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

Sandra Thiel, Andrea I. Ciplea, Ralf Gold and Kerstin Hellwig

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

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system. Approximately more than 2 million people worldwide are affected by MS. Initial symptoms usually appear between the age of 20 and 40, with an increasing incidence in females, 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,
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 tri-
merist 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 contraindi-
cated. Only interferon-β has approval for treat-
dment during lactation.3

Sufficient case numbers for assessing safety are
only available for substances with many years of
experience, such as interferon-β4 and glatiramer
acetate.5 Data on more than 300 first trimester
exposed pregnancies could so far only be col-
lected for natalizumab6 and fingolimod.7
Particularly for newer substances such as alemtu-
zumab, ocrelizumab, or cladribine as well as
recently approved drugs (siponimod, ozanimod,
ofatumumab), sufficient experience for evaluat-
ing the safety of exposure during pregnancy is
lacking.

Available data often stem from accidental preg-
nancies 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 disa-
bility 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 sig-
nificant increase during the first 6 months post-
partum,9 is meanwhile well known and repeatedly
and reproducibly proven.10,11 However, recently
published data demonstrated no increase in post-
partum relapse rate in women with mild to mod-
erate disease activity and a DMT treatment rate
of 41.2%.12 The impact of DMTs, especially the
withdrawal of DMTs prior to conception, on dis-
ease 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 natalizumab13,14 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 alemtu-
zumab, 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 breast-
feeding can reduce the postpartum relapse risk as
well, has been controversially discussed,18,21–23
although a recent meta-analysis confirms the pro-
tective 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 miss-
ing.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 desir-
ing to become pregnant, especially in the era of
highly effective DMTs, still need to be investi-
gated. Therefore, with each novel DMT new
challenges await neurologists and patients,
namely the best procedure for minimizing risks
for mothers (concerning disease activity and dis-
ability) while ensuring the health of the newborns
and children.

Therefore, the German Multiple Sclerosis and
Pregnancy Registry (Deutsches Multiple Sklerose
und Kinderwunschregister; DMSKW) was estab-
lished 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 pub-
lished. 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) and developmental delays. 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 or self-reported NMOSD];
- 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...
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 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.
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), the children’s medical check-up booklet (Kinderuntersuchungsheft), 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 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) 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 and the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) 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, 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.

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 was also included. In order to capture patient reported markers of disability, the teleEDSS 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.
| 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                                                              |           |
| Variable                      | Operational definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Data source                                                                 | Interview       |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------|
| Medical history               |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                      | PRO measurement and in addition, if available, medical record | Enrollment     |
| MS disease duration           | Disease duration at conception calculated from date of diagnosis and LMP.                                                                                      |                                                                 | PRO measurement | 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                |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                      | PRO measurement | Enrollment     |
| 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              |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                      | PRO measurement | First trimester |
| 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 | Second trimester |
| 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 | Third trimester |
| 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                                                               |                |
| Variable | Data source | Operational definition |
|----------|-------------|------------------------|
| Maternal death | PRO measurement and in addition, if available, medical records | Death of the mother up to 6 years postpartum |
| Maternal weight | PRO measurement and in addition, if available, medical records | Maternal pre-delivery body weight in kg |
| Disease activity during pregnancy | PRO measurement and in addition, if available, medical records | Date, symptoms, and therapy of relapses during pregnancy |
| Relapses | PRO measurement and in addition, if available, medical records | Type, dose, period, and number of times administered during pregnancy |
| MRI | PRO measurement and in addition, if available, medical records | MRI during first and third trimesters of pregnancy and in case of relapses during pregnancy |
| EDSS | PRO measurement and in addition, if available, medical records | EDSS during first and third trimesters of pregnancy and in case of relapses during pregnancy |
| IAPEX | PRO measurement and in addition, if available, medical records | Type, period, and number of cycles during pregnancy |
| Corticosteroid exposure | PRO measurement and in addition, if available, medical records | Type, dose, period, and type and number of times administered during pregnancy |
| DMTs | PRO measurement and in addition, if available, medical records | Type, doses, period, and exact date of discontinuation of all DMTs during pregnancy |
| Pregnancy outcome | PRO measurement and in addition, if available, medical records, maternity log, and medical check-up booklet | Date and gestational age of spontaneous abortion, spontaneous/preterm labour, maternal indications, fetal indications, and full-term live birth |
| Newborn body measurement characteristics | PRO measurement and in addition, if available, medical records, maternity log, and medical check-up booklet | Birth weight, birth length, head circumference at birth, sex, Apgar score |
| Mode of delivery | PRO measurement and in addition, if available, medical records, maternity log, and medical check-up booklet | Vaginal delivery (spontaneous, induced, vacuum, forceps extraction), cesarean section, elective or emergency |
| Birth complications | PRO measurement and in addition, if available, medical records, maternity log, and medical check-up booklet | Type of any maternal or fetal complication during delivery |
| Wellbeing of the child | PRO measurement and in addition, if available, medical records, maternity log, and medical check-up booklet | 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 applications during the first 8 weeks postpartum, and death during the first 8 weeks postpartum |

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<sup>3</sup> 6 months pp<sup>3</sup> 12 months pp<sup>3</sup> 2 years pp<sup>3</sup> 3 years pp<sup>3</sup> 4 years pp<sup>3</sup> 5 years pp<sup>3</sup> 6 years pp<sup>3</sup> |
| 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               |           |
| 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 at 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 |
| (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 | 6 months pp |
| 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               |           |
| Variable               | Operational definition                                                                 | Data source                                                                 | Interview        |
|------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------|
| Medical check-up       | Date, body weight, body length, head circumference, and anomalies in infant’s regular   | PRO measurement and in addition, if available, medical check-up booklet      |                  |
|                        | 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                                                                    |                                                                              |                  |
| Developmental delays   | Type, date, and therapy of any suspicion of infant’s developmental delay. ‘landmarks    | PRO measurement, ‘landmarks of development’ from Michaelis and in addition,  | 12 months pp     |
|                        | of development’ from Michaelis\(^{37}\) is assessed ±4 weeks around the child’s birthday| available, medical check-up booklet, and medical records                      | 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, immunoabsorption; 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.
| Operator/endpoint | Definition |
|------------------|-----------|
| **Operational definitions** | |
| MS | MS diagnosis according to the current MS criteria<sup>38</sup> |
| NMOSD | NMOSD diagnosis according to the criteria defined by Wingerchuk et al.<sup>39</sup> |
| 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)<sup>49</sup> |
| Second trimester | Time period between gestational day 84 and gestational day 195 (GW 12 + 0 to 27 + 6)<sup>49</sup> |
| Third trimester | Time period between gestational day 196 and end of pregnancy (GW 28 + 0 until childbirth)<sup>49</sup> |
| 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)
### 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

**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

**Fetal death**
Indicated by the fact that after separation the fetus does not breathe or show any other evidence of life

**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

**Early neonatal deaths**
Neonatal death occurring during the first 7 days of life

**Late neonatal deaths**
Neonatal deaths occurring after the seventh day but before 28 completed days of life

**Duration of gestation**
Measured from the first day of the LMP in completed weeks

**Extremely preterm**
Less than 28 completed weeks [less than 196 days]

**Very preterm**
From 28 completed weeks to less than 32 completed weeks [196 to 223 days]

**Late preterm**
From 32 completed weeks to less than 37 completed weeks [224 to 258 days]

**Term**
From 37 completed weeks to less than 42 completed weeks [259 to 293 days]

**Post-term**
42 completed weeks or more [294 days or more]

**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] < 10th percentile for sex and gestational age using national analysis of the neonatal collective in Germany pediatric growth curves 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, rated in accordance with the CDC Metropolitan Atlanta Congenital Defects Program [MACDP] classification of birth defects and the guidelines of the European network of population-based registries for the epidemiological surveillance of congenital anomalies [EUROCAT] by a teratologist from the Mainz births registry

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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                                                                                          |
| 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 |
| Fetal death                        | Indicated by the fact that after separation the fetus does not breathe or show any other evidence of life                                                                                                 |
| 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                                                                                                                                       |
| Early neonatal deaths              | Neonatal death occurring during the first 7 days of life                                                                                                                                                  |
| Late neonatal deaths               | Neonatal deaths occurring after the seventh day but before 28 completed days of life                                                                                                                     |
| Duration of gestation              | Measured from the first day of the LMP in completed weeks                                                                                                                                               |
| Extremely preterm                  | Less than 28 completed weeks [less than 196 days]                                                                                                                                                        |
| Very preterm                       | From 28 completed weeks to less than 32 completed weeks [196 to 223 days]                                                                                                                                |
| Late preterm                       | From 32 completed weeks to less than 37 completed weeks [224 to 258 days]                                                                                                                               |
| Term                               | From 37 completed weeks to less than 42 completed weeks [259 to 293 days]                                                                                                                                |
| Post-term                          | 42 completed weeks or more [294 days or more]                                                                                                                                                             |
| 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] < 10th percentile for sex and gestational age using national analysis of the neonatal collective in Germany pediatric growth curves 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, rated in accordance with the CDC Metropolitan Atlanta Congenital Defects Program [MACDP] classification of birth defects and the guidelines of the European network of population-based registries for the epidemiological surveillance of congenital anomalies [EUROCAT] by a teratologist from the Mainz births registry |
Operator/endpoint Definition

### Major structural anomalies
Conditions that account for most of the deaths, morbidity and disability related to congenital anomalies\(^\text{52}\)

### 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\(^\text{52}\)

### 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\(^\text{53,54}\)

#### Developmental delays
Diagnosed by the pediatrician in the medical check-up booklet or measured with the questionnaire 'landmarks of development' from Michaelis.\(^\text{37}\) 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\(^\text{®}\))

#### Hospitalization
Child needs inpatient treatment for any medical reason, excluding hospitalizations due to accidents

#### Postnatal growth deficiency
Postnatal size (weight, length or head circumference) \(\leq 10\text{th percentile for sex and age using German pediatric growth curves}\(^\text{55}\) 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.\(^\text{38}\) 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.\(^\text{36}\) In some sub-studies treating neurologist\(^\text{36}\) 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 \(\geq 6.0\)

#### Steroid use
High-dose corticosteroid treatment or intrathecal steroid treatment due to a relapse.

### Data analysis

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 distributed variables are compared using standard statistical tests, while the categorical variables are compared using chi-square or Fisher’s exact test as appropriate. The significance level is set at \(p \leq 0.05\).
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).
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...
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 natalizumab62 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 all21 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 patients66 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 characteristics69 or MS relapses.70 PRO was validated against nation-wide registry data71 or medical records72,73 and the agreement found to be very good especially for birthweight71–73 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. 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.

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. 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%. However, the spontaneous abortion rate might be higher in population-based settings, 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. However, in registries of low incidence outcomes, as the DMSKW, a lost to follow-up rate > 5% increases the potential impact of bias. 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%. 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.

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Drafting the work: Sandra Thiel, Kerstin Hellwig
Critical revision of the manuscript for important intellectual content: Andrea Ciplea, Ralf Gold
Statistical analysis: Sandra Thiel

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ORCID iDs
Sandra Thiel https://orcid.org/0000-0002-5113-8451
Kerstin Hellwig https://orcid.org/0000-0003-4467-9011

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