The MSBase pregnancy, neonatal outcomes, and women's health registry

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***Abstract*:**

Background: Family planning and pregnancy decisions are key considerations in the management of women with multiple sclerosis (MS), who are typically diagnosed between the ages of 20–40 years. Despite a strong evidence base that pregnancy is not harmful for women with MS, many knowledge gaps remain. These include: best management strategies through pregnancy in the era of highly effective disease-modifying therapies (DMT); foetal risks associated with DMT exposure *in utero* or in relation to breastfeeding; knowledge base around the use of assisted reproductive technologies; the long-term impact of pregnancy on disease outcomes, as well as the impact of long-term DMT use on women's health and cancer risk.

Methods: Here, we describe the new MSBase pregnancy, neonatal outcomes and women's health registry. We provide the rationale for, and detailed description of, the variables collected within the registry, together with data acquisition details.

Conclusion: The present paper will act as a reference document for future studies.

Keywords: Multiple Sclerosis, Women's Health, Pregnancy, Neonatal Outcomes, Registry, MSBase

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Introduction

Multiple Sclerosis (MS) is typically diagnosed between the ages of 20–40 years with a 3:1 female-to-male preponderance.[1,2] The burden of incident and early MS course is, therefore, disproportionately weighted towards women of childbearing age. Discussions of family planning are frequent in clinical practice. Whilst clinician advice moved away from discouraging pregnancy in women with MS thanks to the seminal pregnancy in MS (PRIMS) study of the late 1990s,[3] and subsequent confirmatory studies,[4,5] much still remains unknown.

Pregnant women with MS are excluded from clinical trials of disease-modifying therapy (DMT) efficacy due to teratogenicity concerns. With limited evidence to guide DMT use during and after pregnancy, some neurologists still choose to withhold DMT from patients during these periods.[6] However, our awareness of short and long-term sequelae of recurrent inflammatory disease activity due to DMT cessation before conception has also increased, leading to widespread and rapid changes in practices of DMT use during pre-conception, in pregnancy and during breastfeeding.[7] We need to now generate data to better understand and stratify maternal and foetal risks and benefits.

Real-world, observational, studies have demonstrated a rapidly changing MS-pregnancy treatment landscape. The introduction of more effective therapies has allowed women with moderate disability to consider pregnancy.[8–10] Further, recent evidence from the MSBase Registry demonstrates that greater than 60% of women today conceive whilst on MS DMT,[11] consistent with trends described by others.[12–14] Recent consensus suggests that MS platform therapies can be continued safely until pregnancy is confirmed.[15] However, our work demonstrates that women are increasingly conceiving on higher efficacy therapies,[11] with still limited safety data available. This speaks to the need for systematic, long-term, prospective databasing to confirm safety or, alternatively,

quantify teratogenic risks of DMT use in the peripartum period. Observational real-world registries such as MSBase provide an ideal platform for monitoring of women with both DMT-exposed and unexposed pregnancies and neonatal outcomes at scale.

Women with MS have fewer children than the general population.[16–18] Whether this is due to reduced fertility, sexual dysfunction, comorbidities, or the MS prodrome remains unclear.[19] An alternative explanation to reduced fecundity is instead that psychosocial issues drive family planning decisions in women with MS.[20–22] Additionally, it remains unclear whether the use of assisted reproductive technology (ART) does indeed lead to increased relapse activity after use, with varying results across cohorts.[23] Questions of fecundity, and impact of ART on disease activity require resolution.

The impact of pregnancy on long-term MS outcomes also remains unresolved.[7] Pregnancy has variously been reported to be beneficial, slowing the time to wheelchair use, or net neutral.[24] In studies that found a beneficial effect of pregnancy, including our own,[25] the issue of reverse causality remains: are women with milder MS are more inclined to become pregnant than those with more aggressive disease? There is also the question of multi-parity. It has been suggested that the beneficial effects of pregnancy may only be realised with two or more pregnancies.[26] However, recent data from the MSBase Registry demonstrates that multiparity confers no additional benefit over a single pregnancy in the delay of a clinically isolated syndrome (CIS).[27] Critically, there are no published studies examining the effect of pregnancy during the progressive phase of MS. Therefore, integration of detailed pregnancy, and breastfeeding data, together with long-term clinical and treatment data, will further allow elucidation of the impact of pregnancy on long-term disease outcomes.

The safety of long-term DMT use in women with MS, although generally reassuring, remains unknown. To date, the risk of breast, cervical or other invasive cancers do not appear to be increased in women exposed to DMTs but population-based studies that include data on comorbidities and links with national cancer databases are rare.[28,29] Furthermore, these events are rare, and rigorous collection of long-term data is needed to fully understand these risks and adapt screening programs for women with MS. Gynaecological infections as a complication of DMT exposure remain anecdotal and are highly likely to be under reported. Understanding the role of physiological hormonal changes that women experience as they traverse from the premenopausal or reproductive years through the postmenopausal years, are increasingly thought to contribute to disease progression in some, and requires ongoing detailed interrogation.[7]

The MSBase pregnancy, neonatal outcomes and women's health registry

The MSBase pregnancy, neonatal outcomes and women's health registry is designed for the prospective, longitudinal ascertainment of pregnancy and neonatal outcomes, together with information regarding fertility, comorbidities and safety in all women with MS.

Objectives

Our overarching objective is to build a comprehensive, international, prospective, observational pregnancy, neonatal outcomes and women's health registry, integrated into the MSBase Registry to conduct safety, efficacy and clinical outcomes research. Specific areas addressed:

Pregnancy outcomes

- Use of assisted reproductive technology (ART);
- Discontinuation of DMT pre-conception, DMT use in pregnancy and timing of resumption of DMT and DMT identity postpartum;
- Intrapartum and postpartum relapse activity;
- Delivery methods;
- Maternal and obstetric complications;
- Breastfeeding duration and exclusivity and DMT use during breastfeeding.

Neonatal outcomes

- Pregnancy outcomes including term/preterm births with and without malformations; terminations and miscarriages;
- Reasons for miscarriage/termination;
- Birthweight;
- Major and minor malformations or congenital abnormalities according to EUROCAT

classifications, and as they relate to DMT use.

Women's health outcomes

- Facilitate prospective studies of the impact of pregnancy and breastfeeding on long-term disease outcomes of women with all MS phenotypes;
- Establish the long-term safety of DMTs in relation to female-specific malignancies and infections as captured *via* MedDRA;
- Determine the effect of hormonal changes through a women's lifespan on MS outcomes.

Methods

Study ethics and consent

The pregnancy, neonatal outcomes and women's health register is integrated within the MSBase Registry [registered with World Health Organisation (WHO) International Clinical Trials Registry Platform ID ACTRN12605000455662]. The MSBase Registry has ethics approvals or exemptions granted by each participating site's institutional review board. MSBase was approved by the Alfred Health Human Research Ethics Committee and by the local ethics committees in participating centres.

Leadership

The pregnancy, neonatal outcomes and women's health registry is governed by an International Clinical and Scientific Leadership Group comprising eight MSBase members at this time. The governance committee includes clinicians and scientists with expertise in MS, pregnancy and women's health.

Data acquisition

Data will be collected during outpatient neurology visits, reflecting real-world, routine clinical care. All women regardless of clinical course (CIS, RRMS, SPMS, PPMS) will be followed from any stage of pregnancy planning or conception.

Mothers will be encouraged to provide confirmatory documentation when reporting birthweights, and congenital abnormalities. Congenital abnormalities will be reported according to EUROCAT classification criteria for neonatal complications and malformations (see Table 1).[30] Each foetus/neonate from multiple births will be tracked individually, with prospective documentation of neonatal outcomes at birth. Detailed breastfeeding data including periods of exclusive and non-exclusive breastfeeding will be captured. Maternal comorbidities will be captured using MedDRA. Data will be anonymised and aggregated for the purposes of analysis and reporting. However, country of pregnancy/birth information will be available to account for country-specific clinico-legal practices and cultural norms that may impact pregnancy, maternal or neonatal outcomes.

The pregnancy, neonatal outcomes and women's health registry is fully integrated with detailed demographic, clinical, paraclinical and DMT use data in the MSBase Registry.[31] Therefore, clinical outcomes [peripartum relapse, expanded disability status *scale* (EDSS) scores], together with DMT-exposure in pregnancy (or, in the instance of long-lasting DMT, the gap between last dose and pregnancy start) will be accurately ascertained. Safety events and their relation to DMTs are recorded using MedDRA functionality. Comparator cohorts using identically ascertained clinical outcomes data are readily available for all analyses. For example: DMT-unexposed pregnancies in the context of safety and neonatal outcomes studies; or women who have never had a pregnancy in the context of long-term outcomes studies.

Data quality checking

The Registry has been designed with inbuilt data checking procedures including date plausibility checks, and queries for very low ($\leqslant$2500 g) or very high ($\geqslant$4500 g) birthweights.

Safety monitoring

Data within the MSBase Registry are de-identified, as such, each participating site is responsible for local safety compliance and reporting.

Registry limitations

At present, we will not be capturing pregnancy data as it relates to males with MS fathering children with healthy mothers, a recognised understudied area. However, we hope to build this capacity in the future. Secondly, we recognise that this registry may largely capture health,

Table 1. Pregnancy, neonatal outcomes and women's health register data fields.

Field	Definition
Patient ID[a]	Patient globally unique identifier (system generated)
Maternal ethnicity	Admixed; African; Asian; European; Hispanic; Indigenous; Inuit; Jewish; Middle-Eastern; Other
Last menstrual period[b]	Date of last menstrual period
Estimated delivery date[b]	Based on ultrasound
Assisted reproductive technology method	None; IVF; IUI; ovulation drugs; other
Pregnancy end date[a]	End date of pregnancy
Gestation period	Length of pregnancy, auto-calculated by system
Pregnancy outcome	Ongoing; term delivery healthy (⩾37 weeks); pre-term delivery healthy (<37 weeks); term delivery with congenital abnormality (⩾37 weeks); pre-term delivery with congenital abnormality (<37 weeks); miscarriage (<20 weeks); miscarriage (⩾20 weeks); ectopic pregnancy; elective termination; neonatal death (>20 weeks)
Obstetric/maternal complications	None; unknown; antepartum haemorrhage; cervical incompetence; chorioamnionitis; gestational diabetes; intrauterine growth restriction; low birth weight; large for gestational age; oligohydramnios; polyhydramnios; positional deformity; pre-eclampsia/eclampsia; pregnancy-induced hypertension; premature membrane rupture; placental abruption; placenta previa; pre-term labour; Rh incompatibility; thromboembolism; toxoplasmosis; cytomegalovirus; herpes; measles; parvovirus B19; rubella; chlamydia; group B strep; listeriosis; syphilis; other
Delivery method	Vaginal delivery; vaginal delivery assisted; elective Caesarean; emergency Caesarean
Reason for termination/ miscarriage	Unknown; maternal medical; non-medical DMT exposure; cardiac malformation; Down's syndrome; other chromosomal abnormality; gastroschisis; limb shortening defect; neural tube defect; unviable foetus; other
Congenital abnormality (EUROCAT classification)	Unknown; amniotic bands; anal atresia/stenosis anencephaly; cerebral palsy; chromosomal defect – other; cleft lip without cleft palate; cleft palate only; clubfoot; coarctation of the aorta; craniosynostosis; cystic kidney disease; diaphragmatic hernia; Down's syndrome (trisomy 21); encephalocele; endocardial cushion defect; extra or horseshoe kidney; gastroschisis; hypospadias; inguinal hernia; limb reduction defects; metabolic disorders; neural tube defects; omphalocele; polydactyly; pyloric stenosis; renal agenesis and dysgenesis; renal collecting system anomalies; small intestinal atresia/stenosis; spina bifida; tracheo-esophageal fistula; undescended testicle; ventricular septal defect; other
Birth weight	Grams or pounds and ounces
Sex[a]	Female; male
Breastfeeding	Yes; no
Breastfeeding start date[c]	Start date of breastfeeding
Exclusive breastfeeding end date	End date of exclusive breastfeeding
All breastfeeding end date[c]	Date that all breastfeeding including non-exclusive breastfeeding ended
Comorbidities	Captured *via* integrated MedDRA functionality

[a]Denotes compulsory fields (minimum dataset).
[b]Mandatory field, but only one of the two required (bidirectional calculation).
[c]Compulsory if Breastfeeding 'yes' selected.
DMT, disease-modifying therapies; IUI, intrauterine insemination; IVF, in vitro fertilisation

pregnancy and neonatal outcomes of women seen in tertiary referral centres; therefore, those women managed outside a tertiary-referral context could be underrepresented.

Preliminary results

MSBase currently databases over 75,000 patient datasets from 36 countries. This includes 20,495 women of childbearing potential (aged 18–45) currently enrolled in the registry, of whom 14,012 are under 40 years of age across Asia, Australasia, Europe, the Middle East and North African Region, North America, and South America.

To date, the MSBase Registry has recorded 18,682 pregnancies, reported both prospectively and retrospectively. In the short time since implementation of the new Pregnancy Registry within MSBase (11 May 2020) we have captured data on 58 pregnancies that have ended (8 miscarriages, 1 elective termination, 17 pre-term births, and 32 term births), as well as a further 49 newly conceived pregnancies with no outcomes yet reported (data extracted 10 January 2021). These 107 prospectively reported pregnancies have been contributed from Australia (26), Belgium (6), Canada (1), Spain (3), Italy (2), Kuwait (39) and Turkey (30).

Discussion

We need a strong evidence base to counsel women with respect to pregnancy planning, the choice of DMT use in the intrapartum period, impact of DMT exposure on neonatal outcomes, and the impact of pregnancy on long-term MS outcomes. In addition, evidence pertaining to safety of long-term DMT exposure as well as the effect of hormonal changes on disease outcome require larger longitudinal data collection. A number of MS pregnancy registries have been developed to address these important questions including the German, Canadian, United States (US) pregnancy Registers, together with others currently in development across the UK, Denmark, Italy, Sweden and France.[14,15,32,33]

MSBase is working in collaboration with a number of these large, established MS Registries through the Big MS Data Group Network (BMSD), including the Danish MS Registry, the Swedish MS Registry, the Italian MS Registry and the French Registry of Multiple Sclerosis (OFSEP). The BMSD have developed a core protocol with aims to collect and combine data on rates of serious adverse events (SAEs) in patients with MS exposed to approved DMTs as well as pregnancy outcomes in women with MS (for those registries collecting pregnancy data). The protocol details variables to be collected, including the use of the EUROCAT classification of foetal defects, ensuring consistency of data collection across registries. This will permit the merging of data, to form a larger pregnancy cohort, increasing power of results and permitting the reporting of potentially very rare adverse events.

Knowledge gaps regarding fertility, delivery methods, and maternal/obstetric complications, together with long-term MS outcomes in women with and without pregnancies impact evidence-based clinical advice available to women contemplating pregnancy.

The consequence of disease-modifying drug use during conception and breastfeeding on foetal and neonatal outcomes requires long-term monitoring to identify any adverse effects associated with therapy use during critical developmental periods. Unbiased, comparator datasets with identically ascertained data are critical to identify DMT-associated teratogenic risks. Our new MSBase pregnancy, neonatal outcomes and women's health registry has been designed to facilitate the collection and analysis of meaningful data without becoming too onerous for the clinician. This Registry has been developed to allow safety and clinical outcomes studies in an era where pregnancies are increasingly exposed to DMT use.[11] We believe that our Registry will contribute meaningfully to answering questions related to safety and clinical outcomes in pregnant women, for those planning pregnancy and aid in the development of comprehensive, tailored pregnancy guidelines.

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Author contributions

Conception and study design: VGJ, OS, KH, AVDW, HB, LR and OG. Drafting the manuscript: VGJ. Editing and reviewing of the manuscript: all authors.

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Conflict of interest statement

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