9 Fertility Preservation in Women with Autoimmune Diseases Treated with Gonadotoxic Agents

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Abstract

Auto-immune diseases commonly affect women of reproductive age group. These women most often need chemotherapeutic agents which may cause significant gonado-toxicity. Therefore, fertility preservation techniques must be offered to women undergoing treatment for auto-immune diseases before starting such therapy. This chapter discusses in detail the various fertility preservation techniques available with their merits and de-merits.

Keywords

Auto-immune diseases · Gonadotoxic drugs · Fertility preservation options

Autoimmune diseases are common in women of reproductive age and are commonly treated with gonadotoxic agents like cyclophosphamide. However, the aspect of fertility preservation treatment has not received much importance in these women. As the survival rates of these patients have improved, long-term aspects including fertility preservation are gaining significance [1].

9.1 Risk and Mechanism of Gonadotoxicity

Significant number of young women with SARDs is exposed to gonadotoxic drugs, which may lead to premature ovarian failure and infertility. The most commonly used such drug is cyclophosphamide, which is mainly used for life or organ threatening autoimmune disorders such as SLE with renal involvement or ANCA-associated systemic vasculitis [2]. CYC is toxic to both male and female gonads. The risks and benefits of these immunosuppressive agents must be explained to the

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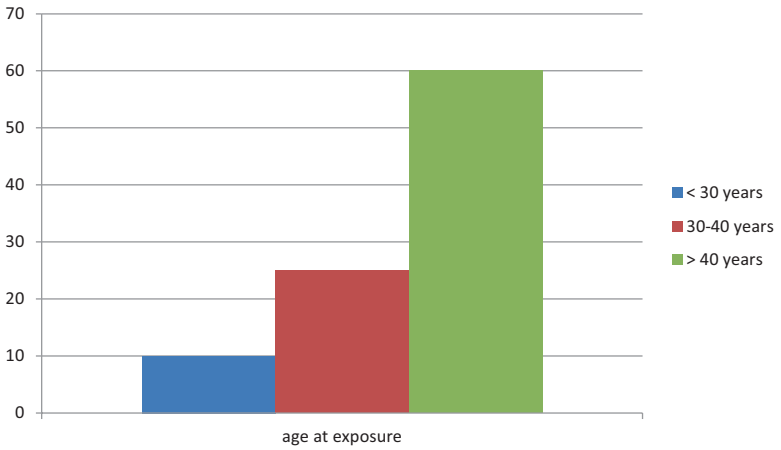
young patients prior to treatment as issues related to fertility may be an important concern to many of them.

Cyclophosphamide is an alkylating agent which exerts its action by preventing cell division via covalent binding and cross-linking of a variety of macromolecules [3]. Alkylating agents have potentially severe side effects like bone marrow suppression, gonadal toxicity and increased chances of infections and malignancies. The damage induced is usually reversible in tissues with rapidly dividing cells such as bone marrow, gastrointestinal tract and thymus. However, the toxicity to ovaries is progressive and irreversible, where the number of germ cells is determined since foetal life and cannot be regenerated. Alkylating agents are not cell-cycle specific, and it is believed that they act on undeveloped oocytes and pregranulosa cells of primordial follicles. This toxicity is mediated by metabolite phosphoramide mustard [4].

The gonadotoxicity of CYC is dependent mainly on the following:

1. Age at exposure
2. Cumulative dose.

The risk of premature ovarian failure and infertility is directly proportional to age at exposure. Before menarche, CYC does not seem to cause significant ovarian toxicity. In patients <30 years of age, studies have shown the risk of amenorrhoea to be around 10% as compared to >50% in women above 40 years. In general, greater the ovarian reserve at the time of exposure, lesser is the damage caused. Data suggests that women <20 years of age at drug exposure have <5% chance of ovarian failure with initial course of CYC as compared to women >30 years (25–50%) and >40 years (75%) [5–8].



The level of gonadal dysfunction is also dependent on the dose of CYC that the lady receives. The cumulative CYC dose is an independent risk factor for ovarian toxicity, regardless of how the medication is used. Cumulative dose of 12 g/m^2 or higher has been shown to be significantly more gonadotoxic than 8 g/m^2 [9]. The

evidence regarding the effect of duration of CYC treatment and baseline severity of disease on gonadotoxicity is less convincing.

9.2 Measures for Fertility Preservation

Various fertility preservation strategies are available for women exposed to chemotherapy, including the following:

1. Administration of GnRH agonist
2. Embryo cryopreservation
3. Ovarian tissue cryopreservation
4. Unfertilized ovum cryopreservation.

Each method has its own advantages and disadvantages in terms of availability, efficacy, cost, need for male partner and effect on primary disease, hence shall be discussed subsequently.

9.2.1 Administration of GnRH Agonist

The use of GnRH agonist to protect ovaries from the toxicity of chemotherapeutic agents has been considered for over two decades. Several possible mechanisms have been postulated through which GnRH analogues may exert this protective action. These include the following:

(a) Decreased levels of circulating gonadotropins, thereby putting the ovaries in an artificial pre-pubertal state. This hypogonadotropic milieu decreases the number of primordial follicles entering the vulnerable differentiation stage.
(b) Decreased blood supply to ovaries leading to lesser concentration of chemotherapeutic agents in the ovarian tissue.
(c) Up regulation of an intragonadal anti-apoptotic molecule such as sphingosine-1-phosphate by GnRH agonist.

The efficacy of GnRH agonist in fertility preservation has remained controversial for many years. Until the previous decade, most of the data was from observation studies carried out in young pre-menopausal women with breast cancer or lymphoma and was considered to be non-conclusive due to lack of randomized controlled trials. However, over the last 10 years, multiple RCTs have been conducted worldwide on the use of GnRH agonists concurrently with chemotherapy both for malignancy and for SLE. Meta-analysis of these studies has proven the efficacy of this pharmacological intervention in preserving ovarian function [10]. Though the earlier literature appeared stronger for prevention of POF and less convincing in terms of pregnancy rates, the recent POEMS/S0230 trial which was an international, phase 3, randomized study extended this benefit to increased

pregnancy rates (21% vs. 11%) [11]. Also, a recent systematic review and meta-analysis of data from premenstrual women with early breast cancer concluded POF rates of 14% vs. 30% and pregnancy rates of 10% vs. 5% in women receiving chemotherapy with or without GnRH agonist co-treatment, respectively [12]. Cochrane Database Systematic Review in March 2019 concluded that GnRH agonist appears to be effective in protecting the ovaries during chemotherapy, in terms of maintenance and resumption of menstruation, treatment-related premature ovarian failure and ovulation. Evidence for protection of fertility was insufficient and needs further investigation as per the authors [13].

It needs to be emphasized that the use of GnRH agonist has not been associated with any significant effect on the course of SLE. Also, the preservation of ovarian function in itself is highly significant in women with SLE as POF leads to premature atherosclerosis which is the leading cause of death in SLE. The odds ratio for preservation of cyclic ovarian function vs. POF has been reported to be as high as 6.8 in women receiving GnRH agonist treatment before and during gonadotoxic chemotherapy [14].

9.2.2 Embryo Cryopreservation

Ovarian stimulation followed by in vitro fertilization and embryo cryopreservation is considered to be the gold standard technique for fertility preservation in young women desirous of future fertility prior to chemotherapy for malignancies. However, in case of women with SLE, the path physiology of the disease per se may alter this decision. Though the exact aetiology of SLE is unknown, the role of female hormones has been suggested for many years as 90% of affected patients are females. Increased flares have been reported in post-menopausal women who receive hormone replacement therapy with E+P. Males with SLE also have been proven to have altered sex hormones with higher oestrogen to androgen ratio, all suggesting a role of oestrogen in disease pathogenesis. Therefore, the safety of IVF procedures where ovarian hyperstimulation leads to markedly increased oestradiol levels has been questioned [15].

It has been recommended that ovarian hyperstimulation must be discouraged in women with SLE during active flare (and 6–12 months thereafter) and in SLE patients with major previous thrombotic events, uncontrolled hypertension, pulmonary hypertension, advanced renal disease and severe valvulopathy/heart disease [16]. If the disease is stable, IVF may be performed but only in expert hands and after detailed couple counselling. These women need to be under close and continuous monitoring during IVF procedures. The most threatening condition associated with ovarian stimulation in women with SLE is thrombosis. At present, no specific type of gonadotropins has been shown to offer a clear advantage in the prevention of thrombosis. However, as most cases of thrombosis have been associated to OHSS, the main aim in these women is to avoid OHSS by using all preventable strategies such as mild stimulation protocols, coasting, use of GnRH agonist as trigger for ovulation, embryo freezing, etc.

9.2.3 Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation is a possible fertility preservation technique especially for young unmarried girls who do not have a male partner and hence cannot opt for embryo freezing [17]. It provides additional benefit of restoring oestrogen activity in the body following ovarian tissue autotransplantation though the survival of this tissue may be limited in time. However, this technique requires two surgical procedures: one to excise the ovarian tissue and second for auto-grafting. It is not widely available for poor patients in a country like India.

9.2.4 Unfertilized Ovum Cryopreservation

Aspiration and preservation of both mature and immature oocytes have been proven to be efficient alternative techniques for fertility preservation in women scheduled for gonadotoxic chemotherapy. While the aspiration of mature oocytes generally requires ovarian stimulation with gonadotropins (like IVF procedures), immature oocytes can be aspirated during a natural menstrual cycle without any hormonal stimulation. This in vitro maturation of immature oocytes (IVM) provides a hope for the patients who are in flare and in whom use of chemotherapy is imminent where other techniques that lead to increased oestradiol levels cannot be used. Though the success of these procedures is in the form of case reports and small case series till now, they appear to offer good opportunity. Literature reports clinical pregnancy rates of 25–45% per cycle with in vitro and in vivo matured oocytes with cryopreservation/vitrification [18, 19].

9.3 Comparison of Fertility Preservation Techniques

	Option	Advantages	Disadvantages
1	GnRH agonist	Simple to use Inexpensive No need of male partner Minimal side effects No risk of SLE flare Efficient Potential to preserve ovarian function	Symptoms of hypo-oestrogenism during treatment Not effective in all women
2	IVF and embryo freezing	Efficient Available at many centres Not very costly	Need for male partner May cause disease aggravation
3	Ovarian tissue cryopreservation	High potential Restores hormonal function in addition to fertility	Need for surgical procedure Not easily available Expensive
4	Oocytes preservation	High potential	Investigational Expensive Not widely available

In summary, fertility preservation options must be seriously considered and discussed in all young patients prior to starting gonadotoxic chemotherapy. Such techniques help young women to cope better emotionally with their chemotherapy, as there is a hope of being able to have a biological child in the future.

References

1. Katsifis GE, Tzioufas AG (2004) Ovarian failure in systemic lupus erythematosus patients treated with pulsed intravenous cyclophosphamide. Lupus 13(9):673–678
2. Austin HA, Klippel JH, Balow JE et al (1986) Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 314:614–619
3. Hall AG, Tilby MJ (1992) Mechanisms of action of, and modes of resistance to, alkylating agents used in the treatment of haematological malignancies. Blood Rev 6(3):163–173
4. Bines J, Oleske DM, Cobleigh MA (1996) Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol 14(5):1718–1729
5. Huong DLT, Amoura Z, Duhaut P et al (2002) Risk of ovarian failure and fertility after intravenous cyclophosphamide. A study in 84 patients. J Rheumatol 29:2571–2576
6. Mok CC, Ho CTK, Chan KW, Lau CS, Wong RWS (2002) Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. Arthritis Rheum 46:1003–1013
7. Mok CC, Lau CS, Wong RWS (1998) Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. Arthritis Rheum 41:831–837
8. Wetzels JFM (2004) Cyclophosphamide induced gonadal toxicity: a treatment dilemma in patients with lupus nephritis? Neth J Med 62(10):347–352
9. Ioannidis JPA, Katsifis GE, Tzioufas AG, Moutsopoulos HM (2002) Predictors of sustained amenorrhoea from pulsed intravenous cyclophosphamide in premenopausal women with systemic lupus erythematosus. J Rheumatol 29:2129–2135
10. Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM (2010) Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. Breast Cancer Res Treat 122(3):803–811
11. Moore HCF, Unger JM, Phillips K-A et al (2015) Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 372:923–932
12. Lambertini M, Moore HCF, Robert CF et al (2018) Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol 36:1981–1990
13. Chen H, Xiao L, Li J, Cui L, Huang W (2019) Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev 3:CD008018
14. Blumenfeld Z, Zur H, Dann EJ (2015) Gonadotropin-releasing hormone agonist cotreatment during chemotherapy may increase pregnancy rate in survivors. Oncologist 20(11):1283–1289
15. Askanase AD, Buyon JP (2002) Reproductive health in SLE. Best Pract Res Clin Rheumatol 16:265–280
16. Bellver J, Pellicer A (2009) Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome. Fertil Steril 92(6):1803–1810
17. Meirow D, Levron J, Eldar-Geva T et al (2005) Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med 353:318–321
18. Oktay K, Cil AP, Bang H (2006) Efficiency of oocytes cryopreservation: a meta-analysis. Fertil Steril 86:70–80
19. Chian RC, Huang JY, Gilbert L et al (2009) Obstetric outcomes following vitrification of in vitro and in vivo matured oocytes. Fertil Steril 91(6):2391–2398