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IMPACT OF MULTIPLE SCLEROSIS ON INFERTILITY AND IMPACT OF INFERTILITY TREATMENTS ON MULTIPLE SCLEROSIS RELAPSES IN SLOVENIA: MEDICAL OUTLINE, LEGAL AND ETHICAL OUTCOMES

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Abstract Multiple sclerosis (MS) is an autoimmune inflammatory disorder of the central nervous system. It is common in the reproductive period and can lead to infertility and significant disability. The treatment on multiple sclerosis is recently more successful and enables better quality of life, therefore rising hope and desire for the future parents, also in terms of successful infertility treatments. In this context the couples should be managed concerning the detrimental effect of the disease itself on fertility, detrimental effect of the drugs used for treatment on gonads and in terms of the implementation of drugs used for ovarian stimulation and their impact on the basic disease (MS). Article finds solutions on the legal outcomes in situations where infertility treatments may negatively impact the progress of MS, as well as the solutions on how to (successfully) provide infertility treatments to the patients with MS. It proposes interdisciplinary approach between gynecologists and neurologists to perform required weighting of benefits and risks (burdens), deriving from specific action or treatment, whereas for the patients who shall not undergo infertility treatments due to their medical status, related to MS, it proposes storage of gametes under conditions, set by the law.

Keywords
multiple sclerosis, infertility and in vitro fertilization, MAR, ZZNPOB and ZPacP, medical ethics.

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1 Introduction

Chronic neurological diseases (including multiple sclerosis – MS) often occur during the reproductive period. Increasingly, however, successful treatments for such neurological diseases provide people with an ever-improving quality of life, thus enabling childbirth and parenthood. While pregnancy mostly happens spontaneously, if after a year of regular unprotected intercourse at least three times a week there is no pregnancy, we consider the couple infertile. At that time, the couple should be referred to a reproductive gynecologist, who first performs diagnostic procedures and, based on the results, decides on further therapeutic procedures involving either medication, surgery, or assisted reproduction procedures (hereinafter also referred to as AR, ART or MAR).

Treatment options for infertile couples with chronic neurological diseases depend upon answers to several possibilities. We need to know whether the disease itself affects the diminished ovarian reserve (DOR is a condition in which the ovary loses normal reproductive potential, compromising fertility; the condition may result from disease, injury and the normal aging process) and whether the medication we use to treat the underlying disease is gonadotoxic (treatment such as chemotherapy with is toxic to the gonads). It is important not to aggravate the underlying disease with assisted reproduction procedures and to perform these procedures in the most optimal conditions possible. Any treatment of infertile couples with chronic diseases must be interdisciplinary and individual, as the small number of such patients provides little solid data in the literature on which we can rely exclusively.

Regulation in the Republic of Slovenia allows medical treatments which are performed according to the medical doctrine, and in which benefits for the patients can be expected and in which the benefits should outweigh any risks (and burdens) deriving from specific medical treatment or service. Additionally, for every first procedure of biomedically assisted reproduction, there is a requirement of a prior consent on the part of the *competent professional body* (strokovno posvetovalno telo), consisting of a gynecologist, an embryologist, a social worker and a lawyer. Furthermore, every procedure involving donated gametes shall be subjected to additional approval by the National Commission for Biomedically-Assisted Reproduction.

The purpose of this article is to evaluate both the legal and ethical outcomes of the situation when there is the possibility of risk of MS relapses in the course or as a result of infertility treatments. We also will evaluate the legal possibilities for individuals suffering from MS and who seek infertility treatments both presently and in the future. We offer grounds for this evaluation not only by exploring the medical background of both conditions (MS, infertility), but also by providing the legal framework for specific situations, from which we can then derive significant legal (and ethical) burdens.

2 Multiple sclerosis

Multiple sclerosis is an autoimmune inflammatory disorder of the central nervous system of unknown etiology, characterized by demyelination (condition that results in damage to the protective covering – known as myelin sheath – that surrounds nerves) and variable degrees of axonal loss. The disease affects mostly young women (between ages 20 and 40 years) and is one of leading causes of disability in young adults (Orton, 2006: 932–936; Kister, 2013: 1018–1024).

The etiology of MS, although unknown, presumably involves interaction between genetic, environmental, and other factors triggering an aberrant autoimmune attack resulting in damage to myelin and axons (Bruck & Stadelmann, 2005: 221–224). The first clinical event in these patients, can be optic neuritis, incomplete myelitis, or brainstem syndrome (Miller, 2005: 281–288). The course of MS can be variable with a significant proportion of patients experiencing some progression following the initial relapsing remitting phase leading to significant disability (Weinshenke, 1989: 133–146; Lublin & Reingold, 1996: 907–911).

Much progress has been made in the past two decades in treating MS with the advent of effective immunomodulatory therapies which can potentially slow down the progression and alter the disease course.

2.1 Multiple sclerosis and infertility

Fertility seems to be reduced even before the diagnosis of MS and continues to be reduced in established disease (Cavalla, 2006: 231), however, some researchers have reported no effect of MS on fertility (Nielsen, 2011: 546–552; Alwan, 2012: 399–414).

Women with MS are known to have fewer children, which is probably also due to social reasons linked to both having fewer opportunities for finding a partner and avoiding pregnancy connected to physical and/or mental problems. One of the causes of infertility may be accompanied by disorders of the hypothalamic-pituitary-ovarian axis, which are reflected in irregular menstrual cycles and infertility (Thone, 2015: 41-45; Grinsted, 1989: 226- 241). There are additional reports of a lower chance of pregnancy due to an imbalance of sex hormones and gonadotropins, as well as a DOR (Thone, 2015: 41-45; Grinsted, 1989: 241–244).

The best predictor of ovarian reserve is the antral follicle count, the number of which is counted by ultrasound in combination with the serum concentration of Anti-Müllerian hormone (AMH). The serum concentration of AMH does not change according to the different phases of the menstrual cycle (Dewailly, 2014: 370–385). Serum AMH levels rise during childhood, peak at puberty, then remain relatively constant until the age of 30, and then slowly decrease to undetectable menopausal values, indicating a slow disappearance of follicles (Kelsey, 2011: e22024; Lee, 2012: 970–975). Serum AMH levels are known to be lower in autoimmune diseases (Lawrenz, 2011: 1193-1197; Şenateş, 2013: e29–e34).

In a study, Thone and colleagues confirmed that serum AMH levels were lower in MS patients with higher relapse rate (Thone, 2015: 41-45). MS patients have lower serum AMH levels and more patients have very low AMH. Untreated patients are significantly more likely to have very low AMH compared to treated ones (Thone, 2015: 41-45). The biological mechanism of DOR in MS patients is not at present well-understood. However, primary ovarian insufficiency (also known as premature ovarian failure; hereinafter POI). POI is known to be more common in MS patients as well as in various other autoimmune diseases. Similar low serum concentrations of AMH were also observed in systemic lupus erythematosus and Crohn's disease (Lawrenz, 2011: 1193-1197; Şenateş, 2013: e29–e34).

The question arises as to whether MS is a cause of infertility or just the diminished ovarian reserve, which in itself does not signify infertility for young women. The problem arises with postponing parenthood to later years, as AMH is known to decline with age. Thus, POI occurs earlier than in the general population of healthy women and the reproductive period is shorter and completed more quickly. In cases of an estimated poor ovarian reserve, and the patient has no partner and is at risk of POI, we should consider fertility preservation by cryopreservation of oocites or embryos.

More frequent annual disease relapse is known to be associated with lower serum concentrations of AMH and estradiol, fewer antral follicles, and lower ovarian volume (Sepulvela, 2016: 564-568). In patients with rare disease relapse, the ovarian reserve is the same as in healthy women of the same age in the general population (Sepulvela, 2016: 564-568).

2.2 Impact of multiple sclerosis treatment on infertility

Little is known about how immunomodulators affect the ovarian reserve. Thone and colleagues measured lower serum AMH levels in those women with MS who were not undergoing treatment (Thone, 2015: 41-45). Thone's findings also coincide with the results of Guler and colleagues, who found that healthy, age-matched women had the same serum concentration of AMH as MS patients treated with immunomodulators. This study showed that long-term treatment with immunomodulators did not have a negative effect on the ovarian reserve (Cil et. al., 2010: S98).

However, fertility is known to be adversely affected by treatment with cyclophosphamides and high doses of corticosteroids (Ferrero, 2004: 3-9), leading to POI or even amenorrhoea (Cocco, 2008: 1225-1233; Martinelli, 2009: S167-S170).

3 In vitro fertilization procedure

In vitro fertilization (IVF) represents the treatment of last resort for infertility after medication therapies and surgery prove ineffective. IVF is one of the assisted reproduction techniques (ART) where fertilization occurs outside the body, under *in vitro* conditions (Zegers-Hochschild, 2009: 1520–1524).

IVF procedure inclusion indications are both female and male-factor. Indications in women are as follows: tubal cause of infertility, endometriosis, hormonal disorders, uterine cause of infertility, chromosomal abnormalities, unexplained infertility, complementary treatment to surgical treatment, and failed treatment with medication or surgical procedures. Indications in men include: oligo-, astheno-, teratozoospermia, obstructive azoospermia: (congenital, acquired), non-obstructive azoospermia: (iatrogenic, post-traumatic, unexplained), genetic abnormalities, and unexplained infertility.

In the case of oncological and certain autoimmune diseases, which are either themselves a cause of a DOR or are linked to treatment that causes POI, we perform procedures to stimulate the ovaries which follows follicular aspiration to obtain oocytes. Oocytes or embryos are then cryopreserved for later use.

IVF includes the following stages:

- ovarian stimulation with gonadotropins in combination with GnRH analogues,
- control of the number and growth of ovarian follicles using ultrasound examination,
- maturation of oocytes by administering human chorionic gonadotropin (hCG) or GnRH agonists,
- aspiration of ovarian follicles and isolation of oocytes,
- preparation of oocytes and semen in the laboratory for ART procedures,
- fertilization and control of embryo growth and development,
- embryo transfer (ET),
- hormonal support to the corpus luteum.

3.1 Ovarian stimulation with gonadotropins in combination with GnRH analogues (agonists or antagonists)

Ovarian stimulation with gonadotropins is performed in order to promote multi-follicular development and consequently obtain numerous oocytes (Zegers-Hochschild, 2009: 1520-1524). This improves the pregnancy rate and birth rate in IVF procedures. The numerous ovarian follicles synthesize estradiol (E_2) in

granulosa cells, resulting in high non-physiological serum E2 levels, leading to premature LH (luteinizing hormone) surge. To prevent the spontaneous LH surge and consequently spontaneous ovulation, gonadotropins are used in combination with GnRH analogues (agonists or antagonists), which represents an important contribution to improving the IVF procedures (Fleming, 1988: 376-81; Kolibianakis, 2006: 651–71).

A combination of gonadotropins and GnRH analogues is used for ovarian stimulation. The duration of ovarian stimulation depends on the type of GnRH analogues used. GnRH analogues induce down-regulation by affecting the pituitary-hypothalamic axis so that spontaneous LH surge and consequent ovulation do not occur. GnRH agonists first have an agonistic effect with a sharp surge of FSH and LH (*flare up effect*), followed by receptor desensitization, which occurs within 10 to 14 days after continuous administration of the gonadoliberin agonist.

Compared to GnRH agonists, GnRH antagonists immediately and directly inhibit the release of gonadotropins by competitive binding to pituitary GnRH receptors (Al-Inany, 2011: CD001750). They inhibit the LH surge and prevent premature ovulation and luteinization without the initial *flare-up* effect (Ditkoff, 1991: 1811–1817). The advantage of this protocol is the ability to prevent ovarian hyperstimulation.

3.2 Impact of in vitro fertilization on multiple sclerosis relapses

IVF procedures are performed due to various causes of infertility (tubal, endocrinological, and male-factor infertility and endometriosis), but not due to the MS disease itself. Thus, infertility and IVF in MS patients are connected purely by chance.

Although it is difficult to accurately evaluate how IVF procedures affect the underlying disease, it appears that they may affect MS relapses, primarily at the expense of external hormone intake. GnRHs and sex hormones are known to play an important role in immune pathogenesis (Gonzales, 2010: 6-13; Jacobson, 1994: 2516-2523).

Although relatively few women with MS undergo IVF procedures, nevertheless they must be accurately informed of the significantly increased risk of relapse after ovarian stimulation with a combination of gonadotropins and GnRH agonists. The woman's safety is very important and therefore we should take every precaution to decrease the negative impact on the underlying disease through assisted reproduction procedures.

After ovarian stimulation with a combination of gonadotropins and GnRH analogues for 10 – 14 days, there is a 3 to 8-fold increase in serum estradiol and progesterone concentrations. There is also an increase in GnRHs and its receptors, not only due to their expression in the hypothalamus and pituitary gland but also in the immune system, as evidenced by an increased number of monocytes and CD4 T lymphocytes (Chen, 1999: 743-750). Thus, we can conclude that GnRH plays an important role in the relapse of autoimmune diseases. It is difficult to explain why the increased serum concentration of steroid hormones has a different effect in pregnancy when it does not exacerbate the underlying disease, unlike in women undergoing ovarian stimulation procedures. This is probably attributable to the effect of different receptors in different target cells (Correale, 2012: 682-94).

Current research suggests exacerbation of the disease following assisted reproduction procedures (Hellwig, 2013: 219-224). The largest survey was conducted in France. Over an 11-year period, 32 women with MS were treated and 70 IVF procedures were performed; in 48 a combination of gonadotropins and GnRH agonists was used and in 19 a combination of gonadotropins and GnRH antagonists. A significant increase in annual disease relapse rate was recorded in the 3-month period after IVF procedures compared to the 3-month and 1-year period before the procedures. The increase in annual relapse rate was associated with the use of GnRH agonists and women whose procedures were unsuccessful. The negative effect of GnRH agonists is explained by the direct effect of immune system stimulation by the proliferation of mononuclear blood cells, especially B and T cells (Correale, 2012: 682-94).

The association with unsuccessful procedures, however, can be explained by a drop in sex hormones, which is the same as after childbirth, when disease relapses are also more frequent (Confavreux 1998: 285-291). Another reason may be stress, which is also a potentially possible cause of more frequent disease relapses (Mitsonis, 2009: 315-335; Mohr, 2004: 731).

Despite the use of potentially safer GnRH antagonists, Presipino reported a case of a woman affected by relapsing remitting MS who developed acute left ventricular dysfunction of the heart in the context of a severe brainstem relapse, one month after an attempt of IVF (Prestipino, 2018: 1-2).

3.3 Multiple sclerosis in men and infertility

Although there has not been much research in this area, it is known that men with MS have many sexual dysfunction and endocrine system disorders, which can lead to decreased fertility. Sexual dysfunction disorders occur in 73 percent of men due to erectile dysfunction; in 50 percent of men due to orgasmic and ejaculatory disorders; and, in 40 percent of men due to a decreased libido (Haensch, 2006: S3-S9). Hormonal abnormalities are reflected in lower serum concentrations of LH, FSH, and testosterone that are unresponsive to gonadoliberin analogs (Safarinejad, 2008: 1368-1375).

Semen quality is also impaired in these patients, which may be linked to endocrinological abnormalities as well as treatment with immunosuppressive medication (Prévinaire, 2014: 329-336).

4 Legal framework and outcomes

Solving legal issues in healthcare and medicine in Slovenia is often associated with a vivid (and extensive) regulatory landscape. This landscape starts with, *inter alia*, general rules of healthcare and health insurance under the *Health Care and Health Insurance Act* (hereinafter: ZZVZZ), and is followed by the acts relating to health services, namely the *Health Services Act* (hereinafter: ZZDej) and the *Medical Practitioners Act* (hereinafter: ZZdrS), through specific regulations relating to patients' rights - *Patients' Rights Act* (hereinafter: ZPacP), as well as to the regulation related to the other (aspects of) medical services and treatments (Vrtačnik, 2018: 120, Vrtačnik,

2019: 19-21). It also is of importance to remember that the *Code of Obligations* (hereinafter: OZ), the *Criminal Code* (hereinafter: KZ-1) as well as the provisions of *General Administrative Procedure Act* (hereinafter: ZUP) and *Administrative Dispute Act* (hereinafter: ZUS-1) also affect (or are being used in relation) medical treatments and the medical profession. We may conclude, therefore, that the legislative and regulative scheme in Slovenia is both highly complex and partially incoherent (Vrtačnik, 2019: 3). Additionally, autonomous rules and recommendations of the Slovenian Medical Chamber shall be considered, especially in the fields of medical ethics and bioethics (e.g. Code of Medical Deontology, Code of Medical Ethics), as well as in relation to the physician's professional liability (Rules of the Slovenian Medical Chamber Tribunal, followed by the rules of ZZDej, Vrtačnik, 2018: 232-239).

While there is no apparent specific regulation (apart from the general legislation, mentioned above) which would affect treatments in the field of chronic neurological diseases, infertility treatments are governed by the *Infertility Treatment and Procedures of Biomedically Assisted Procreation Act* (hereinafter: ZZNPOB), adopted in 2000, following successful medical practice in this field since early 1980 (Vrtačnik, 2019: 3). By the late 1990's, when it became apparent that the then-existing regulation (Health Measures in Exercising Freedom of Choice in Childbearing Act), had been clearly deficient and had not maintained pace with the progress in the fields of assisted reproduction, the Medical Council established the working group for the preparation of the new legislation (Vrtačnik, 2018: 27). Medical and bioethical experts, legal professionals, as well as theologians were appointed to the working group (Vrtačnik, 2018: 27-28). The ZZNPOB has not been significantly amended or challenged before the Constitutional Court of Slovenia since its adoption. Furthermore, only a few court disputes (before the Administrative Court and Labour and Social Court) have arisen as a consequence of the implementation of the ZZNPOB (Vrtačnik, 2019: 3). Therefore, we consider the ZZNPOB as a stable legislation offering a solid legal framework for the issues related to assisted reproduction in Slovenia. Certain changes to the ZZNPOB are proposed (Vrtačnik, 2018: 387-388) due to both the expiry of time and inter-disciplinary development in the field. The provisions of the Oviedo Convention (Convention on Human Rights and Biomedicine) shall be also applied *mutatis mutandis* for the issues related to biomedically assisted reproduction and related research.

For the purposes of this article, the provisions of ZPacP and ZZNPOB are of the utmost importance. The ZZNPOB governs medical measures supporting a man and a woman's efforts to conceive a child, thus promoting the exercise of the right to the freedom of childbearing (Art. 1 of the ZZNPOB). The legislative text follows the dualism of reproductive medical measures, by defining:

a) infertility treatment as determining the causes of infertility or impaired fertility and removing these causes through expert advice, medicines or surgical procedures (Paragraph 1, Art. 3 of the ZZNPOB); and

b) biomedical assistance in procreation as intracorporal and extracorporal (in vitro) fertilization (Art. 4 of the ZZNPOB). Medically related storage (taking and storing gametes of an individual who is at medical risk of becoming infertile) is considered as infertility treatment in this respect (Paragraph 2, Art. 3 of the ZZNPOB).

In the following text, the ZZNPOB regulates:

a) persons eligible to MAR (Articles 5-7);
b) gamete donation (Articles 8-14);
c) entities and individuals entitled to perform MAR (Articles 15-18);
d) National Commission for Biomedically-Assisted Reproduction (Državna komisija za OBMP, Articles 19-21);
e) execution of AR procedures (Articles 22-29);
f) handling with human gametes and (early) embryos (Articles 30-31);
g) storage of human gametes and (early) embryos (Articles 34-37);
h) scientific and research work (Art. 38);
i) reporting and records (Articles 39-40);
j) maternity and paternity of AR conceived children (Articles 41-42);
k) penal provisions (Articles 43-46); and
l) final provisions (Articles 46-48).

The ZPacP, adopted in 2008, on the other hand, governs patient's rights (Par. 1 Article 1 of ZPacP) with a goal to ensure *equitable, appropriate, safe and quality healthcare services* (Par. 2 Art. 1 of ZPacP). The rights under ZPacP do not interfere with any of the patients' rights determined by other legislative acts or international treaties (Par.

1 Art. 4 of ZPacP), whereas the rights, arising from the health insurance, shall be claimed under provisions of related legislation and by-laws (see ZZVZZ, above). The remainder of the legislative text of ZPacP includes:

- General provisions (Section I., Articles 1-4);
- Provisions on patient's rights (Section II. – Articles 5-53);
- Provisions on patients' obligations (Section III., Art. 54);
- Authorities of the Human Rights Ombudsman (Section IV. Art. 55);
- Procedures for claiming of patients' rights (Section V. – Articles 56-84);
- Provisions on supervision (Section V. – Article 85);
- Penal provisions (Section VI. – Articles 86-87);
- Transitory and final provisions (Section VII. – Articles 88-92).

The provisions of ZPacP shall be used in any medical treatments and services (Idents 22. and 23. of Art. 2 of ZPacP), including infertility treatments (Vrtačnik, 2018: 98-109) and procedures related do diagnosing and treating chronic neurological diseases.

For solving the question on whether infertility treatments are justified and permitted where there is a risk that such treatments either will have a negative impact on the state of MS disease in a specific patient or will influence the relapse of MS disease in a specific patient, the provisions of Article 12 of ZPacP shall be carefully observed, stipulating:

> *"patient is eligible to medical procedure or treatment,…,*
> - *shall it be needed under the medical doctrine,*
> - *shall it be expected to benefit the patient,*
> - *and if it expected for the benefits to overweight the risks and burdens."*

Such provision (in its last ident) represents a clear example of the transition of *basic principles* of medical ethics to the (mandatory) legal regulation. Said provision corresponds to the principle of *medical utility*, which is traditionally recognized as the weighing of benefits and risks (burdens) deriving from specific therapeutic decisions or actions (Vrtačnik, 2019: 260-265). The principle of medical utility derives from *utilitarian theories,* which are considered as part of teleological or consequentialist

theories (as opposed to deontological theories) and involve the evaluation of consequences of specific action (by evaluating positive and negative outcomes) over absolute attachment to the single, possibly objective (ethical or moral) rule or principle (Vrtačnik, 2019: 242-245). However, some authors highlight (Beauchamp, Childress, 2013: 203), in the said context, that while on the one hand *utilitarian ethics* predominantly seek to find general welfare in society to reach (common) equilibrium between rights and obligations of stakeholders, on the other hand *medical utility* is oriented exclusively toward maximizing benefits for a specific person (patient). Therefore, medical utility is attached to the utilitarian paradigm only in the sense of a basic concept (weighing risks and benefits), while it clearly departs from such paradigm regarding the addressee of such weighing (Vrtačnik, 2018: 261). For the same reasons medical utility shall not be equated with *economic utility in treatment*, which evaluates positive and negative outcomes of specific medical treatment in terms of the overall economic sustainability of the medical system.

The principle of *medical utility* is also strongly correlated with the principles of *beneficence* and *non-maleficence*. In the world of contemporary medicine and medical ethics it became apparent that medical treatments cannot consider the principle of non-maleficence *(primum non nocere)* as an absolute prerequisite, especially in relation to invasive procedures in diagnostics and treatment (Vrtačnik, 2018: 261). Some of the procedures are clearly invasive (i.e. harmful in terms of the physical and/or psychological interference into the patient's integrity). However, they nevertheless must be permitted (and also needed) if we are to achieve overall medical benefit for the patient. The weighing under the *principle of utility* therefore shall be seen as a struggle to combine positive and negative effects of specific medical treatments to achieve ultimate (overall) *benefit* for the patient.

Taking these all into account, the evaluation between the benefits and risks (burdens) under Art. 12 of ZPacP shall be done exclusively on a *medical basis* and in relation to the *specific patient* (that is, on a case by case basis). Such evaluation shall be performed in accordance with the *best medical doctrine* and exclusively *to the benefit* of the patient, meaning to best serve (or preserve) the patient's overall medical status.

Based on a review of Chapters 2 and 3 above, it is evident there is a relatively small number of patients with both conditions present (infertility and multiple sclerosis) meaning there is little solid data in the literature on which we can rely exclusively. Therefore, any general rule on the dependency of infertility and multiple sclerosis (in legal terms, under conditions, set under Art. 12 of ZPacP) is difficult to determine. On the other hand, the medical literature certainly gives some (empirical, case report) evidence on the MS relapses due to infertility treatment, also with some serious consequences (ventricular dysfunction of the heart, severe brainstem relapse, etc.), which must not be overlooked. Therefore, we believe the evaluation on risks and benefits arising from a certain therapeutic decision shall be done cautiously and individually by each patient, considering his or her current medical status, also taking into consideration the individualistic nature of Art. 12 ZPacP. However, gynecologists alone should not be responsible for this evaluation. Instead, consultation (and cooperation) with neurologist(s) is strongly needed to achieve overall pathological assessment. The neurologist is the only professional that is fully acquainted with the status of MS disease in each patient and that is best equipped for the evaluation, and to evaluate whether there might be a more suitable time for infertility treatment in a later period of time, considering the development of disease and expected treatment (options) in the future. On the other hand, the gynecologists are able to determine how the development of MS disease can be detrimental to fertility and to assess whether any delay of MAR treatments in patients with MS may significantly lower the possibilities of conception (due to age-related issues and diminishing of ovarian reserve). In other words, a team (multi-discipline) effort is required under these circumstances. For these purposes, also highly relevant are the issues concerning the level of success expected from proposed infertility treatments and the extent to which possible relapses of the MS are expected and the gravity of any such relapses. With respect to infertility treatments (alone), it has been acknowledged so far that those which either offer no or very little (up to 1 percent) chance of success do not outweigh any risks or negative consequence in the patients' physical or psychological integrity and shall be therefore rejected as *futile* (absolute futility, Vrtačnik, 2018: 263, ASRM, 2013: e6-e9). However, for the infertility-related procedures in which greater than 1 percent chances of success are estimated, the evaluation on risks and benefits shall be performed individually (possible *relative* futility, Vrtačnik, 2018: 263). It seems logical to conclude that more risk correlates with higher chances of success and *vice versa*, even though therapeutic decisions must never be made purely on mathematical equations (Vrtačnik, 2018: 264). It also is

important for a dynamic therapeutic assessment to be completed if any of the medical conditions (infertility, MS) may deteriorate or ameliorate in future time.

In this regard, it shall be observed that ZZNPOB (as *lex specialis*), includes (in Articles 5 and 6) legal and other requirements for procedures of biomedically-assisted reproduction to be executed in Slovenia (married or cohabitant partners of opposite sex, of full age, capacity, in fertile period, positive sociological assessment for upbringing of a child, informed consent, etc.), which is crucial when a decision on approval (by the competent professional body or National Commission for Biomedically-Assisted Reproduction, see above) is deliberated. Additionally, the case-law of the Administrative Court of the Republic of Slovenia has clearly established (see Judgment Reg. No. I U 1669/2013 of April 15th, 2014) that no rejection of AR procedures shall be based on criteria which are not prescribed by law. On the other hand, regarding the criteria of *medical indication* (inclusion indication) the court held that such requirement derives *mutatis mutadis* from Articles 2 and 3 of ZZNPOB and that procedures of biomedically-assisted procreation may only be performed in cases of *confirmed medical indication* (Judgment Reg. No. I U 877/2015 of September 29th, 2015). An unsettled question is whether *contraindication* (which appears existent in relation between infertility treatments and MS relapse) may serve as a (formal) reason for rejecting the approval of MAR treatment. Considering that the general provisions of ZZNPOB (especially those listed in Article 2) are clearly oriented into (general, overall) the welfare of parents and a child, the answer shall be possibly affirmative (especially in cases of *severe contraindications*). However, despite this dilemma, every physician may base his or her therapeutic decision upon the provision of Article 12 of ZPacP, which is not diminished in any way by the provisions of ZZNPOB (absence of any direct opposite provisions).

Where the medical decision on the inclusion of an infertility programme for the MS patient is positive/affirmative (based on the provisions of ZPacP), close interdisciplinary monitoring of the development of both medical conditions is needed. On the other hand, in situations where a negative decision is made, possible future inclusion of such patient into MAR programmes shall be considered in the best *benefit* of a patient. In this respect, it is important that ZZNPOB allows medically related storage of gametes, stipulating that infertility treatments also include: "*collection and storage of male or female gametes, belonging to individuals which are, according to the findings of medical science in danger of becoming infertile or infertile.*" (Par. 2, Art. 3 of

ZZNPOB). Gametes can be stored up to five years, with possible prolongation for an additional five years by approval of the National Commission for Biomedically-Assisted Reproduction (Article 35 of ZZNPOB). In addition to provisions of ZZNPOB, provisions of the Act on Quality and Safety of Human Tissues and Cells, for the Purposes of Medical Treatment (ZKVČTC), and the Act Regulating the Obtaining and Transplantation of Human Body Parts for the Purposes of Medical Treatment (ZPPDČT) shall be also considered relevant (Vrtačnik, 2019: 9-16).

5 Conclusion

Multiple sclerosis is an autoimmune disease of the central nervous system which can lead to significant disability and most often occurs during the reproductive period. Therefore, MS patients should be treated in terms of the disease itself and its potential impact on fertility. It remains unclear whether MS is a cause of infertility or just the diminished ovarian reserve, which in itself does not signify infertility for young women but which shortens the reproductive period. There is little solid data in the literature on which we can rely exclusively. We still do not know if MS causes infertility due to disorders of the hypothalamic-pituitary-ovarian axis, which are reflected in irregular synthesis of sex hormones. Little is also known about how autoimmune diseases cause a decrease in ovarian reserve or even POI. Encouraging are the results that treatment with immunomodulators is becoming more successful and appear to have no detrimental effect on ovarian reserve. In case the MS patient needs ovarian stimulation for IVF procedure or acquisition of oocytes for cryopreservation, it is safer to use gonadotropins in combination with GnRH antagonists than GnRH agonists.

Therefore, every physician shall weigh the risks and burdens in order to arrive at a specific therapeutic decision to meet the requirements of Article 12 of ZPacP and to best serve ethical principles of utility and beneficence in treatment. Regarding infertility treatments, an interdisciplinary approach (between gynecologists and neurologists) is strongly encouraged in order to achieve the best possible (overall) outcomes for the specific patient. The evaluation concerning risks and benefits arising from a certain therapeutic decision shall be made cautiously and individually by each patient. Medically related storage of gametes should be offered to MS patients (Article 3 of ZZNPOB) to help mitigate (minimize) the risks that derive from deterioration of fertility status (e.g. due to the loss of ovary reserve), and to

allow for the possibility of infertility treatments in the future should they become necessary.

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