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Pregnancy and Infant Outcomes From an Ongoing Worldwide Enhanced Pharmacovigilance Program of Cladribine Tablets: 7-Year Results of MAPLE-MS

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RESEARCH IN CONTEXT

1. **Since 2017, there has been a single MCA (an atrial septal defect) reported to the global patients safety database.**
2. **The prevalence of MCA among live births following exposure to cladribine tables is in line with published estimates from MS populations treated with DMTs (3.0%) and the general population (2.5%).[1,2]**

OBJECTIVES

To assess pregnancy and fetal outcomes after exposure to cladribine tablets in:

1. **Women with multiple sclerosis (MS) exposed to cladribine tablets during pregnancy or within 6 months before conception (maternal cohort)**
2. **Pregnancies fathered by men with MS exposed to cladribine tablets within 6 months before conception (paternal cohort)**

INTRODUCTION

With its use being contradicted during pregnancy, **limited information exists concerning pregnancy and infant outcomes** on exposure to **cladribine tablets** before or during pregnancy in women with MS.

MAPLE-MS, an enhanced pharmacovigilance program, uses a global patient safety database **to assess pregnancy outcomes after exposure to cladribine tablets**.

METHODS

- Data for this **7-year interim analysis of MAPLE-MS** were collected between August 22, 2017 and April 1, 2024.
- The primary outcome is the **prevalence of major congenital anomalies (MCAs) among live births** (fetal outcome).
- Secondary pregnancy outcomes include live birth, elective termination, spontaneous abortion, ectopic pregnancy, and stillbirth.
- The prevalence of each outcome, including 95% confidence interval (CI), was calculated; cases were reported prospectively and retrospectively.

RESULTS

- Pregnancy outcomes are shown in **Table 1**.
- In the maternal cohort, 336 pregnancies were reported.
  - Mother's median age at last menstrual period (LMP): 31 years (interquartile range [IQR] 27, 35)
- In the paternal cohort, 47 pregnancies were reported.
  - Mother's median age at LMP: 34 years (IQR 32, 36)

Table 1. Case Disposition of Pregnancies by Cohort

Variable, n (%)	Maternal cohort (N=336)	Paternal cohort (N=47)
Known	157 (46.7)	16 (34.0)
Unknown/lost to follow-up[a]	101 (30.1)	20 (42.6)
Pending	78 (23.2)	11 (23.4)

[a]Cases are declared "unknown" 24 months after date of initial report and when no pregnancy outcome is present in the database.

- Timing of exposure to cladribine tablets in relation to known pregnancy outcomes is shown in **Table 2**.

Table 2. Timing of Exposure to Cladribine Tablets

Timing	Maternal exposure, outcome known (N=157), n (%)	Paternal exposure, outcome known (N=16), n (%)
Before pregnancy	95 (60.5)	11 (68.8)
1 month	6 (3.8)	4 (25.0)
2 months	10 (6.4)	0 (0.0)
3 months	10 (6.4)	0 (0.0)
4 months	14 (8.9)	1 (6.3)
5 months	12 (7.6)	0 (0.0)
6 months	5 (3.2)	0 (0.0)
Unknown[a]	38 (24.2)	6 (37.5)
First trimester	34 (21.7)	NA
After first trimester	0 (0.0)	NA
Unknown timing	28 (17.8)	5 (31.3)

[a]Cases within 6 months before date of LMP but exact timing is unknown.
LMP, last menstrual period; NA, not applicable

Primary outcome: MCA

- In the maternal cohort, there was one reported MCA (an atrial septal defect); the first reported since 2017. Exposure for this case occurred 3 months before pregnancy. The prevalence of MCA (excluding genetic anomalies) was 1.1% of live births (1/89; 95% CI: 0.0, 6.7).
- In the paternal cohort, no cases of MCAs were observed in live births (0/13).
- These results align with published estimates from the general and MS poulations.[1,2]

Secondary outcomes

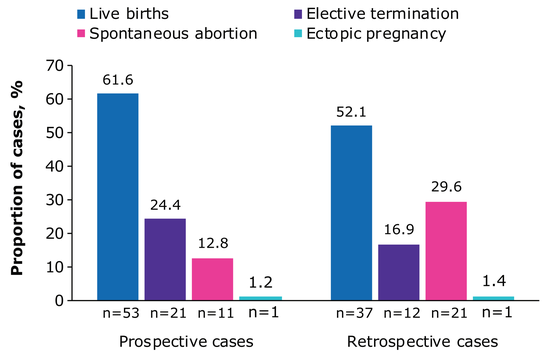
- Known pregnancy outcomes for the maternal (N=157) and paternal (N=16) cohorts are shown in **Table 3** and by case reporting type in **Figure 1**.

Table 3. Prevalence of Pregnancy Outcomes in Pregnancies With Known Outcomes, by Maternal and Paternal Cohorts

Pregnancy outcome, n (%), [95% CI]	Maternal exposure (N=157)	Paternal exposure (N=16)
Live birth[a]	90 (57.3), [49.5, 64.8]	13 (81.3), [56.2, 94,2]
Pre-term delivery[b]	6 (6.7), [2.8, 14.1]	1 (7.7), [0.0, 35.4]
SGA[b,c]	1 (1.1), [0.0, 6.6]	0 [0.0, 26.6]
Elective termination[a]	33 (21.0), [15.3, 28.1]	0 [0.0, 22.7]
Patient decision/wish[d]	17 (51.5), –	–
Other[c,e]	16 (48.5), –	–
Spontaneous abortion[a]	32 (20.4), [14.8, 27.4]	2 (12.5), [2.2, 37.3]
Ectopic pregnancy[a]	2 (1.3), [0.1, 4.8]	0 [0.0, 22.7]
Stillbirth[a]	0 [0.0, 2.9]	1 (6.3), [0.0, 30.3]

[a]The denominator is the number of pregnancies with known outcomes in the cohort. [b]The denominator is number of live births in the cohort. [c]Defined by MedDRA Preferred Term; prevalence of SGA might reflect underreporting. [d]The denominator is the total number of elective terminations in the cohort. [e]'Other' includes unknown, n=12 (36.4%); no consent, n=2 (6.1%); termination of pregnancy due to fetal anomaly, n=1 (3.0%); and medical reason, n=1 (3.0%).
CI, confidence interval; SGA, small for gestational age

Figure 1. Known Pregnancy Outcomes (Maternal Cohort) by Case Reporting Type (Prospective and Retrospective)



CONCLUSIONS

- **Among pregnancies with known outcomes, the majority were live births and low rates of elective termination and stillbirth were reported. One case of an MCA has been observed since the launch of cladribine tablets.**
- **Although interpretation is limited by the high loss to follow-up and the relatively small number of pregnancies with known outcomes, the results are in line with previous reports.[1,2]**
- **The data uphold current prescribing recommendations to avoid pregnancy during treatment; however, they also do not demonstrate increased rates of adverse outcomes following treatment exposure.[3]**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

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Supplementary Materials

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