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Multiple sclerosis and pregnancy as a significant social problem in modern neurology

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Abstract
Along with the increasing number of reported cases, multiple sclerosis, one of the main causes of disability among young adults, is nowadays an increasingly common health problem. Considering the fact that it occurs mainly between 20 and 40 years and affects women more often, the question of the impact of the disease on pregnancy becomes obvious. In view of the wide selection of drugs for various purposes and often highly individualized forms of therapy, it seems also important to determine the safety profile of these agents in relation to the health of the pregnant woman and the fetus. All of this is a significant challenge for neurologists and obstetricians and is the subject of many research and studies. The awareness of society, especially women, in the face of the growing problem seems to be equally important. This paper summarizes the current state of knowledge on these issues.

Keywords: pregnancy, women's health, reproductive health, mulitple sclerosis, neurology

Introduction

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease. It affects only 2 out of 100,000 people in Japan or in sub-Saharan Africa, however, in North America or Northern Europe, the incidence sometimes reaches as much as 100 people out of 100,000 [1] [2]. While the average European incidence in the last three decades is about 83 per 100,000 people, in Poland it is estimated slightly less, as 55-57 people per 100,000 [3] [4]. There are many types of disease. The most common is the relapsing- remitting form (RRMS) [5]. Those

who suffer from it on a daily basis may not feel any symptoms, and these affect them once in a while when there is a relapse. Slightly less often, only 15% of cases, is primary progressive (PPMS) [6]. The mixed type with secondary progressive characteristics (SPMS) is even more rare [7]. Finally, we also distinguish the type of progressive relapsing (PRMS) [8]. Diagnosis is usually based on McDonald's criteria, which, apart from clinical symptoms, also include MRI findings and examination of the cerebrospinal fluid [9]. The prognosis varies depending on the type of disease and individual aspects of a given patient, but it usually leads to disability and more frequent hospitalizations, drastically reducing the quality of life [10].

The treatment of multiple sclerosis is not limited to a single drug that would be a cure-all solution [11]. On the contrary, there are many treatment strategies based on a wide range of drugs that are constantly expanding [12]. These drugs, however, do not cure, and are known as disease-modifying agents (also widely named as disease-modifying treatment - DMT). It should be noted that one group of drugs are those used to control relapses, and other drugs are used to control the disease, reduce the number of relapses, and slow the progression of neurological deficits (DMT as mentioned) [13]. It should also be noted that the progressive forms of the disease are much more difficult to treat [14]. The wide range of drugs differs not only in terms of the nature of the disease, but also in the level of tolerance in a given patient, which makes the treatment of multiple sclerosis even more difficult and requires more individualization from the physician [15].

Nowadays, multiple sclerosis, like many other autoimmune diseases, is an increasingly common health problem. All over the world, more and more new cases are found, which makes MS one of the most serious social problems in modern neurology [16] [17]. It is worth adding that multiple sclerosis is one of the leading causes of disability in young adults [18]. Considering the fact that it occurs mainly between 20 and 40 years and affects women slightly more often, the question of the impact of the disease on pregnancy becomes obvious for a researchers [19]. An equally important issue is the influence of conventional types of therapy on the course of pregnancy and childbirth. As already mentioned, there are many possible options, they also differ in purpose according to the type of disease, which makes it difficult to create uniform guidelines and indications for the care of a pregnant patient suffering from MS. All of this is a real challenge for neurologists and obstetricians and is the subject of extensive research. The purpose of this paper is to collect and summarize the results of these studies gathered using the Pubmed database . The authors wanted the vast majority of the works cited in this study to come from the last five years and, in exceptional cases, not to exceed ten years, which ensures the most up-to-date knowledge in the field of described issue.

The impact of pregnancy on multiple sclerosis

One of the changes in the pregnant woman's organism is the adaptation of the immune system to the presence of a semiallogenic fetus. Otherwise, it would be exposed to a harmful and potentially lethal immune response. The inhibition of this response is mainly due to hormonal changes. In addition to enabling fetal development, immunomodulation may also have a beneficial effect on the course of autoimmune diseases such as MS, but also on psoriasis and rheumatoid arthritis.

One of the positive effects of pregnancy on MS is the reduction in the frequency of relapses. This is especially noticeable in late pregnancy, when the concentration of sex hormones, both estrogens (estradiol, estriol) and progesterone, is the highest. The study conducted by Confavreux showed a decrease in the relapse rate up to 70% in the third trimester [20]. In the same study, an increase in the relapse rate postpartum was observed, however, after a year after childbirth, the rate was as high as before pregnancy. According to Salemi et al., During pregnancy the relapse rate decreases, but the increase in the first 3 months postpartum was not statistically significant [21]. Another reported effect on the course of MS is an overall improvement in the prognosis of patients who have been pregnant several times. It is expressed in a lesser degree of disability and a longer time to achieve it. An Australian study found that pregnant women are potentially less likely to develop MS [22].

Although pregnancy has an undeniably positive effect on the course of MS, further observations of patients should be made to assess the long-term effects of pregnancy on the course of the disease.

Pregnancy and treatment of multiple sclerosis

As mentioned, there are many drugs that are used to treat multiple sclerosis. Discussion of their selection depending on the type, course and phase of the disease would significantly exceed the scope discussed in this paper. Instead, we focused on discussing individual drugs in terms of their safety during pregnancy, together with a summary of the strategy for their selection in this aspect. Pregnancy may sometimes alleviate the course of the disease and allow the complete discontinuation of therapy, however, discontinuation may sometimes have more serious consequences, and in many cases it is recommended to conduct treatment before, during and after pregnancy, while breastfeeding.[23] [24] [25].

Interferon beta (IFN-β) seems to be a safe drug during pregnancy, which was reflected in the decision of the EMA (European Medicines Agency), which has authorized the use of this medicine before, during and after pregnancy. Numerous studies confirm that there are no significant differences in children born to mothers taking and not taking this drug [26] [27] [28]. This may be due to, inter alia, the fact that it does not pass through the

placenta due to its structure [29]. Breastfeeding is similarly safe, although some of the drug passes into the milk [30] [31].
Glatiramer acetate does not cross the placenta as well . In its case, studies also show that there is no significant effect on children from pregnancies of mothers receiving treatment for MS and using GA, and breastfeeding is similarly safe [27] [32] [31]. It is worth noting that discontinuation of treatment, either with GA or with the aforementioned interferon beta, may lead to increased relapses of MS postpartum, this is presumed to be due to the latency period before resuming treatment becomes effective again [33].
Similar results seem to apply to Dimethyl Fumarate [34]. However, the collected data are too uncertain and conducted on too narrow groups to consider this drug safe. There is, however, evidence that it should not be used while breastfeeding [35].
Teriflunomide has a proven teratogenic effect on the fetus which it has demonstrated in animal studies [36]. Although many studies conducted on human fetuses do not seem to confirm this, and the observed embryotoxic effects do not differ in their amount from the general population, this drug is rather not recommended for use in pregnant patients [37] [38]. The same applies to Fingolimide . This drug is not recommended for use by EMA [39]. There are studies showing its harmfulness to the fetus [40]. However, many studies, while proving the occurrence of fetal defects, also indicate no differences in their frequency compared to the general population [41] [42].
Natalizumab is safe for the fetus during pregnancy and breastfeeding [43] [44]. It has also been shown that stopping its use during pregnancy can lead to a severe relapse after having a baby [45]. In addition, children born to mothers taking Natalizumab should be examined for anemia and thrombocytopenia, as these, although not teratogenic, may sometimes occur as a result of such therapy [46]. Alemtuzumab seems to be similarly safe, however, its use during breastfeeding is not recommended as it accumulates in high concentrations in mother's milk [47] [48]. In addition, it can cause autoimmune thyroiditis, the underactive effect of which affects the development of the fetus, which makes its use during pregnancy questionable overall [49] [50]. Such complications are not present as ocrelizumab is taken, but for similar reasons, its use during breastfeeding is also not recommended [51] [52].
Although many of the drugs presented here appear to be safe, some of them even have EMA endorsements, the American Food and Drug Administration (FDA) is more conservative about the safety of these drugs. According to the FDA, category B (meaning "no evidence of fetal harm in animal studies") only has Glatiramer Acetate. Interferon beta, like Natalizumab or Alemtuzumab, as well as Dimethyl Fumarate have category C (which means "evidence of fetal harm in animal studies or no available data"). The teratogenic Fingolimide has the same category. Category X (i.e. "not indicated for use during pregnancy due to evidence of fetal harm in humans") is for Teriflunomide only.

Conclusions

Due to its epidemiology, multiple sclerosis is an important and more and more frequent problem in patients who become pregnant and constitutes a serious clinical challenge. The problem is also of a social nature, the fear of getting pregnant among patients undergoing treatment for MS and their lack of awareness and knowledge about the impact of the disease on pregnancy and vice versa, may lead to the abandonment of reproductive plans, which often has a tragic impact on mental health and well-being. The study of these compounds is of significant clinical importance and may contribute to building more and more awareness among physicians and, perhaps more importantly, women of childbearing age.
The choice of therapy among pregnant women suffering from multiple sclerosis is difficult and highly individualized. The disease itself seems to have a fairly favorable course during pregnancy, which is associated with changes in the woman's body at that time, which sometimes makes it possible to completely suspend treatment for this period. Although the safety of possible therapies for the mother and the fetus should be taken into account, it must not be forgotten that discontinuation of treatment may have an even worse impact on their health. This is especially true in progressive types of MS. While it is possible to waive therapy, it should be done, but if the risk of relapses or the progression of neurological deficits is high, it is imperative to choose the safest drugs possible. It should be remembered that there are no clear guidelines as to the selection of the drug, only a set of general rules and observations that can facilitate the decision-making can be gathered.
Fingolimod or Teriflunomide, due to its teratogenicity, should not be used in pregnant and breastfeeding women. On the contrary, drugs such as IFN-β or Natalizumab seem to be a promising option. Glatiramer Acetate also seems safe, similarly Ocrelizumab seems to be safely usable. As for Dimethyl Fumarate and Alemtuzumab, it is still difficult to define an unequivocal position, so they should be avoided. It seems generally reasonable to continue those therapies that were given before pregnancy, as long as there is no requirement to discontinue specific medications proven to be teratogenic.
It should be emphasized that multiple sclerosis, even of a progressive nature, is not a clear contraindication to pregnancy [53]. Patients should be aware that in most cases, appropriate therapy allows for a smooth transition through this period and the birth of a healthy child, without negatively affecting the mother's health as well. On the other hand, however, it should be remembered that consulting such a decision with a doctor may

significantly facilitate the selection of therapy, and at the same time have a positive effect on the results of treatment and the course of pregnancy.

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