Gestational outcomes of patients with multiple sclerosis: A tertiary centre experience

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Background. Multiple sclerosis (MS) is a disease that predominantly affects the young female population. It is important for an obstetrician to know the effects of pregnancy on MS, and vice versa.
Objective. To demonstrate the impact of MS on pregnancy outcomes.
Methods. We retrospectively evaluated demographic features, clinical characteristics, and obstetric outcomes of 47 pregnancies in 24 patients with MS, between January 2007 and December 2016.
Results. Patients were divided into three groups: (*i*) 35 pregnancies in patients with MS who were in remission at the beginning of pregnancy; (*ii*) 10 pregnancies in patients with MS whose disease was exacerbated at the beginning of pregnancy; and (*iii*) 2 pregnancies in patients with active MS whose symptoms were relieved after becoming pregnant. The overall early pregnancy loss rate was 36.2%, whereas it was 60% and 31.4% in the exacerbation and remission groups, respectively; and the overall preterm delivery rate was 30%, while it was 29.1% and 50% in the remission and exacerbation groups, respectively.
Conclusion. Miscarriage and preterm delivery seem to be significant obstetric complications in pregnant women with MS.

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Multiple sclerosis (MS) is a chronic neuroinflammatory disease of the central nervous system (CNS) that causes demyelination and neurodegeneration in the spinal cord and brain.[1,2] It progresses with relapses and remissions.[1,2] Its overall prevalence is 33 per 100 000, and a large number of people worldwide are estimated to be affected by the disease.[1,3] Although the prevalence varies considerably among different countries,[4,5] MS is the leading cause of neurological disability in the young adult population following traumatic events.[6] MS is more common in women than men, with a female-to-male ratio of approximately 3:2.[7]

MS is a multifactorial disease in which genetic susceptibility, environmental factors and immunopathological processes together induce inflammation, demyelination and degeneration of the CNS.[1,8-13] Although there are several theories about the pathogenesis of this disease, the exact cause has not yet been identified.[9,14-18]

The diagnosis is frequently made according to the revised 2010 McDonald criteria, which include clinical findings, laboratory results and radiological screening patterns.[19] The clinical courses that were described by the National Multiple Sclerosis Society in 1996 were revised in 2013. The frequently seen clinical courses are: (*i*) relapsing-remitting MS; (*ii*) secondary progressive MS; and (*iii*) primary progressive MS. Furthermore, a clinically isolated syndrome and a radiologically isolated syndrome, which are accepted as preceding phases, have been described.[20]

As MS is a disease that predominantly affects the young female population, it is important for an obstetrician to know the effects of pregnancy on MS, and vice versa. Recent studies indicate that pregnancy may have a positive effect on the disease, whereas MS may affect the birth weight of the infant, and the type of delivery. The postpartum period and lactation may also have an impact on the progress of MS.[21-29]

There is no consensus on the treatment of MS during pregnancy. However, discontinuation of disease-modifying drugs during pregnancy is recommended, owing to concerns about the possible teratogenic effect of the drugs.[30-34]

The aim of the present study was to evaluate the clinical progression of MS during pregnancy, and the pregnancy outcomes of patients with MS, in a single-centre retrospective study.

Methods

The study was approved by the ethics committee of Hacettepe University (ref. no. GO 17/425). The study was conducted in accordance with the Declaration of Helsinki. The patients provided informed consent for participation in the research study, and their privacy was protected.

We retrospectively evaluated the demographic features, clinical characteristics and obstetric outcomes of patients with MS, within the framework of the antenatal care programme of the Division of Perinatology, Hacettepe University, between January 2007 and December 2016. The study sample consisted of 47 pregnancies in 24 patients with MS. Data were obtained from the Hacettepe University Perinatal Medicine database.

The diagnosis of MS was made according to clinical findings that were supported by ancillary tests performed by neurologists. Systemic neurological examination, laboratory tests, and radiological imaging procedures were used for the definitive

diagnosis. Magnetic resonance imaging, evoked potentials and, in some cases, even lumbar punctures for oligoclonal bands were performed. However, when pregnancy was confirmed, immunomodulatory drugs were stopped, as there is a lack of evidence on the safety of these medications for the fetus. During exacerbations, steroid treatment was administered. Antenatal follow-up of the patients was done in the Division of Perinatology. The follow-up was carried out by the Hacettepe University Hospital Neurology Department, along with the Division of Perinatology. In this small series, we did not classify the cases according to the clinical course of MS; however, we divided the pregnancies into three groups according to the presence of MS-related complaints that necessitated steroid treatment during pregnancy, as follows: (*i*) absence of additional MS-related complaints that necessitated steroid treatment (*n*=35); (*ii*) presence of MS-related complaints before gestation, but with disappearance of signs and symptoms after pregnancy (*n*=2); and (*iii*) presence of MS-related complaints after pregnancy that necessitated steroid treatment (*n*=10). MS-related complaints were defined as the presence of ocular symptoms (ptosis and/or diplopia), bulbar symptoms (dysarthria, dysphagia and fatigable chewing) and/or proximal limb weakness.

Statistical analysis was conducted by using Statistical Package for the Social Sciences version 22 (IBM Corp., USA)). Means and standard deviations (SDs) were used for numerical values, and percentages were calculated.

Results

The mean (SD) age of the patients was 28.0 (5.1) years. The mean gravidity and parity were 2.0 (1.5) and 1.0 (0.0), respectively. The mean (SD) gestational age at birth was 261.0 (24.0) days. The mean (SD) birth weight of the infants was 3014.6 (817.9) g. The mean postpartum haemoglobin value was 10.9 (1.5) g/dL, and the mean (SD) 5-min Apgar score was 9 (0.5) (Table 1).

When we evaluated the pregnancy outcomes of the 47 MS pregnancies, we found 15 miscarriages (31.9%), 1 pregnancy termination due to triploidy (2.1%), 1 ectopic pregnancy (2.1%) and 30 deliveries (9 preterm (19.1%) and 21 term (44.7%)). The obstetric outcomes are shown in Table 2.

Table 1. Demographic and obstetric variables with postpartum haemoglobin values (*N*=47)

Variable	*n*	Range	Mean (SD)
Age (years)	47	19 - 39	28 (5.1)
Gravida	47	1 - 7	2 (1.5)
Parity	12	1 - 1	1 (0.00)
Gestational age at birth, days	30	154 - 284	261 (23.9)
Birth weight (g)	30	200 - 4 320	3 014.60 (817.9)
Postpartum haemoglobin (g/dL)	30	7.50 - 13.70	10.90 (1.5)
Apgar score	30	0 - 10	9 (0.5)

Table 2. Pregnancy outcomes (*N*=47)

Variable	*n* (%)
Term	21 (44.7)
Preterm	9 (19.1)
Miscarriage	15 (31.9)
Pregnancy termination	1 (2.1)
Ectopic pregnancy	1(2.1)

MS exacerbation was seen in 10 pregnancies (21.2%), and steroid treatment was required during the pregnancy in these cases. The miscarriage rate was 60% (6 of 10) in this group. The remaining 4 patients delivered without any perinatal complications (2 preterm and 2 term deliveries). Remission was observed in two pregnancies in women with active MS at the beginning of pregnancy; both of these patients delivered at term without any complications. Table 3 shows the outcomes of the remaining 35 pregnancies in patients with MS who were in remission at the beginning of pregnancy. Twenty-four (68.6%) of these patients delivered without any perinatal complications (7 preterm and 17 term deliveries). The overall preterm delivery rate was 30.3% (9 of 30). The gestational ages of the nine preterm deliveries were between 32 weeks and 36 weeks 5 days. The mean birth weight of the infants in these nine preterm deliveries was 2 380 g.

Adverse effects of lactation and flare-up of the disease were observed in two pregnancies in the first 6 months of the postpartum period (2 of 30 (6.6%)).

Gestational diabetes mellitus was observed in one patient (2.1%). Neither gestational hypertension nor pre-eclampsia was observed in these pregnancies. Preterm prelabour rupture of the membranes was observed in three patients (all preterm deliveries) (3 of 30 (10%)). There were no major congenital anomalies.

There were 30 births in 47 pregnancies (63.8%). Thirteen (43.4%) infants were delivered by spontaneous vaginal birth (no labour induction), and 17 (56.6%) were delivered by caesarean section (CS). Sixteen (53.3%) infants were male, and 14 (46.7%) were female.

Discussion

MS mostly affects the young adult population, as the mean age of onset ranges from 28 to 31 years.[10] The mean age of the patients in our study was 28 years, which is consistent with the literature.

In this study, the overall early pregnancy loss rate was 36.1% (17 of 47), which is higher than the rate in women without MS.[35] We also found that the early pregnancy loss rates were 31.4% (11 of 35) and 60% (6 of 10) in the remission and exacerbation groups, respectively. This may be due to the injury of the syncytiotrophoblasts, endovascular trophoblasts covering the tip of the spiral arteries, endothelial cells of the spiral veins, superficial/glandular epithelial cells of the decidua (intervillous space of the placenta), induced by MS-related inflammatory processes, and the entrance of cell degradants of these tissues into the maternal circulation. These biological events result in impaired implantation and a disturbed fetal perfusion. These mechanisms might be the reason for the high early pregnancy loss rate in patients with MS.[36]

It has been reported that preterm delivery and intrauterine growth restriction are more frequent in pregnancies of women with MS.[27-29,37] In this study, the prematurity rate was 30.3% (9 of 30), which is consistent with the literature. On the other hand, the preterm deliveries were late preterm births, and the mean birth weight of the neonates was 3 014.60 g, without any perinatal loss. The mean 5-minute Apgar score was 9 in our study group.

In this study, the rate of exacerbation of MS was 21.3%, which is higher than that reported in previous studies.[21,23-25] On the other hand, the miscarriage rate was 60% in patients with MS with disease exacerbation, and only one pregnancy with intrauterine growth

Table 3. Antenatal outcomes of patients with multiple sclerosis according to disease status

	n (%)					
Disease status	**Term + AGA**	**Miscarriage**	**Preterm**	**Macrosomy**	**Pregnancy termination**	**Ectopic pregnancy**
Remission during pregnancy (*n*=35)	17 (48.6)	9 (25.7)	7 (20)	0	1 (2.8)	1 (2.8)
MS exacerbation during pregnancy (*n*=10)	2 (20)	6 (60)	2 (20)	0	0	0
Active MS but remission after pregnancy (*n*=2)	1 (50)	0	0	1 (50)	0	0

AGA = appropriate for gestational age; MS = multiple sclerosis.

restriction was included in this group. These findings may support the theory claiming the adverse effect of placental intervillous space inflammation.[36]

The main strength of the present study was its evaluation of MS in pregnancy in terms of the obstetric outcomes related to the course of the disease. The relatively small number of patients, single-centre experience and retrospective design were the main limitations of the study.

In this study, the CS rate was 56.6%, consistent with the high CS rates for women with MS reported in the literature.[27-29] The indications for CS are complicated in patients with MS, and very much dependent not only on obstetric factors, but also on the severity of clinical symptoms.

Conclusion

Pregnancy in patients with MS necessitates a multidisciplinary antenatal care programme Individualised management is important, to have lower perinatal morbidity and mortality. Patients with MS can be safely allowed to conceive when they are in remission, and their assessed risk is low. Pregnancy has no adverse effects on MS that may lead to serious deterioration of the disease.

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