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2.1 The Reproductive Cycle and Fertility/Infertility

2.1.1 Fertility in General

Sexual maturity in women is generally manifested between the ages of 15 and 45 years [4, 11], with the appearance of female sexual characteristics, biphasic hormone production, and a regular menstrual cycle with ovulation and optimal: fertility [4]. The average age of menarche in the human female is between 12 and 13 years [1]. The length of the menstrual cycle in women varies greatly [13]. It ranges from 21 to 35 days, with the average being 28 days [11]. An anovulatory cycle (i.e., no ovulation in the middle of the menstrual cycle) takes place in 8 % of women [4].

The menstrual cycle is usually divided into two phases – the ovarian and the uterine. The first part of the ovarian cycle is the follicular phase, which is necessary for the maturation of the follicles and the release of an egg [10].

2.1.2 Ovarian Cycle

In the first days of the menstrual cycle the concentration of follicle-stimulating hormone (FSH) rises, consequently stimulating some ovarian follicles. In the course of this process, all but one dominant follicle stop growing, and the remaining one will mature in the ovary. This is known as a tertiary follicle or the Graafian follicle, and

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inside this follicle is the ovum. In addition, estradiol suppresses the production of luteinizing hormone (LH) from the anterior pituitary gland [3, 8].

Ovulation follows as the second phase in the ovarian cycle with an LH surge. Estrogen stimulates the production of LH when the egg has almost matured. This process generally lasts about 48 h and takes place around the twelfth day of the cycle. The function of LH is, on the one hand, to mature the egg and on the other hand, to weaken the wall of the follicle in the ovary.

The fully developed follicle releases its secondary oocyte. As the next step, the secondary oocyte matures into an ootid and then becomes a mature ovum. The mature ovum is released from the ovary into the fallopian tube and, after 24 hours, the unfertilized egg disintegrates in the fallopian tube. Fertilization, if it occurs, will normally be in the ampulla of the fallopian tubes and, if fertilized, the egg directly undergoes embryogenesis [8, 10].

The last part of the ovarian cycle is the luteal phase. FSH and LH induce the remaining parts of the dominant follicle to transform into the corpus luteum. The corpus luteum produces progesterone; a high concentration of progesterone then causes the production of estrogen. Progesterone and estrogen suppress the production of FSH and LH, the hormones that are necessary for the maintenance of the corpus luteum. Consequently, when the levels of FSH and LH fall, the corpus luteum atrophies in the absence of fertilization. In contrast, upon fertilization, the syncytiotrophoblast, and later the placenta as well, produce human chorionic gonadotropin (hCG). hCG allows the corpus luteum to survive because of its similarity to LH. If no fertilization takes place, progesterone triggers menstruation and the next cycle begins. The duration from ovulation until the beginning of menstruation, induced by progesterone, is about 2 weeks [3, 8, 14].

2.1.3 Uterine Cycle

The uterine cycle comprises three phases: the menses, the proliferative phase, and the secretory phase [4]. The follicular phase of the ovarian cycle overlaps the proliferative phase, and the luteal phase of the ovarian cycle corresponds with the secretory phase [8]. The uterine cycle starts with the menses (1st to 4th day), which is a withdrawal bleeding with vasodilatation and vasoconstriction of the uterine spiral arteries, contraction of the myometrium, and rejection of the endometrium [4]. The second phase is the proliferative phase (12th to 17th day). A rising concentration of estrogen leads to the proliferation and growth of the uterus [8]. Estrogen induces the formation of a new layer of the endometrium, the proliferative endometrium, and also stimulates crypts in the cervix to produce fertile cervical mucus [3]. The secretory phase (17th to 28th day) takes place after ovulation [4], and makes the endometrium receptive to the implantation of the blastocyst [8]. The corpus luteum produces progesterone, which increases the blood flow and growth of the uterine spiral arteries [8]. The production of progesterone causes a rise in body temperature [2]. Furthermore, the uterine secretions are increased and contractility of the smooth muscle in the uterus is reduced. If no fertilization takes place, the cycle starts again with the menses [2, 3, 11].

After ovulation, the ovum is viable for about 6–12 h until fertilized. Spermatozoa are viable for about 2–3 days; thus, the best time for fertilization seems to be the 12th to 15th days after the menses [4]. Some environmental factors may negatively influence the cycles and, consequently, influence fertility. For example, stress, sleep dysregulation, and circadian misalignment have been noted as having potential relevance to infertility [7]. An indicator for fertility or infertility seems to be the basal serum level of anti-Müllerian hormone (AMH), which, in an adult woman, should be quantifiable at 1–10 µg/l. Restricted ovarian function is described when the concentration is 0.4–1.0 µg/l [6].

A higher concentration than 1–10 µg/l can be associated with polycystic ovary syndrome [9].

Infertility is defined if a clinical pregnancy is not achieved after 12 months or more of regular unprotected sexual intercourse. There is a general distinction between primary and secondary infertility. The World Health Organization (WHO) defines primary infertility as not achieving a live birth after cohabiting for at least 5 years, during which no contraceptives were used. On the other hand, childbirth in the past, but no subsequent pregnancy under the same conditions, is defined as secondary infertility [5, 12].

The most frequent causes of infertility are hormonal disorders including hypothyroidism, variation of the vaginal secretion, genetic defects, endometriosis or tubal dysfunction, or iatrogenic causes such as chemotherapy [5].

2.2 Epidemiology of Female Fertility in Multiple Sclerosis

Multiple sclerosis (MS) is the most common neurological condition in persons aged 20–40 years and shows a clear female preponderance [15]. Thus, as MS mainly affects women during their reproductive years, and as the lag time from clinical onset to diagnosis has decreased in recent years due to improved diagnosis, there has been increasing interest in MS and pregnancy. In contrast, the issue of fertility and MS has not been studied systematically. The frequency of childlessness in female MS patients may be higher than that in the general population [16]. If true, this may be because women with MS may want to avoid pregnancy for fear of not being able to care for the baby due to disability [17]. Psychological, sociocultural, and relationship factors may all also influence a woman's fecundity. Research on sexual dysfunction (SD) has reported that 30–70 % of MS patients have SD [17], with the most common SDs being reduced libido, sensory dysfunction in the genital and thigh area, and difficulty achieving orgasm [17]. Bladder and bowel incontinence, and weakness and increased spasticity during sexual activity may also interfere with intimate behavior and relationships [17, 18]. A significant correlation was found between SDs and bladder/ bowel incontinence and reduced sensitivity [19]. SDs may have a significant negative impact on quality of life, with otherwise able women having fewer pregnancies. A Danish cohort study suggested that reduced reproductive activity could be due to the subtle symptoms of as yet undiagnosed MS affecting the wish or ability to have children [20].

It is also possible that various hormonal or medication-related factors may induce infertility in women with MS. A Finnish study found that, compared with the general population of Finnish women, women with MS were more likely to have artificial insemination [21]. Some studies have found abnormal levels of sex hormones and gonadotropins, i.e., higher levels of prolactin, LH, and FSH, in female MS patients compared with healthy controls [18, 22]. Others have reported that females with MS have a reduced ovarian reserve, which is strongly correlated with impaired fertility [23, 24]. Infertility may also be caused by medication. For example, cyclophosphamide, an immunosuppressive drug used to treat malignancies and various autoimmune diseases including MS, can cause ovarian failure; definitive amenorrhea occurs in 33 % of treated women [14]. Cyclophosphamide exposure during the first trimester of pregnancy can have a teratogenic effect on the fetus [26, 27], including severe hydrocephalus, micrognathia, and bilateral radial aplasia [27]. In a recent retrospective cohort study of medical records, 10/105 women with MS on this treatment were exposed during the first trimester of pregnancy and went on to give birth. Of these, 4 had preterm deliveries and one child was small for gestational age. In addition, one woman had a voluntary abortion due to the fetus' exposure to cyclophosphamide in utero; the results seem to indicate that cyclophosphamide treatment prior to pregnancy does not affect the outcome. However, the cohort was small and perhaps more research should be done to verify whether cyclophosphamide treatment is safe to prescribe to young women who are planning a pregnancy [26] as long as they have a wash-out period prior to conception. It has been recommended that cyclophosphamide treatment be ceased 3 months prior to the patient trying to conceive [28]. Another strong immunosuppressant drug, mitoxantrone, may also cause infertility in MS. In a large retrospective study, mitoxantrone treatment was found to cause long-lasting amenorrhea linked to reduced ovarian reserve in 17.3 % of women under the age of 45 [28].

It has also been suggested that autoimmunity can generally cause infertility [29]. Autoimmune primary ovarian insufficiency (POI) may be one cause of infertility in MS patients. However, it is thought that POI is related to other autoimmune diseases and not to MS. Furthermore, studies show that the frequency of the comorbidity of other autoimmune disorders in women with MS does not differ from that of a control population [25]. It should be noted that research results regarding infertility caused by MS are conflicting, and published studies are scarce. MS may impair fertility, but, given that MS and infertility are both common in young women of child-bearing age, this observation may be a chance effect rather than a "cause-effect". The preservation of fertility in MS patients may have a considerable impact on their quality of life. Further research about fertility and MS is required.

2.3 Assisted Reproductive Techniques (ARTs) and MS

Assisted reproductive techniques were introduced successfully with the delivery of the first in-vitro baby, Louise Brown, in 1978. Since then, the methods, with different hormonal approaches, have increased extensively (see below).

2.3.1 ARTs and Hormonal Approaches in General

Infertility treatment protocols of different durations and different treatment types are now available for use. The length of a single stimulation is mainly dependent on the type of downregulation involved: downregulation with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is commonly applied to downregulate the hypothalamic-pituitary gland axis and to prevent an uncontrolled LH surge and ovulation.

GnRH agonists start with an agonistic receptor action, subsequently block the receptor for extended period of time due to a longer half-life. This leads to hypoestrogenic (“climacterium-like”) side effects after 10 to 14 days.

GnRH antagonists, in contrast, directly and rapidly inhibit gonadotropin release within several hours through competitive binding to pituitary GnRH receptors [10].

Stimulations with GnRH agonists are longer (“long protocol”) than those with the use of antagonists (“short protocol”). The use of antagonist protocols compared with GnRH agonist protocols seems to be correlated with a large reduction in ovarian hyperstimulation syndrome (OHSS), but with similar live-birth rates.

Controlled ovarian hyperstimulation is performed with different gonadotropins; mainly human menopausal gonadotropins (HMGs) and recombinant human follicle-stimulating hormone (rFSH), or a combination of both. Clomifen, an antiestrogen, is mainly used in insemination approaches. After successful stimulation, controlled ovulation is induced with hCG, followed by progesterone to support the luteal phase. Fertilization is mostly achieved by intrauterine insemination (IUI), in-vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI).

2.3.2 ARTs and MS: Existing Studies

Five observational studies on the effects of ARTs in MS have been published [30–34] – see Table 2.1. In 2006, a French case series found a significant increase in relapses in 6 MS patients following a total of ten IVF attempts [32]. Disease-modifying therapies (DMTs) were stopped at least 1 year before IVF was started. A significant increase in the annualized relapse rate (ARR) after IVF was shown. The increase in the ARR after IVF was observed particularly in those patients using GnRH agonists and this increase was also seen in a second French study [33]. Most women in this second study [33] had never been treated with DMTs or had stopped DMTs prior to ART.

A German nationwide ART and MS registry [30] collected information, with a standardized questionnaire, on women’s disease courses (e.g., disease duration and number of relapses in the year prior to ART, during, and post ART), the use of immunomodulatory treatments, and the stimulation protocol [30]. The ARR increased following unsuccessful (no pregnancy) ART. The ARR increased significantly after ART, but was independent of the different hormonal approaches to downregulation (agonists versus antagonists).

A second German publication [31] included 39 patients who underwent IUI ($n=32$), IVF ($n=15$), and ICSI ($n=31$) and again, a significant increase of the ARR in the 3 months following ART was observed, independent of the different

Table 2.1 Effects of assisted reproductive treatment on multiple sclerosis

Study authors	Design	Sample size (n)/ART cycles (n)	Treatment	Main results	Reference no.
Laplaud et al.	Retrospective case series	6/10	GnRH agonists (n=6) GnRH antagonists (n=4)	Increase in relapse rate 3 months following ART in the group treated with GnRH agonists. No evidence of increase in relapse rate in patients treated with GnRH antagonists	[15]
Michel et al.	Retrospective case series	32/70	GnRH agonists (n=48); GnRH antagonists (n=19) 3 cases lack of data	Increase in relapse rate 3 months following ART in the group treated with GnRH agonists. No evidence of increase in relapse rate in patients treated with GnRH antagonist	[16]
Hellwig et al.	Retrospective case series	6/14	GnRH agonists (n=9); GnRH antagonists (n=5)	Increase in relapse rate 3 months following ART, independent of treatment.	[13]
Hellwig et al.	Retrospective and prospective case series	23/78	GnRH agonists (n=33); GnRH antagonists (n=11)	Increase in relapse rate 3 months following ART in the whole cohort, independent of treatment, and independent of time interval between repetitive stimulations,. Trend for increase in prospectively followed subgroup ($p=0.05$).	[14]
Correale et al.	Prospective	16/26	GnRH agonists in all cases	Increase in relapse rate 3 months following ART Increase in Magnetic Resonance Imaging activity	[17]

ART assisted reproductive treatment, GnRH Gonadotropin-releasing hormone, Magnetic Resonance Imaging

hormonal approaches to downregulation, with GnRH agonists or antagonists. No significant differences were seen between the ARR and the use of different gonadotropins, or between the ARR and different time intervals between stimulations. None of the women who became pregnant had a relapse. Most women in that study did not receive any MS therapy. In a recent study from Argentina [35], a cycle of ART was associated with a sevenfold increase in clinical relapse risk, consistent with a ninefold increase in risk of Gd-enhancing lesion activity.

Although the exact mechanism for the increase in relapse risk of women with MS after ART is not fully understood, it is well established that hormones may alter the short-term course of the disease (e.g., animal studies, pregnancy) [36–38]). At least some of the studies suggest that the downregulation with GnRH agonists might account for the relapse risk [32–34]. The Argentinian study [35] tried to elucidate immunological mechanisms, which might explain the increase in disease activity: ART treatment is associated with an increase in estrogen and progesterone levels, although these levels are significantly lower than those observed during normal pregnancy [20, 21]. It has also been found that estrogen mediated an increase in different immune cells/factors (anti-MOG antibody-secreting cells and B-cell survival factor BAFF, and the anti-apoptotic Bcl-2 protein), triggering MS disease activity [34]. Also discussed were possible effects of the GnRH receptor itself, which is expressed on immune cells, with an upregulation of the receptor by GnRH suggesting an autocrine function in immune cells. Several proinflammatory cytokines, e.g., interleukin (IL)-8, IL-12, interferon (IFN)- γ , and transforming growth factor (TGF)- β are upregulated by ART, and ART also facilitates immune cell transmigration across the blood–brain barrier [34].

In addition to the rapidly changing hormonal levels during ART, several other factors might contribute to an increased MS relapse risk. Most of the women with MS undergoing ART stopped their DMTs before ART stimulation [30–34]. In addition, ART represents an extremely stressful life event, normally preceded by several years by the unfulfilled wish to become pregnant. Therefore, an essential hope to finally become pregnant is often linked to the beginning of ART. Although elusive, stressful life events may induce increasing disease activity in MS patients, and decreased hypothalamic-pituitary-adrenal (HPA) function may play a role in increased susceptibility to disease activity [39, 40]. Interestingly, while pre-ART stress does not predict IVF failure, failure of IVF is particularly associated with distress in the affected women [41].

Overall, ART involves complex and dynamic interactions between hormonal and immune factors, which could affect the course of an autoimmune disease, explaining increased disease activity.

2.4 Concluding Remarks

Further research is required to investigate whether fertility is reduced in women with MS.

Although all available data demonstrate a significant increase in disease activity after “unsuccessful” ART, women with MS should not be discouraged from

undergoing ART. According to a Cochrane review, the use of antagonists compared with long GnRH agonist protocols seemed to be associated with a large reduction in OHSS, and there was no evidence of a difference between the groups in live-birth rates [42]. Therefore, we suggest to preferentially use a downregulation approach with GnRH antagonists. However, the final choice of the best hormonal treatment depends on the recommendations of ART specialists. We also recommend, where possible, that MS patients stay on pregnancy-compatible DMTs during ART, although so far studies are lacking showing an effect of relapses post-ART. Finally, neurologists and other healthcare professionals treating women with MS should be aware of this risk, and discuss the pros and cons of the procedure with their patients.

References

1. Anderson SE, Dallal GE, Must A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart. *Pediatrics*. 2003;111:844–50.
2. Brodin T, Bergh T, Berglund L, Hadziosmanovic N, Holte J. Menstrual cycle length is an age-independent marker of female fertility: results from 6271 treatment cycles of in vitro fertilization. *Fertil Steril*. 2008;90:1656–61.
3. Broom TJ, Matthews CD, Cooke ID, Ralph MM, Seamark RF, Cox LW. Endocrine profiles and fertility status of human menstrual cycles of varying follicular phase length. *Fertil Steril*. 1981;36:194–200.
4. Haag P, Hanhart N, Müller M. *Gynäkologie und Urologie*. 2008/2009. p. 20–2.
5. Haag P, Hanhart N, Müller M. *Gynäkologie und Urologie*. 4. Auflage. 2009. p. 230–1.
6. Kamel HM, Amin AH, Al-Adawy AR. Basal serum anti-Müllerian hormone (AMH) is a promising test in prediction of occurrence of pregnancy rate in infertile women undergoing ICSI cycles. *Clin Lab*. 2014;60:1717–23.
7. Kloss JD, Perlis ML, Zamzow JA, Culnan EJ, Gracia CR. Sleep, sleep disturbance, and fertility in women. *Sleep Med Rev*. 2014;22:78–87.
8. Losos JBR, Peter H, Johnson GB, Singer SR. *Biology*. New York: McGraw-Hill; 2002. p. 1207–9.
9. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet*. 2007;370:685–97.
10. Silverthorn DU. *Human physiology: an integrated approach*. 6th ed. 2013. p. 850–90. ISBN-13: 978-0321814838 or ISBN-10: 0321814835 [Pearson]
11. Vassena R, Vidal R, Coll O, Vernaev V. Menstrual cycle length in reproductive age women is an indicator of oocyte quality and a candidate marker of ovarian reserve. *Eur J Obstet Gynecol Reprod Biol*. 2014;177:130–4.
12. WHO. <http://www.who.int/reproductivehealth/topics/infertility/definitions/en/>.
13. Widmaier EPR, Hershel R, Strang KT. *Vander's human physiology: the mechanism of body function*. 12th ed. 2010. p. 555–631. ISBN-13: 978-0073378305 or ISBN-10: 0073378305 [McGraw-Hill Education]
14. Yasuzumi G, Yabumoto N, Saito K, Tsubo I. In vivo production of nucleolar channel system in human endocervical secretory cells. *J Submicrosc Cytol*. 1981;13:639–47.
15. Niedziela N, Adamczyk-Sowa M, Pierzchala K. Epidemiology and clinical record of multiple sclerosis in selected countries: a systematic review. *Int J Neurosci*. 2013;124:322–30.
16. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. *Brain*. 1995;118:253–61.
17. Cavalla P, Rovei V, Masera S, et al. Fertility in patients with multiple sclerosis: current knowledge and future perspectives. *Neurol Sci*. 2006;27:231–9.

18. Lombardi G, Celso M, Bartelli M, Cilotti A, Del Popolo G. Female sexual dysfunction and hormonal status in multiple sclerosis patients. *J Sex Med.* 2011;8:1138–46.
19. Ghezzi A. Sexual dysfunction in multiple sclerosis. *Int MS J.* 1999;5:44–53.
20. Nielsen NM, Jorgensen KT, Stenager E, et al. Reproductive history and risk of multiple sclerosis. *Epidemiology.* 2011;22:546–22.
21. Jalkanen A, Alanen A, Airas L. Pregnancy outcome in women with multiple sclerosis: results from a prospective nationwide study in Finland. *Mult Scler.* 2010;16:950–5.
22. Grinstead L, Heltberg A, Hagen C, Djursing H. Serum sex hormone and gonadotropin concentrations in premenopausal women with multiple sclerosis. *J Intern Med.* 1989;226:241–4.
23. Cil AP, Leventoglu A, Sonmezer M, et al. Assessment of ovarian reserve and Doppler characteristics in patients with multiple sclerosis using immunomodulating drugs. *J Turk Ger Gynecol Assoc.* 2009;10:213–9.
24. Thone J, Kollar S, Noursome D, et al. Serum anti-Müllerian hormone levels in reproductive-age women with relapsing remitting multiple sclerosis. *Mult Scler.* 2015;21:41–7.
25. McCombe PA, Stenager E. Female infertility and multiple sclerosis: is this an issue? *Mult Scler.* 2015;21:5–7.
26. Patti F, Messina S, D'Amico E, Lo Fermo S, Zappia M. Pregnancy outcomes in multiple sclerosis patients previously treated with cyclophosphamide. *Acta Neurol Scand.* 2014;130:41–4.
27. Paladini D, Vassallo M, D'Armiento MR, Cianciaruso B, Martinelli P. Prenatal detection of multiple fetal anomalies following inadvertent exposure to cyclophosphamide in the first trimester of pregnancy. *Birth Defects Res A Clin Mol Teratol.* 2004;70:99–100.
28. Amato MP, Portaccio E. Fertility. Pregnancy and childbirth in patients with multiple sclerosis: impact of disease-modifying drugs. *CNS Drugs.* 2015;29:207–20.
29. Sen A, Kushnir VA, Barad DH, Gleicher N. Endocrine autoimmune diseases and female infertility. *Nat Rev Endocrinol.* 2014;10:37–50.
30. Hellwig K, Beste C, Brune N, et al. Increased MS relapse rate during assisted reproduction technique. *J Neurol.* 2008;255(4):592–3.
31. Hellwig K, Schimrigk S, Beste C, Muller T, Gold R. Increase in relapse rate during assisted reproduction technique in patients with multiple sclerosis. *Eur Neurol.* 2009;61(2):65–8.
32. Laplaud DA, Leray E, Barriere P, Wiertlewski S, Moreau T. Increase in multiple sclerosis relapse rate following in vitro fertilization. *Neurology.* 2006;66(8):1280–1.
33. Michel L, Foucher Y, Vukusic S, et al. Increased risk of multiple sclerosis relapse after in vitro fertilisation. *J Neurol Neurosurg Psychiatry.* 2012;83(8):796–802.
34. Correale J, Farez MF, Ysraelit MC. Increase in multiple sclerosis activity after assisted reproduction technology. *Ann Neurol.* 2012;72(5):682–94.
35. Hellwig K, Correale J. Artificial reproductive techniques in multiple sclerosis. *Clin Immunol.* 2013;149(2):219–24.
36. Voskuhl RR, Palaszynski K. Sex hormones in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. *Neuroscientist.* 2001;7(3):258–70.
37. Voskuhl RR, Gold SM. Sex-related factors in multiple sclerosis susceptibility and progression. *Nature Reviews. Neurology.* 2012;8(5):255–63.
38. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med.* 1998;339(5):285–91.
39. Heesen C, Gold SM, Huitinga I, Reul JM. Stress and hypothalamic-pituitary-adrenal axis function in experimental autoimmune encephalomyelitis and multiple sclerosis – a review. *Psychoneuroendocrinology.* 2007;32(6):604–18.
40. Gold SM, Mohr DC, Huitinga I, Flachenecker P, Sternberg EM, Heesen C. The role of stress-response systems for the pathogenesis and progression of MS. *Trends Immunol.* 2005;26(12):644–52.
41. Pasch LA, Gregorich SE, Katz PK, Millstein SG, Nachtigall RD, Bleil ME, et al. Psychological distress and in vitro fertilization outcome. *Fertil Steril.* 2012;98(2):459–64.
42. Gonzalez DA, Diaz BB, Rodriguez Perez Mdel C, Hernandez AG, Chico BN, de Leon AC. Sex hormones and autoimmunity. *Immunol Lett.* 2010;133(1):6–13.

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