide, observational, cohort study of pregnant women with MS or NMOSD, founded in 2006. As the study procedure has undergone important adaptation in recent years, described here is the updated methodology including data source and acquisition as well as variables collected within the DMSKW.

Results: As of December 2020, the DMSKW database comprises 2579 pregnancies, 2568 with MS and 11 with NMOSD. Women are enrolled at a median gestational week of 11 (range: 0.02–42.1), have a median postpartum follow up of 1.2 years (range: 0–9.2) with 76% of all pregnancies being exposed to a DMT, mostly in the first trimester. Spontaneous abortion and preterm birth occurred in 7% and 10%, respectively; 19% of all women suffered from at least one relapse during pregnancy, with a minimum of 6% during the third trimester of pregnancy.

Conclusion: The DMSKW is a valuable structure in providing safety data on drug exposure during pregnancy and lactation in combination with information on disease activity up to 6 years postpartum. This article will be the reference for describing the methods of future publications from the DMSKW.

Keywords: breastfeeding, child development, disease-modifying therapies, multiple sclerosis, pregnancy

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system. Approximately more than 2 million people world-wide are affected by MS. Initial symptoms usually appear between the age of 20 and 40, with an increasing incidence in females,[1] therefore mostly young women of reproductive age suffer from MS.

In the last two decades, relapsing remitting MS (RRMS) has become a treatable disease and numerous disease-modifying therapies (DMT) have been approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or are under investigation in clinical trials. As women are in general advised to use efficient contraception while on DMTs during clinical trials and also after market introduction,

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only limited data are available concerning risks to the fetus or child with DMT exposure during pregnancy and lactation. In accordance with the EMA Guideline on risk assessment of medical products on human reproduction and lactation, at least 300, optimally 1000, prospective first trimester exposed pregnancies are required to assess the safety of these treatments.[2] No DMT is approved for use during pregnancy or lactation without restrictions, most are even contraindicated. Only interferon-β has approval for treatment during lactation.[3]

Sufficient case numbers for assessing safety are only available for substances with many years of experience, such as interferon-β[4] and glatiramer acetate.[5] Data on more than 300 first trimester exposed pregnancies could so far only be collected for natalizumab[6] and fingolimod.[7] Particularly for newer substances such as alemtuzumab, ocrelizumab, or cladribine as well as recently approved drugs (siponimod, ozanimod, ofatumumab), sufficient experience for evaluating the safety of exposure during pregnancy is lacking.

Available data often stem from accidental pregnancies in pivotal studies, small case reports, or case series. However, the study design with the highest evidence level, the randomized clinical trial, is difficult to perform with pregnant women for ethical reasons, therefore prospective cohort studies or high-quality registries with a close-meshed, longitudinal data collection are the best realistic real-world option for acquiring safety data during pregnancy, lactation, and long-term follow-up.[8]

Besides safety aspects, disease activity and disability during pregnancy and postpartum as well as the identification of predictors of severe relapses are also important. The typical disease course in DMT unexposed pregnancies, with a reduced relapse rate during the third trimester and a significant increase during the first 6 months postpartum,[9] is meanwhile well known and repeatedly and reproducibly proven.[10,11] However, recently published data demonstrated no increase in postpartum relapse rate in women with mild to moderate disease activity and a DMT treatment rate of 41.2%.[12] The impact of DMTs, especially the withdrawal of DMTs prior to conception, on disease activity and maternal disability risk during pregnancy and postpartum has not yet been

sufficiently investigated. Case reports and small case series describe severe rebound relapses after withdrawal of natalizumab[13,14] or fingolimod,[15] even during pregnancy.[16,17] Whether this can be prevented by bridging with basic DMTs and what potential advantages cycling DMTs, like alemtuzumab, ocrelizumab, or cladribine, could have are still uncertain.

Some studies have also shown that DMTs before conception reduced the relapse risk during the first 3 months postpartum.[18–20] Whether breastfeeding can reduce the postpartum relapse risk as well, has been controversially discussed,[18,21–23] although a recent meta-analysis confirms the protective effect.[24] Moreover, breastfeeding may not be sufficient to protect women with active disease from postpartum relapses, and DMT restart may be required, however valid safety data are missing.[25] This reinforces the importance of lactation studies in order to determine breast milk transfer and support women to breastfeed safely while being treated for MS.

The best management strategies for women desiring to become pregnant, especially in the era of highly effective DMTs, still need to be investigated. Therefore, with each novel DMT new challenges await neurologists and patients, namely the best procedure for minimizing risks for mothers (concerning disease activity and disability) while ensuring the health of the newborns and children.

Therefore, the German Multiple Sclerosis and Pregnancy Registry (Deutsches Multiple Sklerose und Kinderwunschregister; DMSKW) was established in 2006, as a nationwide monocentric observational cohort study for pregnant women with MS. In 2012, after several case reports and case series,[14,16,26–34] the first original publication with 335 pregnancies, 119 exposed to basic DMTs and 216 unexposed pregnancies,[18] mainly focusing on the impact of basic DMT exposure at conception and exclusive breastfeeding on relapse rates during pregnancy and postpartum was published. As many important and practice-relevant findings were able to be obtained over the years, objectives have been adapted as new DMTs have been approved.

Since then, data acquisition was improved and adapted and women with neuromyelitis optica spectrum disorders (NMOSD)[35] were included,

as well as questionnaires to measure the Expanded Disability Status Scale (EDSS)[36] and developmental delays.[37] The follow-up period was also extended to up to 6 years for live births and up to 6 months for miscarriages. Thus, aiming to provide a comprehensive advisory basis for treating neurologists, MS/NMOSD-patients and their partners, from the desire to have children up to kindergarten age.

The methodology of the DMSKW is described in this article as a reference for further publications.

Objectives and updated methodology

German Multiple Sclerosis and Pregnancy Registry

The DMSKW was founded in 2006 for pregnant women with MS. It is a nationwide monocentric observational cohort study and meanwhile one of the largest MS and pregnancy registries worldwide. It is a real-world data collection, with and without DMT treatment, and allows the prospective and longitudinal follow-up of maternal disease activity, pregnancy outcomes, and child development along with perceptions regarding fertility, breastfeeding behavior, and measurement of DMT concentrations in serum and breastmilk.

The DMSKW is approved by the local institutional review board of the Ruhr-University Bochum (Registration Number: 18-6474-BR) and all patients give their informed consent.

Rationale and objectives

Primary objectives of the DMSKW are

- To determine the impact of DMT exposure during pregnancy on pregnancy outcomes;
- To determine the impact of DMT exposure during pregnancy or breastfeeding on child development up to kindergarten age;
- To determine the impact of DMT exposure prior to, during, and after pregnancy on MS disease activity and disability.

Further secondary objectives are

- To determine the prevalence of vaccinations during pregnancy in women with MS/NMOSD and their offspring;

- To determine the fertility of MS/NMOSD-women;
- To determine the impact of assisted reproductive technology (ART) on MS/NMOSD disease activity;
- To determine the excretion of DMTs into human breastmilk;
- To identify predictors that impact MS/NMOSD disease activity and disability progression;
- To evaluate the pregnancy and disease course in women with NMOSD;

Methods

Population. Women from all over Germany and few from other German speaking countries can enrol in the registry (Figure 1). As the DMSKW is meanwhile well established, two thirds of the participants are recruited through recommendations either by their treating neurologists or MS-nurses. The remaining one third is recruited via advertisements on the DMSKW website, patient recommendations, or in online seminars which are offered regularly nationwide in cooperation with the national MS society (DMSG).

To be eligible to participate in the registry, candidates must meet the following eligibility criteria:

- Ability to understand the purpose of the registry;
- Provide informed consent;
- Self-reported MS [clinical isolated syndrome (CIS), RRMS, primary progressive MS (PPMS), and secondary progressive MS (SPMS) diagnosis according to the current MS criteria[38] or self-reported NMOSD[39]];
- Self-reported, ongoing, and intact pregnancy at the time of enrollment

Candidates will be excluded from study entry if any of the following exclusion criteria exist:

- Unable or unwilling to provide informed consent.

Data acquisition/data source. Data are generated in telephone interviews with a standardized questionnaire. Interviews are conducted by research assistants and study nurses with basic training and who are regularly trained in all affairs of the DMSKW study procedures, in MS disease treatment, etiology, and mechanisms, concerning
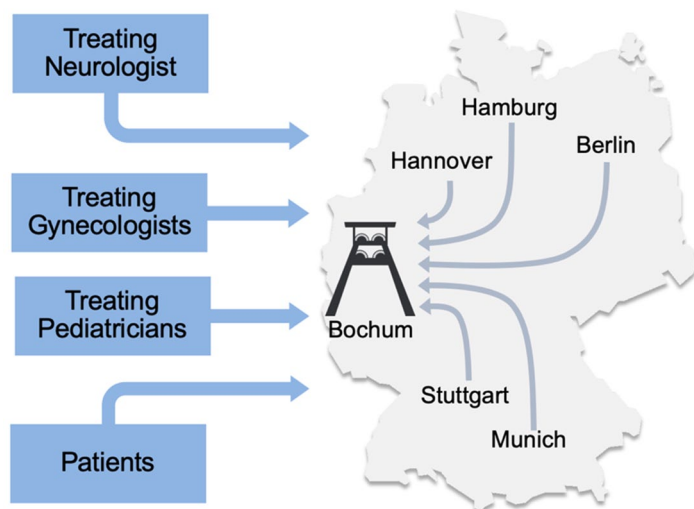
Figure 1. Recruitment and data acquisition from all over Germany in the German Multiple Sclerosis and Pregnancy Registry.
Cities shown in this figure are examples. Women are recruited all over Germany.

can be classified as prospective or retrospective depending on the outcome of interest. However, some data sets are classified as retrospective, if the main outcome defined for a specific objective was known at enrolment. This is the case, for example, if a woman contacted the DMSKW due to a relapse during pregnancy or if a woman was enrolled due to a rare event (immunoadsorption/plasmapheresis during pregnancy, deciding to breastfeed with DMT exposure). Solely reported malformations, developmental delays or other negative pregnancy outcomes without a further rare event do not lead to retrospective enrollment.

Participants are contacted in every remaining trimester during pregnancy after enrolment, in month 2 and 6 after delivery and yearly around the child's birthday up to 6 years postpartum (Figure 2). In the case of abortion or stillbirth, patients are contacted after 3 months and 6 months. If a further pregnancy occurs, it will also be registered and followed up, assuming the mother's consent.

Besides baseline characteristics, a detailed history of MS is obtained along with data on exposure to medications and potential confounders. Follow-up interviews gather further information on the state of pregnancy and delivery, any alteration in disease activity, outcome of pregnancy, medication, breastfeeding habits, and well-being of the child.

pharmacovigilance and the reporting of Serious Adverse Events (SAEs), in Good Clinical Practice (GCP) compliant working and regarding the actually applicable data protection laws (Federal Data Protection Act DSGVO).

All pregnancies are followed prospectively. With the exact date of enrollment into the registry, pregnancies
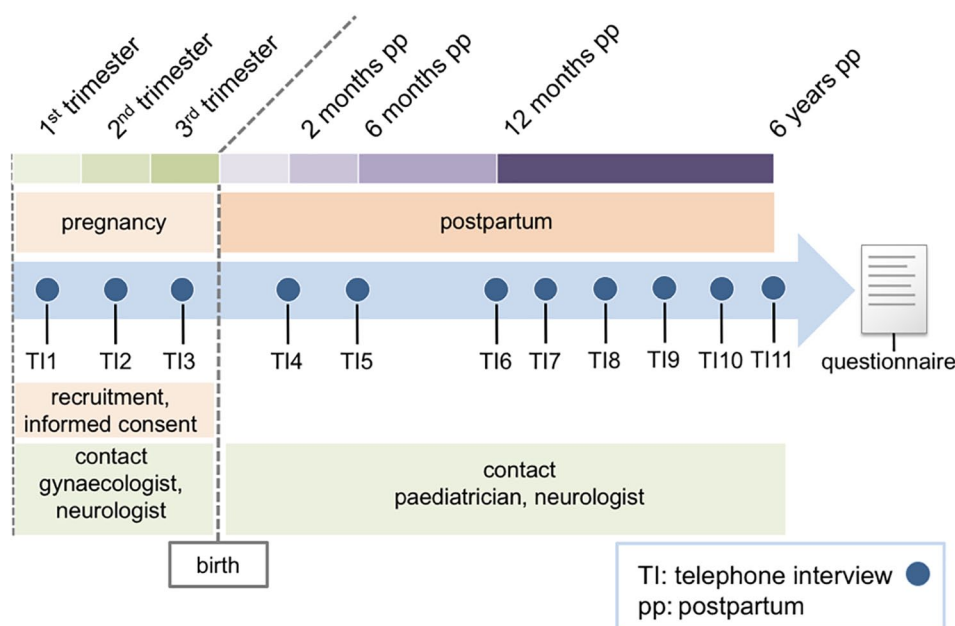

Figure 2. Timeline of data acquisition in the German Multiple Sclerosis and Pregnancy Registry.

Pregnancy complications and child outcomes such as length, weight, head circumference, and documented anomalies are additionally taken from official medical documents such as the maternity log (Mutterpass),[40,41] the children's medical check-up booklet (Kinderuntersuchungsheft),[42] and the vaccination card, if available. In Germany every woman receives a maternity log from the gynecologist when a pregnancy is confirmed. Therein, all gynecological and other relevant examinations, tests, and hospitalizations are documented by the gynecologist during the entire pregnancy. In the children's medical check-up booklet, provided for every child after birth, the pediatrician tracks the health condition, body measurements, any anomaly, and development in regular intervals from birth up to the age of 17. In the children's vaccination card, all vaccinations are documented. Copies of the medical check-up booklet and vaccination card are gathered as a medical verification, if possible, in every case where developmental delay, malformations, or other abnormalities are reported and in as many cases as possible to verify the body measurements and vaccinations up to the age of 6.

Six important milestones of interest for the first year of life (turning to voices, reaching for objects, rolling over, sitting without support, first words, and standing alone) based on gross motor, fine motor adaptive and language items of the Denver Developmental Screening Test[43] are chosen to further assess child development. Age when reaching developmental milestones is documented in months.

In addition, two established questionnaires have been included in the standardized questionnaire of the DMSKW: (1) a for Germany validated early child development questionnaire ('landmarks of development' from Michaelis)[37] is used to detect developmental delays (considers the five domains of child development: physical motor function, motor function of fingers and hands, cognitive development, language development, and social competence) and (2) the EDSS is used as a marker for disability and is determined via the tele-EDSS using a modified questionnaire according to Lechner-Scott.[36]

As data are recorded in close cooperation with treating physicians (Figure 1), data sources also include hospital discharge reports, clinical records, and physicians' letters. Treating physicians are requested to answer a verification questionnaire in any case of complications (e.g. severe relapses and malformations) during pregnancy and the follow-up period (Table 1). All documented congenital abnormalities are evaluated and classified according to the guidelines of the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects[44] and the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)[45] by a teratologist from the Mainz births registry.

Adjustment of data acquisition over the years. Over the years, the DMSKW questionnaire has been repeatedly improved and adapted to new research questions and projects. As the effect of MS and/or DMTs on fertility is poorly investigated,[46,47] a fertility questionnaire for the subgroup of women, who achieved pregnancy with ARTs, was launched in 2013.

Since 2014, NMOSD diagnosis has been included in the inclusion criteria as a separate disease entity, also affecting mostly young women of reproductive age.[48]

In 2017, the child development sub-study was started and the postpartum follow up extended from 2 years to 6 years. The questionnaire 'landmarks of development' from Michaelis as an instrument for evaluating developmental delays[37] was also included. In order to capture patient reported markers of disability, the teleEDSS[36] was also included systematically in 2017, to compare disease activity and disability over the follow up time of six years.

An unavailability of young mothers during the first 6 weeks postpartum was recognized, therefore, the interview scheme was changed from 1 month, 3 months and 6 months to 2 months and 6 months after delivery as of 2019. Interviews at 3 months and 6 months were also introduced in cases where pregnancies do not result in live births.

Operational definitions and study endpoints. Table 2 provides an overview of all operational definitions and study endpoints used for data analysis in the DMSKW. One of the most important dates for analysis is the last menstrual period (LMP), therefore, it is checked for plausibility based on the calculated due date and gestational week at delivery. If the minimal data set (Table 2) is not fulfilled, the data set is not entered in statistical analysis.

Table 1. Recorded variables and data source.

Variable	Operational definition	Data source	Interview
Baseline characteristics			
Enrollment	Date of entry into the cohort	PRO measurement	Enrollment
LMP	First date of the last menstrual period prior to pregnancy according to the documentation in the maternity log	PRO measurement and in addition, if available, maternity log	
Expected date of delivery	Calculated due date according to the documentation in the maternity log	PRO measurement and in addition, if available, maternity log	
Age	Age at conception calculated from date of birth and LMP	PRO measurement	
BMI	BMI at conception calculated from body weight at conception and body length	PRO measurement	
Gestational age	GW at enrollment calculated from LMP and date of entry into the cohort	PRO measurement and in addition, if available, maternity log	
Inclusion criteria			
Diagnosis	Date of MS/NMOSD diagnosis	PRO measurement and in addition, if available, medical record	Enrollment
Pregnancy status	Ongoing pregnancy according to the documentation in the maternity log	PRO measurement and in addition, if available, maternity log	
Potential confounder			
Drug exposure	Type, doses, periods, and indication of any administration of a medical drug including folic acid and vitamin D during the last 8 weeks prior to pregnancy	PRO measurement and in addition, if available, medical record	Enrollment
Tobacco abuse	Date, dose, and frequency of former or ongoing tobacco use including e-cigarettes and shisha at the time of enrollment	PRO measurement	
Alcohol abuse	Date, dose, and frequency of former or ongoing alcohol use at the time of enrollment	PRO measurement	
Drug abuse	Type, date, dose, and frequency of former or ongoing illegal drug use at the time of enrollment	PRO measurement	
Caffeine use	Dose and frequency of ongoing caffeine use at the time of enrollment	PRO measurement	
Infertility treatment	Type, dates, and doses of any administration of a medical drug as well as date and type of any invasive treatment accompanied with an infertility treatment according to the stimulation protocol	PRO measurement and in addition, if available, medical record and IVF stimulation protocol	
Socioeconomic status			
Marital status	Categories: married, steady partnership, single, divorced, widowed	PRO measurement	Enrollment
School education	Categories: without school diploma, secondary school diploma, high-school diploma	PRO measurement	
Occupational activity	Categories: without vocational training, apprentice, completed vocational training, student, university degree	PRO measurement	

(Continued)

Table 1. (Continued)

Variable	Operational definition	Data source	Interview
Medical history			
MS disease duration	Disease duration at conception calculated from date of diagnosis and LMP	PRO measurement and in addition, if available, medical record	Enrollment
MS disease activity	Number of all former relapses. Date and treatment of all relapses during the last 2 years prior to pregnancy, during the last year prior to a highly effective DMT treatment and during a highly effective DMT treatment. Former IA/PLEX treatments prior to pregnancy. Date and Lesion of the last MRI prior to pregnancy. EDSS prior to pregnancy	PRO measurement, Tele-EDSS and in addition, if available, medical record	
DMTs	Type, doses, period, and reason of discontinuation of all former DMTs prior to pregnancy. Type, doses, period, and exact date of discontinuation of the DMT at LMP	PRO measurement and in addition, if available, medical record	
Symptomatic MS treatment	Type, dose, period, reason for therapy, and reason for discontinuation of all former and ongoing symptomatic MS treatments	PRO measurement and in addition, if available, medical record	
Co-morbidities	Type, date of onset, and date of recovery of other diseases accept of MS	PRO measurement and in addition, if available, medical record	
Family history			
Chronic diseases	Type and date of onset of chronic diseases of the child's father	PRO measurement	Enrollment
Former pregnancies	Date, course and outcome of all former pregnancies of the mother. Births defects, developmental delays, ADHS, autism, disability, or other serious disorders and chronic diseases of the older siblings	PRO measurement	
Negative pregnancy outcomes	Birth defects, miscarriage, preterm birth, chromosomal abnormalities, developmental delay among parents and siblings, including child's father parents and siblings	PRO measurement	
Pregnancy course			
Prenatal examinations	Any prenatal diagnostic test performed prior to enrollment or anytime during pregnancy. Ultrasound level 1, Ultrasound level 2, nuchal scan, serological tests for chromosomal abnormalities (e.g. triple test), amniocentesis, chorionic villus sampling, glucose tolerance test	PRO measurement and in addition, if available, maternity log and medical record	First trimester Second trimester Third trimester 2 months pp
Pregnancy complications	Type, date, and therapy of any pregnancy complication including infections, preeclampsia/eclampsia, and gestational diabetes	PRO measurement and in addition, if available, maternity log and medical record	
Drug exposure	Type, doses, periods, and indication of any administration of a medical drug including folic acid, vitamin D and vaccinations during pregnancy	PRO measurement	
Tobacco abuse	Date, dose, and frequency of tobacco use including e-cigarettes and shisha during pregnancy	PRO measurement	
Alcohol abuse	Date, dose, and frequency of alcohol use during pregnancy	PRO measurement	
Drug abuse	Type, date, dose, and frequency of illegal drug use during pregnancy	PRO measurement	
Caffeine use	Dose and frequency of caffeine use during pregnancy	PRO measurement	

(Continued)

Table 1. (Continued)

Variable	Operational definition	Data source	Interview
Maternal death	Death of the mother up to 6 years postpartum	If available, medical records	
Maternal weight	Maternal pre-delivery body weight in kg	PRO measurement and in addition, if available, maternity log	2 months pp
Disease activity during pregnancy			
Relapses	Date, symptoms, and therapy of relapses during pregnancy	PRO measurement and in addition, if available, medical records	First trimester Second trimester Third trimester 2 months pp
Corticosteroid exposure	Type, dose, period, and type and number of times administered during pregnancy	PRO measurement and in addition, if available, medical records	
IA/PLEX	Type, period, and number of cycles during pregnancy	PRO measurement and in addition, if available, medical records	
MRI	Date, use of imaging agent, new and enhancing lesions during pregnancy	PRO measurement and in addition, if available, medical records	
EDSS	EDSS during first and third trimesters of pregnancy and in case of relapses during pregnancy	Tele-EDSS and in addition, if available, medical records	
DMTs	Type, doses, period, and exact date of discontinuation of all DMTs during pregnancy	PRO measurement and in addition, if available, medical records	
Pregnancy outcome			
Outcome of pregnancy	Date and gestational age of spontaneous abortion, extrauterine gravidity, elective abortion (medical and social indication), stillbirth, preterm, and full-term live birth	PRO measurement and in addition, if available, medical records, maternity log, and medical check-up booklet	2 months pp
Newborn body measurement characteristics	Birth weight, birth length, head circumference at birth, sex, Apgar score	PRO measurement and in addition, if available, maternity log, and medical check-up booklet	
Mode of delivery	Vaginal delivery (spontaneous/induced, vacuum/forceps extraction); cesarean section (elective/urgent/emergency)	PRO measurement and in addition, if available, maternity log	
Birth complications	Type of any maternal or fetal complication during delivery	PRO measurement and in addition, if available, maternity log, and medical records	
Wellbeing of the child	Period of hospitalization and therapy of any infection, neonatal jaundice, below standard weight, adaptation disorder during the first 8 weeks postpartum. Type, dose, period, and indication of medical drug application during the first 8 weeks postpartum. Indication, period and therapy of hospitalizations during the first 8 weeks postpartum. Death during the first 8 weeks postpartum	PRO measurement and in addition, if available, maternity log, and medical check-up booklet	

(Continued)

Table 1. (Continued)

Variable	Operational definition	Data source	Interview
Congenital abnormalities	Type, date, and therapy of any suspicion of a major or minor structural birth defect in pregnancies ending in a live born infant or in pregnancy loss	PRO measurement and in addition, if available, maternity log, medical check-up booklet, and medical records	
Breastfeeding			
Type of breastfeeding	Categories: no breastfeeding, exclusive breastfeeding, non-exclusive breastfeeding	PRO measurement	2 months pp[a] 6 months pp[a] 12 months pp[a] 2 years pp[a] 3 years pp[a] 4 years pp[a] 5 years pp[a] 6 years pp[a]
Supplemental feeding	Date of introduction of first supplemental feeding, date and reason for weaning	PRO measurement	
Menstruation	Date of first menstruation postpartum	PRO measurement	
Drug exposure	Type, dose, period, indication, and period of restriction of any medical drug application during lactation	PRO measurement and in addition, if available, medical records	
Disease activity postpartum			
Relapses	Date, symptoms, and therapy of relapses up to 6 years postpartum	PRO measurement and in addition, if available, medical records	2 months pp 6 months pp 12 months pp 2 years pp 3 years pp 4 years pp 5 years pp 6 years pp
Corticosteroid exposure	Type, dose, period, and type and number of times administered up to 6 years postpartum	PRO measurement and in addition, if available, medical records	
IA/PLEX	Type, period, and number of cycles up to 6 years postpartum	PRO measurement and in addition, if available, medical records	
MRI	Date, use of imaging agent, and new lesions up to 6 years postpartum	PRO measurement and in addition, if available, medical records	
EDSS	EDSS in case of relapses during the first year postpartum and once a year up to 6 years postpartum	Tele-EDSS and in addition, if available, medical records	
DMTs	Type, doses, period, and reason for discontinuation of all DMTs up to 6 years postpartum	PRO measurement and in addition, if available, medical records	
Symptomatic MS treatment	Type, dose, period, indication, and reason for discontinuation of all symptomatic MS treatments up to 6 years postpartum	PRO measurement and in addition, if available, medical records	

(Continued)

Table 1. (Continued)

Variable	Operational definition	Data source	Interview
Medical condition postpartum			
Severe diseases	Type, period, and therapy of any severe maternal disease up to 6 years postpartum	PRO measurement	2 months pp, 6 months pp, 12 months pp, 2 years pp, 3 years pp, 4 years pp, 5 years pp, 6 years pp
Hospitalization	Reason, period, and therapy of any maternal hospitalization up to 6 years postpartum	PRO measurement	
Regular drug use	Type, dose, period, and indication of any regularly (at least for 4 weeks) administered medical drug up to 6 years postpartum	PRO measurement	
Maternal death	Death of the mother up to 6 years postpartum	If available, medical records	
Body weight	Maternal body weight 6 months postpartum	PRO measurement	6 months pp
Child development			
Congenital abnormalities	Type, date, and therapy of any suspicion of a major or minor structural birth defect	PRO measurement and in addition, if available, medical check-up booklet, and medical records	6 months pp, 12 months pp, 2 years pp, 3 years pp, 4 years pp, 5 years pp, 6 years pp
(Chronic) diseases	Type, period, and therapy of any infant's (chronic) disease, including serious and opportunistic infections, up to 6 years postpartum	PRO measurement and in addition, if available, medical check-up booklet, and medical records	
Antibiotic therapy	Type, dose, period, and indication of any infant's antibiotic treatment up to 6 years postpartum	PRO measurement and in addition, if available, medical records	
Hospitalizations	Reason, number of nights, date, and therapy of any infant's hospitalization up to 6 years postpartum	PRO measurement and in addition, if available, medical records	
Disability/ADHS/Autism	Type, date of diagnosis, and degree of any infant's disability/ADHS/Autism up to 6 years postpartum	PRO measurement and in addition, if available, medical check-up booklet, and medical records	
Vaccinations	Type and date of any vaccination up to 6 years postpartum	PRO measurement and in addition, if available, vaccination card	

(Continued)

Table 1. (Continued)

Variable	Operational definition	Data source	Interview
Medical check-up	Date, body weight, body length, head circumference, and anomalies in infant's regular medical check-up, conducted at: Immediately after births 3–10 days postpartum 4–5 weeks postpartum 3–4 months postpartum 6–7 months postpartum 10–12 months postpartum 21–24 months postpartum 3 years postpartum 4 years postpartum 5–6 years postpartum	PRO measurement and in addition, if available, medical check-up booklet	
Developmental delays	Type, date, and therapy of any suspicion of infant's developmental delay. 'landmarks of development' from Michaelis[37] is assessed ±4 weeks around the child's birthday	PRO measurement, 'landmarks of development' from Michaelis[37] and in addition, if available, medical check-up booklet, and medical records	12 months pp 2 years pp 3 years pp 4 years pp 5 years pp 6 years pp

ADHS, attention-deficit/hyperactivity syndrome; BMI, body mass index; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; GW, gestational week; IA, immunoadsorption; IVF, in-vitro fertilization; LMP, last menstrual period; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PLEX, plasmapheresis; pp, postpartum; PRO, patient reported outcome.
Medical records include hospital discharge reports, physicians' letters, clinical records, and verification questionnaire neurologist or pediatrician.
[a]Until weaning and first menstruation postpartum.

Table 2. Operational definitions and study endpoints in the German Multiple Sclerosis and Pregnancy Registry.

Operator/endpoint	Definition
Operational definitions	
MS	MS diagnosis according to the current MS criteria[38]
NMOSD	NMOSD diagnosis according to the criteria defined by Wingerchuk *et al.*[39]
LMP	First day of the last menstrual cycle prior to pregnancy
Minimal data set	LMP, date of end of pregnancy, pregnancy outcome, date of first contact
First trimester	Time period between LMP and gestational day 83 (GW 0 + 0 to 11 + 6)[49]
Second trimester	Time period between gestational day 84 and gestational day 195 (GW 12 + 0 to 27 + 6)[49]
Third trimester	Time period between gestational day 196 and end of pregnancy (GW 28 + 0 until childbirth)[49]
Prospective	Data sets are classified as prospective, if the main outcome defined for a specific objective was not known at enrolment
Retrospective	Data sets are classified as retrospective, if the main outcome defined for a specific objective was known at enrolment
Lost to follow-up	Pregnancies are considered as 'lost to follow-up' if the expected date of delivery was reached but data were unobtainable for up to 6 months or, for the child development sub-study, the mother could not be contacted after five attempts.
DMT pregnancy exposure	
Interferon-β 1b formulations	Last interferon-β 1b formulation has been administered at or after the LMP
Glatiramer acetate formulations	Last glatiramer acetate formulation has been administered at or after the LMP
Dimethyl fumarate	Last dimethyl fumarate has been administered at or after the LMP
Azathioprine	Last azathioprine has been administered at or after the LMP
Interferon-β 1a formulations	Last interferon-β 1a formulation has been administered less than 7 days before the LMP or after the LMP
Siponimod	Last siponimod has been administered less than 10 days before the LMP or after the LMP
Peginterferon-β 1a	Last peginterferon-β 1a has been administered less than 2 weeks (14 days) before the LMP or after the LMP
Fingolimod	Last fingolimod has been administered less than 2 months (60 days) before the LMP or after the LMP
Ozanimod	Last ozanimod has been administered less than 3 months (90 days) before the LMP or after the LMP
Natalizumab	Last natalizumab has been administered less than 3 months (90 days) before the LMP or after the LMP
Daclizumab	Last daclizumab has been administered less than 3 months (90 days) before the LMP or after the LMP
Teriflunomide	Last teriflunomide has been administered less than 3 months (90 days) before LMP or after LMP or a plasma concentration above 0.02 mg/L at or after LMP
Alemtuzumab	Last alemtuzumab has been administered less than 4 months (120 days) before the LMP or after the LMP
Ocrelizumab	Last ocrelizumab has been administered less than 6 months (180 days) before the LMP or after the LMP
Rituximab	Last rituximab has been administered less than 6 months (180 days) before the LMP or after the LMP
Ofatumumab	Last ofatumumab has been administered less than 6 months (180 days) before the LMP or after the LMP
Cladribine	Last cladribine has been administered less than 6 months (180 days) before the LMP or after the LMP
Mitoxantrone	Last mitoxantrone has been administered less than 6 months (180 days) before the LMP or after the LMP
Immunoglobulin formulation	Last immunoglobulin formulation has been administered less than 6 months (180 days) before the LMP or after the LMP

(Continued)

Table 2. (Continued)

Operator/endpoint	Definition
Unexposed	Exposure is not declared according to the DMT pregnancy exposure criteria above or the woman/mother has never been treated with DMTs before LMP
Exposure time	Number of days between the last DMT administration and LMP
Breastfeeding	
Exclusive breastfeeding	Defined as at least 2 months of breastfeeding without regular replacement of any meal by supplemental feeding[21]
Exposed during lactation	DMT administration has been performed between breastfeeding start date (usually date of delivery) and weaning date
Pregnancy outcomes	
Live birth	Complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached[50]
Fetal death	Indicated by the fact that after separation the fetus does not breathe or show any other evidence of life[50]
Spontaneous abortion	Fetal death before perinatal period (22 completed gestational week)
Stillbirth	Fetal death during perinatal period (after 22 completed gestational week)
Elective termination	Any induced or voluntary fetal loss during pregnancy
Elective termination with medical reason	Any induced fetal loss during pregnancy due to structural and chromosomal defects of the fetus
Elective termination with social reason	Any voluntary fetal loss during pregnancy due to the social situation of the mother
Neonatal deaths	Deaths among live births during the first 28 completed days of life[50]
Early neonatal deaths	Neonatal death occurring during the first 7 days of life[50]
Late neonatal deaths	Neonatal deaths occurring after the seventh day but before 28 completed days of life[50]
Duration of gestation	Measured from the first day of the LMP in completed weeks[50]
Extremely preterm	Less than 28 completed weeks (less than 196 days)[50]
Very preterm	From 28 completed weeks to less than 32 completed weeks (196 to 223 days)[50]
Late preterm	From 32 completed weeks to less than 37 completed weeks (224 to 258 days)[50]
Term	From 37 completed weeks to less than 42 completed weeks (259 to 293 days)[50]
Post-term	42 completed weeks or more (294 days or more)[50]
Birthweight	First weight of the fetus or newborn obtained after birth according to mother's maternity log or medical check-up booklet of the newborn
Small for gestational age	Birth size (weight, length or head circumference) $\leqslant$ 10th percentile for sex and gestational age using national analysis of the neonatal collective in Germany pediatric growth curves[51] for full term and preterm infants
Congenital abnormalities	Structural changes that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention,[52] rated in accordance with the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects[44] and the guidelines of the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)[45] by a teratologist from the Mainz births registry

(Continued)

Table 2. (Continued)

Operator/endpoint	Definition
Major structural anomalies	Conditions that account for most of the deaths, morbidity and disability related to congenital anomalies[52]
Minor congenital anomalies	Structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual[52]
Child development outcomes	
Chronic diseases	A condition that has lasted or is expected to last more than 3 months and the definition considers the impact of the condition on the child, for example, level of functional impairment or medical need greater than expected for a child of that age[53,54]
Developmental delays	Diagnosed by the pediatrician in the medical check-up booklet or measured with the questionnaire 'landmarks of development' from Michaelis.[37] A child development is considered as delayed, if the sum of achieved, age-appropriated landmarks is below the 90th-percentile.
Antibiotic treatment	Infection treated with an antibiotic preparation according to the register of pharmaceutical drugs in Germany (Rote Liste®)
Hospitalization	Child needs inpatient treatment for any medical reason, excluding hospitalizations due to accidents
Postnatal growth deficiency	Postnatal size (weight, length or head circumference) ⩽ 10th percentile for sex and age using German pediatric growth curves[55] and adjusted postnatal age for premature infants
Disease activity outcomes	
Relapse	New or recurrent neurological symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new neurological findings.[38] The new or recurrent symptoms are required to be at least 30 days following the onset of the previous relapse. Symptoms that occur within 30 days of each other are considered part of the same relapse.
Disability	Since 2017, the EDSS is generally rated with tele-EDSS, a patient self-reported questionnaire.[36] In some sub-studies treating neurologist[56] are contacted.
Disability progression	Worsening of at least 1.5 EDSS points for patients with baseline EDSS = 0; at least 1 point for patients with baseline EDSS 1–5.5; 0.5 point for patients with baseline EDSS ⩾ 6.0
Steroid use	High-dose corticosteroid treatment or intrathecal steroid treatment due to a relapse.

CDC, Centers for Disease Control and Prevention; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EUROCAT, European network of population-based registries for the epidemiological surveillance of congenital anomalies; GW, gestational week; LMP, last menstrual period; MACDP, Metropolitan Atlanta Congenital Defects Program; MS, multiple sclerosis; NMOSD, Neuromyelitis optica spectrum disorders.

Definitions for DMT exposure durations are based on the EMA and FDA recommendations (summary of product characteristics), available data on exposed pregnancies and the pharmacokinetic and pharmacodynamic properties of a DMT, basically corresponding to five half-life times.

Data analysis. Addressing different objectives, the DMSKW conducts analysis of various research questions concerning MS and the desire to have children. Before a data set is analyzed, different measurements are taken to ensure the plausibility, accuracy, consistency, and completeness of data. Predefined automatic data checks are implemented and reviewed for logical errors.

Subsequent review of data is undertaken by a study data manager and key variables are regularly double-checked for accuracy of data entry. A study statistician also conducts reviews of the key variables (e.g. last menstrual period, estimated due date, end of pregnancy, gestational week at birth, weaning date, DMT start and stop dates) from the study database for distributions and values that are illogical. A risk-based monitoring is conducted for informed consent forms and source data verification takes place by directly comparing the primary data source with the registry data from the database. Furthermore, data are validated by medical records and treating physicians in case of severe complications (mainly hospitalizations) or negative pregnancy outcomes.

For every planned analysis, a project-specific statistical analysis plan is created. In general, the means and standard deviations of normally
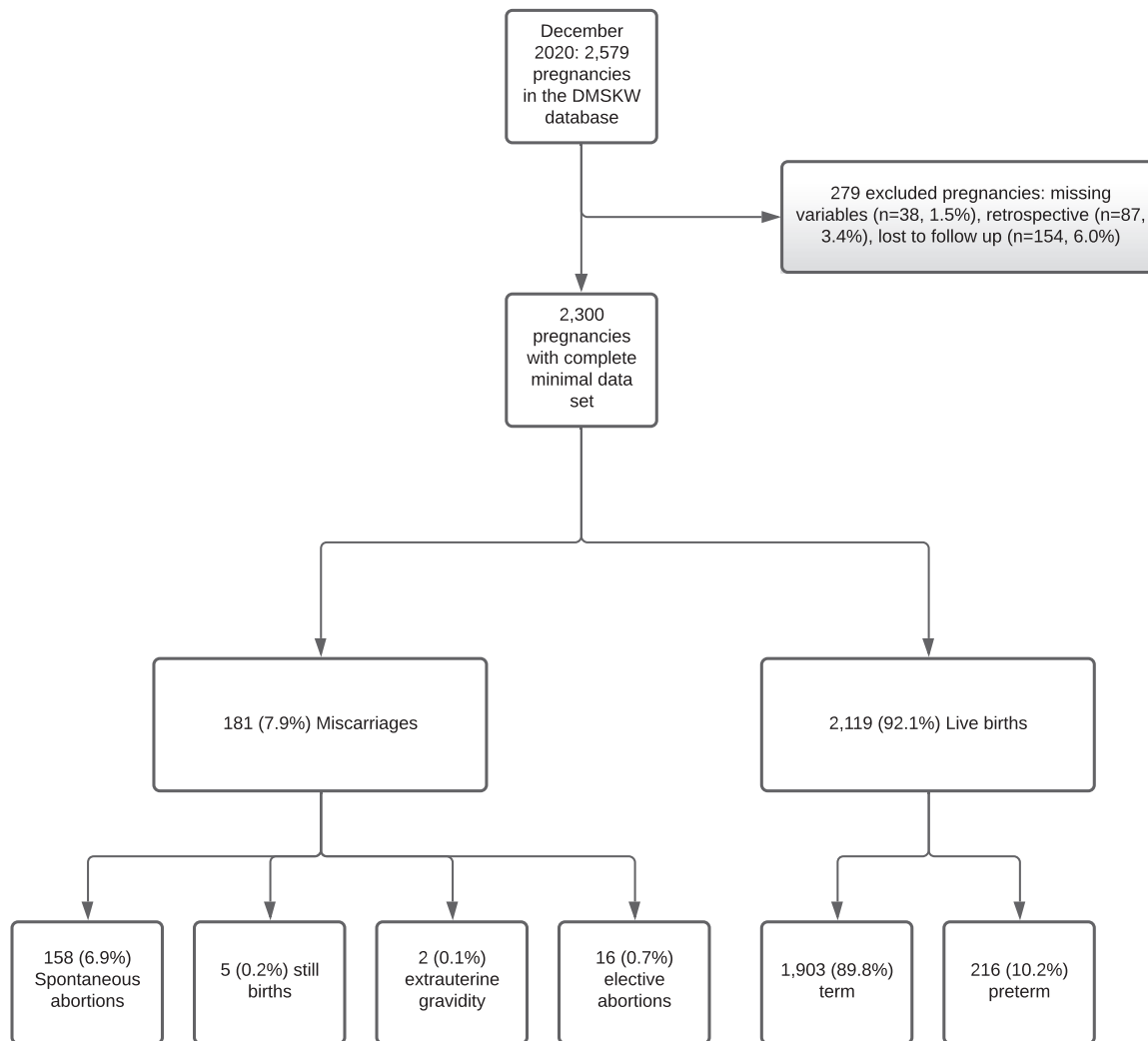
Figure 3. Outcomes of pregnancies entered in the German Multiple Sclerosis and Pregnancy Registry database.

distributed variables (evaluated with histogram, boxplot and Shapiro-Wilk-Test) are compared using two-sample t-tests or for non-parametric variables, the Mann Whitney U test. Alternatively, for more than two comparison groups, the Kruskal–Wallis Rank Sum Test, is used. For binary or categorical variables, the chi-square test (count > 5) or Fisher's exact test (count < 5) is used, respectively. A two-sided $p < 0.05$ is considered as statistically significant. Binary or categorical variables are analyzed in multivariate logistic regression models. Depending on dispersion of the data, count data analysis (Poisson or negative binomial regression or variants thereof) is used to compare relapse rates with a 95% CI and propensity score adjusted logistic regression to account for

bias in a nonrandomized setting. The time until a specific event occurs is determined by Cox regression and using the Kaplan-Meier method. Most analysis are performed using R version 4.0.3 and RStudio version 1.3.1093.

Results

Currently (as of December 2020), the DMSKW database contains 2,579 pregnancy datasets of women with MS or NMOSD ($n = 11$, 0.4%). 6% of these pregnancies are lost to follow up and 3% were enrolled after pregnancy outcome and classified as retrospective cases (Figure 3). In the last three years more than 400 pregnancies per year were able to be consistently recruited (400 in 2018, 490 in 2019 and 500 in 2020).

Table 3. Baseline characteristics of 2,300 pregnancies with complete minimal data set from the German Multiple Sclerosis and Pregnancy Registry.

Variable	2,300 pregnancies with complete minimal data set	Data missing rate
Age at conception, mean (SD), in years	32.1 (4.3)	16 (0.7%)
BMI, mean (SD), in kg/m^2	24.3 (5.2)	134 (5.8%)
Women with secondary school diploma, *n* (%)	112 (5.5)	262 (11.4%)
Women with high school diploma, *n* (%)	875 (42.9)	262 (11.4%)
Women without completed vocational training, *n* (%)	68 (3.4)	276 (12.0%)
Women with University degree, *n* (%)	780 (38.5)	276 (12.0%)
Women smoking at conception, *n* (%)	302 (13.7)	89 (3.9%)
Women smoking during pregnancy, *n* (%)	81 (4.2)	369 (16.0%)
Women with alcohol abuse at conception, *n* (%)	22 (1.0)	122 (5.3%)
Women with alcohol abuse during pregnancy, *n* (%)	7 (0.4)	402 (17.5%)
Women with drug abuse at conception, *n* (%)	19 (0.9)	213 (9.3%)
Women with drug abuse during pregnancy, *n* (%)	2 (0.1)	385 (16.7%)
Gestational week at enrollment, median (range)	11.0 (0.02 to 42.1)	0
Disease duration at conception, median (range) in years	4.9 (–0.5 to 26.6)	35 (1.5%)
Postpartum follow up, median (range) in years	1.2 (0 to 9.2)	132 (5.7%)

BMI, body mass index; n, number of cases; SD, standard deviation.
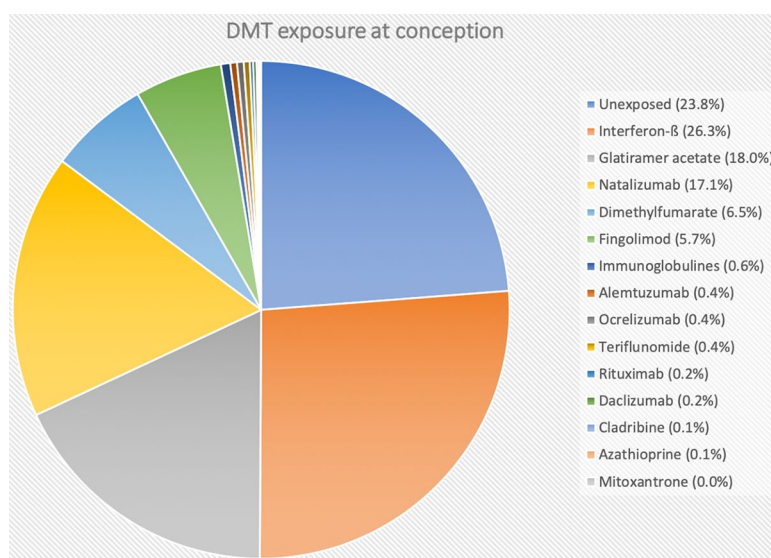
Figure 4. Pie chart representing DMT use at the time of conception.

DMT exposure at conception

- Unexposed (23.8%)
- Interferon-ß (26.3%)
- Glatiramer acetate (18.0%)
- Natalizumab (17.1%)
- Dimethylfumarate (6.5%)
- Fingolimod (5.7%)
- Immunoglobulines (0.6%)
- Alemtuzumab (0.4%)
- Ocrelizumab (0.4%)
- Teriflunomide (0.4%)
- Rituximab (0.2%)
- Daclizumab (0.2%)
- Cladribine (0.1%)
- Azathioprine (0.1%)
- Mitoxantrone (0.0%)

Baseline characteristics of the 2,300 pregnancies with a complete minimal data set are shown in Table 3. Most women are enrolled at the end of the first trimester of pregnancy and have a complete postpartum follow-up of at least one year. Women with a healthy lifestyle are overrepresented in this cohort, only a small proportion of women smoked (4.2%), drank alcohol (0.4%), or consumed illegal drugs (0.1%) during pregnancy.

The majority in the cohort received a DMT at conception, 548 (24%) were unexposed. Approximately one quarter of the pregnancies (*n* = 559; 24%) were exposed to second line therapies (Figure 4), and 5 (0.2%) women received two different DMTs during pregnancy.

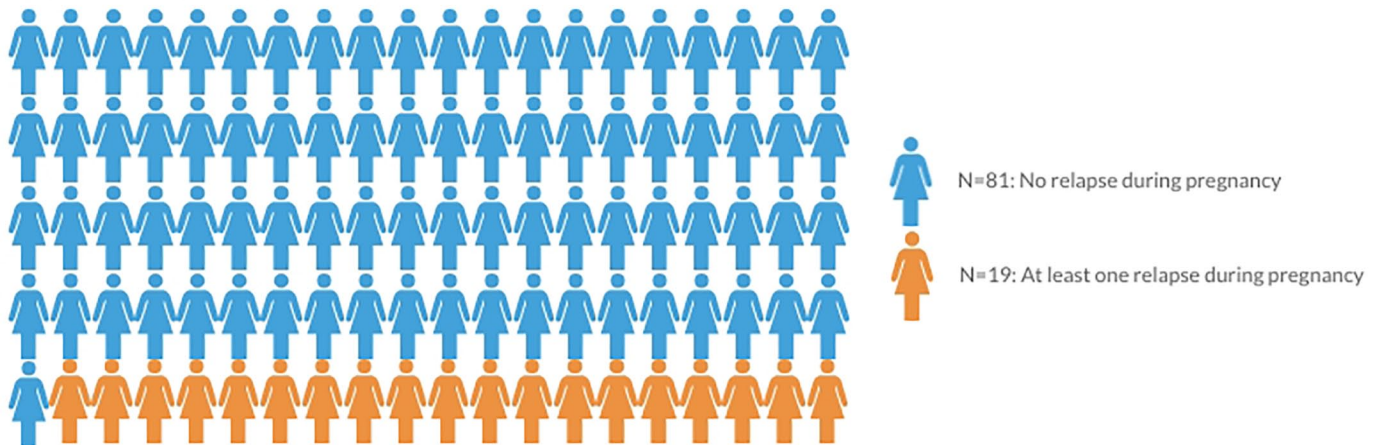The overall spontaneous abortion rate in the registry is 7%, and 10% of all live births are born

Figure 5. Icon array representing the proportion of women suffering from at least one relapse during pregnancy for 100 pregnancies.
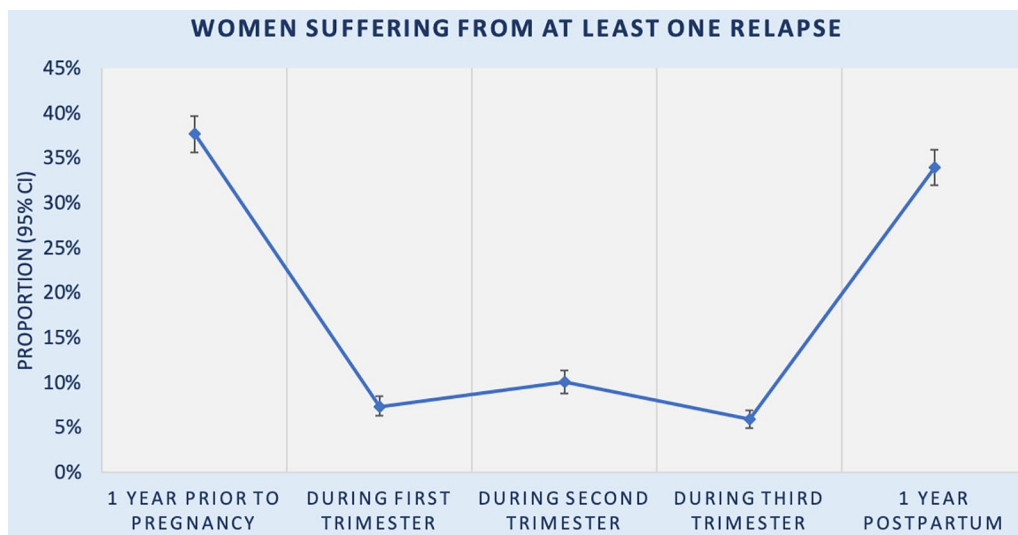

Figure 6. Proportion of women suffering from at least one relapse during the last year prior to pregnancy, during the first, second, and third trimesters, and during the first year postpartum.

preterm. Figure 3 provides an overview of all documented pregnancy outcomes.

At least one relapse occurred in 19% of all women during pregnancy (Figure 5), with a minimum of 6% during the third trimester of pregnancy (Figure 6).

The missing data rates in the registry are low with only 38 (1.5%) pregnancy datasets not evaluable, due to a missing minimal data set (Figure 3). The missing rate in baseline characteristics range from 0%–17.5%, with an increase in missing for

variables concerning alcohol, tobacco and drug abuse during pregnancy (Table 3).

Results already published
In recent years, the DMSKW has been able to answer many practice-relevant questions through targeted evaluation of the collected data and thus has contributed to improving the care of MS and NMOSD patients desiring to have children.[57–59] In the registry's modern, highly treated cohort of women with MS, it was proven that an exposure to

interferon-beta,[60] glatiramer acetate,[61] or natalizumab[62] in the first trimester of pregnancy does not increase the risk for an adverse pregnancy outcomes in comparison with pregnancies unexposed to DMTs. In a case series of 12 women with 13 pregnancies and highly active MS who were treated with natalizumab during their third trimester of pregnancy, mild to moderate hematologic alterations in 10 out of 13 infants were observed, including thrombocytopenia and anemia.[63]

In addition, it was demonstrated that a treatment with ocrelizumab or rituximab prior to conception might be an interesting option for women with RRMS or NMOSD for controlling disease activity during pregnancy and postpartum.[35]

A general protective effect of breastfeeding on postpartum relapses was found.[30] Women who breastfed exclusively had fewer relapses than women who breastfed partially or not at all[21] and breast milk exposure to interferon-β or glatiramer acetate did not increase the risk of common adverse infant outcomes in the first year of life.[64] Furthermore, low breastmilk concentrations of cladribine were able to be measured in one of the lactating patients[65] and also of dimethyl fumarate in two lactating patients,[66] as well as low natalizumab concentrations in three breast milk and two serum samples of breastfed children and contributed further evidence that natalizumab, ocrelizumab, or rituximab might be safe during breastfeeding.[67]

Discussion and limitations

The DMSKW represents a modern, prospective, longitudinal cohort study in a real-world setting, which successfully recruits and follows up pregnant women with MS or NMOSD and their children in Germany. It allows long-term monitoring of disease activity, pregnancy and lactation course as well as child development up to 6 years postpartum in a DMT treatment era. Whereas enrollment rates in other MS pregnancy registries can be challenging (up to 300 exposed pregnancies during a study period lasting 6 years),[68] a continuous enrollment rate of more than 400 pregnancies per year was demonstrated.

Clinical trials, due to their high costs, are restricted to a short follow-up duration and inefficient in generating pregnancy exposure safety data. In addition, post-authorization surveillance activities collect data only for exposed pregnancies, whereby a sufficient control group is missing. In contrast, the DMSKW offers reliable and robust long-term data of high-quality, including a control group that allows the influence of the underlying disease to be excluded in the analysis, and provides a comprehensive advisory basis not only for treating neurologists and MS/NMOSD-patients themselves, but also for regulatory authorities.

The DMSKW is not population-based, although data are mainly patient reported, it is assumed that especially main outcomes such as relapses or pregnancy outcomes are valid. Validation studies from other observational registries with patient reported outcome (PRO) measurement show a good overall agreement concerning pregnancy and birth characteristics[69] or MS relapses.[70] PRO was validated against nation-wide registry data[71] or medical records[72,73] and the agreement found to be very good especially for birthweight[71–73] but also for gestational age, infant hospitalization, method of delivery, smoking during pregnancy or maternal complications during pregnancy.[72] Differences between patient reported MS relapses and physicians were predominantly observed in patient groups with decreased health-related quality of life, associated with a low socioeconomic status.[70] In contrast, the DMSKW has an overrepresentation of women with a healthy lifestyle and a high level of education, so that this factor might be negligible.

This overrepresentation in women with a high socioeconomic status likely results from a selection bias, as the participation in the DMSKW is voluntary. 43% of all women in the cohort have a high school diploma and 39% a university degree, whereas the rate in the German population is 27.3% and 14.1%, respectively.[74] Therefore, more favorable pregnancy outcomes less confounded by other toxins as alcohol and tobacco can be expected. However, as the focus is on the effect of MS itself and the impact of DMT exposure, this bias might be negligible for the registry research questions.

Compared to other cohorts, a high percentage of women in the registry are treated with DMTs at the beginning of pregnancy and a relatively high proportion with highly efficient drugs. In contrast, more than a third of participants reported relapses in the year prior to pregnancy, although other publications observed relapses in 113 out of

227 (50%) women without DMT treatment during the last year prior to pregnancy.[9] These findings deserve further investigation, especially as some studies found relapses in the year prior to pregnancy as a risk factor for postpartum relapses, although this might not be true in highly treated cohorts, as treatment controls the natural disease activity.

Women tend to enroll at the end of the first trimester and importantly, all pregnancies are followed prospectively thereafter. With the exact date of enrollment, the cohort is stratified into retrospective or prospective depending on the outcome of interest, as retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population than cases reported prior to knowledge of outcome.[75]

Spontaneous abortions most frequently occur in early pregnancy, likely before the pregnancy is recognized. Even if the pregnancy is confirmed, it is possible that the pregnancy may not be reported to the registry if the loss occurred before enrollment. Not capturing all early pregnancy losses likely leads to an underestimation of the true early pregnancy loss rate, a common limitation in pregnancy registries.[76] On average, women are enrolled in gestational week 11 and an overall spontaneous abortion rate of 7% was found. The background rate for spontaneous abortion is difficult to identify with precision, but is usually specified as 15%.[77] However, the spontaneous abortion rate might be higher in population-based settings,[78] able to identify pregnancies early. As biases introduced by design differences across studies must be considered, statistical comparisons and risk calculations are mostly conducted with a control group and do not exclusively relate to the risk in the general population. It is expected, that the underestimation of spontaneous abortions is comparable between exposed and unexposed groups from the DMSKW.

Some birth defects (e.g. heart defects, hip dysplasia) and other infant abnormalities (e.g. chronic diseases, developmental delays) may not be evident at birth and are often diagnosed during the first years of life. This is addressed by following up children up to kindergarten age and by calculating birth defect rates among live births in a cohort of at least 1-year-old children. However, the long follow-up period of 6 years in this registry

raises the potential for lost to follow-up. Lost to follow-up is minimized in the DMSKW by close meshed contacts and personal care provided by rarely fluctuating staff. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes, however it is not possible to assess with any certainty what impact these data sets would have on the analyses. In any case, baseline characteristics of women lost to follow-up and women completing the follow-up, are compared in order to estimate the bias due to lost to follow up.

Acceptable follow-up rates have been recommended by thresholds of 60%–80% in cohort studies.[79] However, in registries of low incidence outcomes, as the DMSKW, a lost to follow-up rate > 5% increases the potential impact of bias.[80] Currently, an average lost-to-follow-up rate of 6% was evaluated, however a sudden increase as of 2018 was also observed, as the lost to follow-up rate has been previously evaluated as < 3%.[60,61] The extended follow-up period and a fluctuation in DMSKW staff members as potential impact factors were identified and addressed by increasing the frequency of refresher-training in the DMSKW study procedure and increasing stability in the staff.

Over the past 14 years, the DMSKW has become well established across Germany, underlined by its constant and increasing recruitment, a high level of valid and accurate data accompanied by an acceptable lost to follow-up rate. By becoming one of the largest pregnancy registries, practice-related results can be provided not only for treating physicians, but also for affected MS patients and their partners. The DMSKW works closely with colleagues in research and practice, engages actively in public relations while making relevant results available at national and international conferences as well as in medical journals. Consequently, not only is a scientifically valuable contribution provided but also a positive influence on both the counseling and the care of MS patients desiring to become pregnant.

Author contributions

Concept and design: Sandra Thiel, Kerstin Hellwig

Acquisition, analysis or interpretation: Sandra Thiel, Andrea Ciplea, Kerstin Hellwig

Drafting the work: Sandra Thiel, Kerstin Hellwig

Critical revision of the manuscript for important intellectual content: Andrea Ciplea, Ralf Gold

Statistical analysis: Sandra Thiel

Conflict of interest statement

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