Blood Reviews xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Review

Hormonal replacement therapy in adolescents and young women with chemo- or radio-induced premature ovarian insufficiency: Practical recommendations

A. Cattoni[a,*], F. Parissone[b], I. Porcari[b], S. Molinari[a], N. Masera[a], M. Franchi[b], S. Cesaro[c], R. Gaudino[d], P. Passoni[e], A. Balduzzi[a]

[a] Department of Pediatrics, Università degli Studi di Milano Bicocca, Fondazione Monza e Brianza per il Bambino e la sua Mamma, Azienda Ospedaliera San Gerardo, Via Pergolesi 33, 20900 Monza, Italy
[b] Department of Obstetrics and Gynecology, Azienda Ospedaliera Universitaria Integrata di Verona, Università di Verona, Piazzale Aristide Stefani 1, 37126 Verona, Italy
[c] Pediatric Hematology Oncology, Department of Mother and Child, Azienda Ospedaliera Universitaria Integrata di Verona, Università di Verona, Piazzale Aristide Stefani 1, 37126 Verona, Italy
[d] Pediatric Endocrinology, Azienda Ospedaliera Universitaria Integrata di Verona, Università di Verona, Piazzale Aristide Stefani 1, 37126 Verona, Italy
[e] Department of Obstetrics and Gynecology, Azienda Ospedaliera San Gerardo, Via Pergolesi 33, 20900 Monza, Italy

ARTICLE INFO

Keywords:
Hormone replacement therapy
Iatrogenic premature ovarian insufficiency
Childhood cancer survivors
Hematopoietic stem cell transplantation
Bone mineral density
Puberty induction

ABSTRACT

In women with premature ovarian insufficiency (POI), hormonal therapy (HT) is indicated to decrease the risk of morbidity and to treat symptoms related to prolonged hypoestrogenism.

While general recommendations for the management of HT in adults with POI have been published, no systematic suggestions focused on girls, adolescents and young women with POI following gonadotoxic treatments (chemotherapy, radiotherapy, stem cell transplantation) administered for pediatric cancer are available. In order to highlight the challenging issues specifically involving this cohort of patients and to provide clinicians with the proposal of practical therapeutic protocol, we revised the available literature in the light of the shared experience of a multidisciplinary team of pediatric oncologists, gynecologists and endocrinologists.

We hereby present the proposals of a practical scheme to induce puberty in prepubertal girls and a decisional algorithm that should guide the clinician in approaching HT in post-pubertal adolescents and young women with iatrogenic POI.

1. Introduction

Over the last decades, survival rates of childhood, adolescent and young adulthood (CAYA) cancer have remarkably increased thanks to substantial improvements in the comprehension of cancer molecular biology, refinement of diagnostic techniques and novel treatment strategies [1–3]. Accordingly, a growing proportion of adults, nowadays estimated between 0.1 and 0.5% of the population in Western Countries, have been previously treated for cancer during childhood with cytostatic drugs or radiation or a combination of the two [4,5].

As a consequence, the burden of long-term effects of anti-neoplastic treatments represents a new challenge of the care management of these patients [1,6–8]. Approximately 75% of pediatric cancer survivors experience at least one iatrogenic effect in the long-term [1].

Hypogonadism is a frequent finding after antineoplastic treatment. It can either result from a primary gonadal disorder (hypergonadotropic hypogonadism) or occur as a consequence of deficient gonadotropin secretion, secondary to an impaired hypothalamic-pituitary function (hypogonadotropic hypogonadism).

Among female survivors of pediatric cancer overall, the estimated incidence of primary gonadal impairment resulting in premature ovarian insufficiency (POI) is about 8–10% [8].

Abbreviations: 17βE, 17β-estradiol; CAYA, childhood, adolescent and young adulthood; CED, cyclophosphamide equivalent dose; COC, combined oral contraceptives; EE, ethinylestradiol; FNH, focal nodular hyperplasia; FSH, follicle-stimulating hormone; GvHD, graft *versus* host disease; HRT, hormonal replacement therapy; HSCT, hematopoietic stem cell transplantation; HT, hormonal therapy; MP, micronized progesterone; MPA, medroxyprogesterone acetate; NA, norethisterone acetate; POI, premature ovarian insufficiency; SHBP, sex hormone binding protein; TBI, total body irradiation; VTE, venous thromboembolism

* Corresponding author at: Pediatric Department, Via Pergolesi 33, 20900 Monza, Italy.
E-mail addresses: alessandro.cattoni@unimib.it (A. Cattoni), s.molinari3@campus.unimib.it (S. Molinari), massimo.franchi@univr.it (M. Franchi), simone.cesaro@aovr.veneto.it (S. Cesaro), rossella.gaudino@univr.it (R. Gaudino), abalduzzi@fondazionembbm.it (A. Balduzzi).

https://doi.org/10.1016/j.blre.2020.100730

POI is defined as the combination of oligo/amenorrhea and raised follicle-stimulating hormone (FSH) levels within the menopausal range, recorded at least twice four weeks apart, in patients younger than 40 years [9]. It is the clinical expression of a premature and progressive biological process of ovarian follicles depletion eventually resulting in overt hypoestrogenism.

Hormonal therapy (HT) is indicated to reduce the risk of osteoporosis, cardiovascular diseases and urogenital atrophy and to improve the quality of life of women with POI. In addition, HT is indicated in order to induce the progression of secondary sexual characteristics in pre/peripubertal patients who experienced early-onset POI with pubertal delay or pubertal arrest as a consequence of the detrimental effect of antineoplastic agents on ovarian function.

Children, adolescents and young women with POI should be managed by a multidisciplinary team including gynecologists, pediatricians, endocrinologists, dietitians and psychologists.

As in childhood cancer survivors HT often represents a long-lasting treatment, improving patient's compliance to therapy represents a pivotal challenge in the management of this specific subcohort of patients. In order to achieve this goal, it's paramount to find the best balance between clinical safety and patient's inclination about route, dose and regimen of administration. Several criteria should guide clinicians in selecting the most adequate formulation among those available, tailoring the decision to suit patient's demographic, clinical and psychological profile.

The aim of the present analysis is to provide a practical scheme to induce puberty in prepubertal girls and a decisional algorithm that should guide clinicians in approaching HT in post-pubertal female adolescents and young women with iatrogenic POI.

2. Literature search for the present article

The treatment protocol recommended in this manuscript is drawn from the shared clinical experience of a multicentric and multidisciplinary team including pediatric endocrinologists, gynecologists and onco-haematologists, in the light of a critical and systematical revision of the literature published to date.

The electronic search included three databases: PubMed, EMBASE and Google Scholar. The following keywords were used: hormonal replacement therapy, iatrogenic premature ovarian insufficiency/failure, childhood cancer survivors, bone mineral density, estradiol, puberty induction, hematopoietic stem cell transplantation, among full text articles in English, related to humans and published from 2010 onwards. Furthermore, additional references were identified by a manual search among references cited in the articles retrieved in the first round of search.

3. Risk factors, clinical features and specificities of children, adolescents and young adults with iatrogenic POI

Our target population includes CAYA cancer survivors and patients treated with hematopoietic stem cell transplantation (HSCT) also for non-oncological conditions but who have experienced ovarian insufficiency as a consequence of the conditioning regimen administered before HSCT.

3.1. Childhood cancer survivors: who is at risk of POI?

As previously stated, a remarkable percentage of CAYA cancer survivors experience the cessation of gonadal function, leading to premature ovarian insufficiency, as a consequence of the detrimental effect of antineoplastic treatment on gonadal function.

In 2016, the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium has provided systematic recommendations for the clinical and biochemical follow-up of ovarian function in CAYA cancer survivors and assessed the treatment-related risk of developing POI [10].

Pelvic irradiation and alkylating agents play a pivotal role in the onset of ovarian insufficiency.

DNA interstrand cross-linking agents (namely busulfan, treosulfan, chlorambucil, cyclophosphamide, ifosfamide, nitrogen mustard, melphalan, thiotepa), the triazenes (procarbazine, dacarbazine, temozolomide), and nitrosoureas (carmustine, lomustine and platinum agents) are commonly included in the pharmacological class of alkylating agents. As most pediatric patients undergo polypharmacological treatment regimens, it is difficult to assess the relative risk related to each agent. However, the likelihood of developing POI is dose-dependent. In order to compare the agent-specific gonadotoxicity and to estimate the chemotherapy cumulative detrimental effect, the cyclophosphamide equivalent dose (CED) method has been developed [11]. CED can be calculated according to the equation reported in Appendix 1. CED estimation provides clinicians with concrete tools to adequately counsel patients about the risk of developing iatrogenic POI. According to mathematical models, CED lower than 4000 mg/sm are related to an overall low risk of POI, with a progressive drop in female fertility for increasing doses and with the probability of siring a pregnancy dropping below 50% in case of CED above 8000 mg/sm [1,12].

Also radiation-induced ovarian damage has been proved to be dose-dependent. Since radiotherapy is rarely administered as the only therapeutic strategy, tracking a sterilizing threshold could be cumbersome. However, according to mathematic modeling on the basis of data on the rate of oocyte decline, abdominal radiation doses above 20.3 Gy in infants, 18.4 Gy at the age of 10 years, and 16.5 Gy at the age of 20 years are associated to a remarkably high risk of developing POI [10].

Noteworthy, patients with brain tumors exposed to cranial or cranio-spinal radiotherapy, neurosurgery involving the hypothalamic-pituitary area or diagnosed with tumors infiltrating sellar or suprasellar regions may experience hypogonadotropic hypogonadism [13]. Interestingly, in childhood cancer survivors with a co-occurrence of central hypogonadism and ovarian damage, the latter condition could be disguised due to low gonadotropin levels secondary to the damage involving the hypothalamic-pituitary area.

Although it is still debated, some studies showed that younger age at the time of exposure to chemo- and/or radiotherapy is protective against POI, probably because of the natural decline, with aging, of the primordial follicles, more resistant to chemo- and radio-induced damage [14,15].

3.2. Hematopoietic stem cell transplantation: an independent risk factor for POI

HSCT represents an independent risk factor for POI and therefore deserves to be discussed separately. According to multiple published analyses, the incidence of ovarian failure ranges from 44% to 100% among transplant recipients during childhood, with clinical and demographical heterogeneity of different study cohorts accounting for most of this variability [16–18].

HSCT is progressively becoming the standard-of-care for a growing body of non-oncological conditions, such as hemoglobinopathies, primary immunodeficiencies and inborn errors of metabolism, even though malignancies still represent the most frequent indication for HSCT. While in transplanted cancer survivors the detrimental effect of HSCT on ovarian function plays a synergic role together with chemo- and/or radiotherapy administered as front-line and relapse treatment, in patients with non-malignant disorders the conditioning regimen received before HSCT mainly affects the ovarian reserve *per se*. Furthermore, type of conditioning regimen, age and pubertal status at the time of HSCT also play a pivotal role on gonadal function. In detail, when the conditioning regimen administered in adult women includes total body irradiation (TBI), gonadal failure is extremely frequent and

affects almost 100% of the patients for exposures above 10 Gy [19–21]. Although younger age and pre-pubertal status are protective factors and 40 to 60% of prepubertal girls younger than 10 years at the time of transplantation experience a spontaneous progression of puberty, the risk of a later-onset POI remains high after TBI.

In patients undergoing chemotherapy-only based conditioning regimens, the gonadotoxicity of the most frequently used agents has been assessed. POI has been reported with rates as high as 100% after standard-dose busulfan. [22,23] Conversely, the percentage of girls and young women with biochemical and clinical markers consistent with retained ovarian function after HSCT conditioned with cyclophosphamide or melphalan alone is remarkably higher [24,25].

In addition, graft-*versus*-host disease (GvHD) is a frequent complication experienced by patients after allogenic HSCT. GvHD is a complex, multiorgan disorder mediated by donor T-cells recognizing host alloantigens. Primary target organs of acute GvHD are skin, liver, and gastrointestinal tract, but both mating experiments performed in mice and retrospective analyses in women [26] have demonstrated that severe and chronic GvHD may target the ovary as well. Finally, hypoestrogenism may worsen and emphasize clinical symptoms of vulvovaginal GvHD; though this condition commonly requires a specific therapeutic approach, HT may contribute to provide a relief from dyspareunia, pruritus and mucosal dryness.

4. Hormone therapy options in women with POI: the state-of-the-art

As no studies have been held in the specific setting of chemo- and radiotherapy-induced POI involving CAYA, the clinical approach to this selected class of patients is generally extrapolated from analyses involving adult women with POI due to multiple etiologies, and tailored on the specific needs of the population of younger cancer survivors hereby discussed.

In this paragraph, we provide a detailed overview about hormonal treatment options in adult patients with POI, according to published literature. The practical proposal for the management of iatrogenic POI in CAYA presented in the next session is the result of a process of revision, guided by clinical experience, of the potential treatment solutions hereby presented, according to the specific clinical features and needs related with cancer survivorship listed in Table 1.

In adult women with POI, HT can be administered as either hormone replacement therapy (HRT) or combined oral contraceptives (COC).

4.1. Hormone replacement therapy

The goal of HRT in adult patients with POI is to restore normal serum estrogen concentrations according to age. In non-hysterectomized women, the choice of estrogen therapy should be combined with appropriately dosed progestogen therapy (administered continuously or sequentially) to prevent endometrial hyperplasia and cancer. On the other hand, estrogen-only HRT should be prescribed to hysterectomized women: indeed, there is no therapeutic advantage in prescribing progestins to this selected cohort of patients, with the possible exception of women with residual intra-peritoneal endometriosis.

4.1.1. Estrogens

Estrogen replacement in adult women can be achieved with the following preparations: 1–2 mg of oral 17β-estradiol (17βE) daily, 50–100 micrograms of transdermal 17βE daily or 0.625–1.25 mg of conjugated equine estrogens daily [20,27,28].

The transdermal administration of 17βE seems to be the preferred route as it mimics the physiological serum estradiol concentrations providing a better safety profile than oral formulations [29]. In fact, it avoids the hepatic first pass effect and minimizes the impact of estrogens on the synthesis of hemostatic factors [30]. It also has a more beneficial profile on circulating lipids, markers of inflammation and blood pressure [31]. Finally, transdermal 17βE has been demonstrated to be more effective in achieving a bone mineral density peak and reducing bone resorption markers compared to ethinylestradiol (EE)-based COC [32] (see next sessions).

4.1.2. Progestins

Medroxyprogesterone acetate (MPA) is the only progestin for which available evidences demonstrate the full effectiveness in inducing secretory endometrium together with a full replacement dose of estrogen when used regularly [33,34]. Although it has been showed that MPA may negatively impact on the cardiovascular risk given their effects on lipid profiles, vasomotion [35] and carbohydrate metabolism [36] more than alternative treatment options, many authors consider MPA as the first choice in the setting of HRT, given the wide availability of data about its efficacy. A recent growing body of literature has demonstrated the favorable profile of natural micronized progesterone (MP) in the setting of HRT. Firstly, it has been shown to minimize hormonal-related cardiovascular risks when compared to synthetic progestogens [31] and has a neutral or beneficial effect on blood pressure [37]. Secondly, MP shows one of the best safety profiles in terms of thrombotic risk [38], but this has not yet been studied in the POI population. Though further supporting evidence regarding the effectiveness of oral micronized progesterone is needed, the demonstrated safer pharmacological profile of MP has led the European Society for Human Reproduction and Embryology (ESHRE) to include MP among the recommended progestogens in HRT in adult women with ovarian insufficiency [9].

Several other progestins are available and could be prescribed as a component of combined HRT. The use of dydrogesterone, a synthetic progesterone with enhanced oral bioavailability [39], is listed among the suggested progestins by the ESHRE consensus guidelines [9] but no studies held so far have analyzed its endometrial effects in adult women with POI. The safety profile of norethisterone acetate (NA) in women with POI has been evaluated by Langrish and colleagues in a study comparing transdermal 17βE and vaginal MP *versus* oral EE and NA [31]. Although the Authors concluded that the latter option resulted in a worse profile in terms of blood pressure, renal function and activation of the renin-angiotensin system, discerning the relative contribution of progestogen and estrogen could be difficult and most of the differences reported may be attributed to the more physiological effects of 17βE compared with EE.

When prescribing HRT, clinicians should choose between a sequential and continuous regimen of administration, with the latter preventing withdrawal bleeding. In both cases, the dose of progestogen is based on the concurrent dose of estrogen administered. One of the advantages of the cyclic administration is that it would allow an earlier recognition of a pregnancy: as women with POI may spontaneously, though infrequently, ovulate, in the absence of a withdrawal bleeding

Table 1
Clinical specificities of childhood, adolescent and young adulthood cancer survivors and/or transplanted patients with premature ovarian insufficiency involving the need for a tailored approach to hormonal treatment. Abbreviations: HSCT – hematopoietic stem cell transplantation; GvHD – graft *versus* host disease.

Increased incidence of metabolic syndrome
Higher risk of low bone mineral density – deficient accrual of bone mineral peak
Incomplete development of uterine volume in case of pelvic irradiation
Higher incidence of liver focal nodular hyperplasia and chronic iatrogenic hepatic toxicity
Growth impairment secondary to iatrogenic growth hormone deficiency or due to direct iatrogenic effect of radiation on growth plates
Higher incidence of hypoandrogenism
Chronic skin GvHD, both involving deficient bioavailability of hormones delivered transdermally and increasing risk of poor tolerance to transdermal patches
Vulvovaginal GvHD

the patient should be advised to promptly test for pregnancy [40].

4.2. Combined hormonal contraceptives

COC could be recommended in patients seeking for contraception or rejecting HRT due to its poorer social acceptance.

As the aim of COC is contraception and not mere hormone replacement, estrogen and progestin dosages are higher than in the aforementioned HRT options [27]. As a consequence, given the trend towards a correlation between estrogen dosages and thromboembolic risk, it is generally assumed that HRT exposes patients to a lower risk of vaso-occlusive events. [31] To date, however, no well powered randomized trials comparing HRT and COC in terms of cardiovascular and thromboembolic risk, quality of life assessment or bone health have been held in the specific setting of POI and clinical recommendations can only be extrapolated from post-menopausal women. Spontaneous ovulation and conception, even if rare, could occur in patients with POI with an incidence reported respectively of 20–25% and 5–10% [20,41]. For this reason, COC should be chosen instead of HRT in young women seeking for safe contraception.

Most COC formulations contain EE; however, more recently, the scientific community has shown an increasing interest in natural estrogens such as 17βE or its valerate ester, due to a potentially more physiological and safer pharmacological profile [42].

EE is a potent synthetic estrogen with similar metabolic effects regardless of the route of administration because of its long half-life and slow metabolism [43]. Twenty micrograms of EE are approximately equivalent to 2 mg of 17βE valerate, the latter appearing to have a milder impact on hemostasis, fibrinolysis markers and lipid profile compared to EE [39,44]. However, whether 17βE-containing COC are safer than those formulated with EE in terms of thromboembolism still needs to be systematically demonstrated [45,46].

In a double-blind randomized study, Gaussem and colleagues showed that 17βE and nomogestrol acetate had fewer adverse effects on coagulation and fibrinolysis than EE and levonorgestrel-based COC [47]. However, the clinical impact of these biochemical findings has not been analyzed so far in terms of incidence of venous thromboembolism (VTE) and further studies are needed.

4.3. Hormonal Replacement Therapy with transdermal estrogens versus Combined Oral Contraceptive

4.3.1. Risk of venous thromboembolism

Both estrogen/progestin formulations and route of administration differently impact on the risk of VTE. It has been demonstrated that the risk is increased in patients treated with oral estrogen compared to transdermal or transvaginal routes [38,48–50]. In detail, in the multicenter Estrogen and Thromboembolism Risk (ESTHER) study performed in postmenopausal women, the odds ratio (OR) for venous thromboembolism in women using transdermal estrogens was 0.9 (95% CI, 0.4–2.1) compared to 4.2 (95% CI, 1.5–11.6) in women using oral estrogen preparations [33,38]. Stegeman and colleagues carried out a study on the levels of Sex Hormone Binding Protein (SHBP) as a marker of VTE in patients on HT. Results showed that transdermal 17βE had a neutral effect on SHBP, while oral 17βE 2 mg and oral EE 20 μg increased its levels independently of the progestin used [51].

COC preparations containing 35 μg or more of EE have been demonstrated to show statistically higher odds ratios for VTE than lower doses [52]. In addition, second-generation progestins, such as levonorgestrel, show a safer coagulation profile compared to more recent molecules (gestodene, desogestrel, cyproterone acetate, drospirenone) [52].

4.3.2. Metabolic profile

In a study by Langrish and colleagues, blood pressure levels recorded in 34 women diagnosed with POI and treated with transdermal 17βE-based HRT for at least 12 months were statistically lower than after COC, as a probable result of a more physiological impact on the renin-angiotensin-aldosterone axis [31]. In addition, in a study comparing 10 girls with Turner syndrome *versus* 20 healthy controls, Taboada and colleagues demonstrated that 17βE reduced LDL levels and increased HDL, while EE has been shown to have a negative impact on insulin tolerance [53].

4.3.3. Effects on bone mineral density

It has been demonstrated that 90% of peak bone mass is achieved by the age of 18 years [54]. Therefore, estrogen deficiency in adolescents suffering from POI has a significant impact on bone mineral density (BMD), particularly if estrogen deficiency becomes overt in the phase of intensive bone mineral accrual. [55] In a cohort of 30 randomized women, when comparing EE 30 μg and levonorgestrel 150 μg (COC) to 17βE 2 mg daily and levonorgestrel 75 μg (HRT), Cartwright and colleagues demonstrated that the latter had a more favorable effect on lumbar spine BMD [56]. In addition, it has been demonstrated that treatment with transdermal estradiol and vaginal progesterone had a more beneficial effect on lumbar spine BMD than standard HRT (oral EE and oral norethisterone) [32].

5. Hormone therapy in CAYA patients with iatrogenic POI: proposal for a practical therapeutic management

CAYA cancer survivors and those treated with HSCT for non-oncological conditions may require not only hormone replacement therapy in adulthood, but also hormonal pubertal induction, depending on the age at the time of exposure to antineoplastic treatments. We hereby provide suggestions for the management of HT in both cases.

5.1. Pubertal induction

HT for pubertal induction is indicated whenever girls surviving childhood cancer and/or treated with HSCT present with pubertal delay and a biochemical picture consistent with hypergonadotropic hypogonadism. A complete biochemical assessment is mandatory in order to discriminate physiological pubertal delay from treatment-related ovarian insufficiency.

In this specific setting, HT aims at triggering initial pubertal signs, prompting a proper pubertal height spurt, achieving adequate feminization [57,58] and improving bone mass accrual [59], without compromising height attainment. The timing and the modalities need to be balanced with attention to peer appropriate psychosocial and emotional maturity.

In addition, adequate uterine development is exploited when exposure to estrogens occurs in the physiological window of early adolescence; this decreases the risk of fetal loss in case of future pregnancies. Studies performed in patients with Turner syndrome demonstrate that an early institution of HT results in a larger uterine volume [60].

Multiple National and International Endocrinological Societies agree that HT induction should mimic as far as possible the physiological course of puberty in healthy girls, both in *tempo* and magnitude. Indeed, girls with iatrogenic POI should be allowed to keep up with their peers. As a consequence, though some Authors identify 12–13 years as the ideal age for commencing pubertal induction [61], guidelines dealing with POI in Turner Syndrome (Turner Syndrome Working Group [62], UK [63] and Cincinnati [64] guidelines) agree that initiation of treatment should be undertaken earlier, *i.e.* between 11 and 12 years, in order to facilitate positive psychosocial and psychosexual adaptation. A serum FSH cut-off of $\geq$10 U/L at 10 or more years of age is considered a reasonable indicator of ovarian impairment requiring pubertal induction in girls with Turner Syndrome. However, it is accepted that the clinician should decide whether to postpone pubertal induction, in order to allow the possibility of spontaneous puberty to occur.

Table 2
Criteria to be taken into account when establishing timing, starting dose and formulation for pubertal induction in pre/peripubertal children and eligibility, formulation and route of administration of hormonal therapy in post-pubertal girls and young women.

Pre- and peripubertal girls	Post-pubertal girls and young adults
Factors affecting the timing for starting pubertal induction	Factors affecting treatment eligibility
Family history of pubertal delay	Previous/ active hormone sensitive tumors
Cognitive, psychological and emotional maturity	Demonstrated mutations involving BRCA1–2 genes
Concomitant growth hormone deficiency	Previous thromboembolic events or family history consistent with thrombophilic disorders
Bone mineral density Z score	Factors affecting route of administration
Bone age, height, growth velocity and final height expectation	Liver disease and/or focal nodular hyperplasia
Factors affecting the starting dose of estrogens	HT formulation used at the time of pubertal induction (if HT needed)
Age	Individual preference
Secondary sexual features achieved spontaneously before pubertal arrest or before antineoplastic treatment	Bone mineral density Z/T score
Uterine volume and maturation achieved spontaneously before pubertal arrest or before antineoplastic treatment assessed *via* pelvic ultrasound	Metabolic risk factors
Factors affecting route of administration	Skin chronic GvHD
Skin chronic GvHD	Factors affecting formulation (COC *vs* HRT)
Metabolic risk factors	Need for contraception
Liver disease and/or focal nodular hyperplasia	Individual perception of social acceptance

Abbreviations: GvHD – Graft *versus* host disease; COC – combined oral contraceptives; HRT – hormone replacement therapy; HT – hormonal treatment; BRCA – breast related cancer antigen.

The timing of pubertal induction may also affect the final height achieved by childhood cancer survivors. Patients exposed to cranial, craniospinal or total body irradiation present with a remarkable loss in final height due either to the direct detrimental effect of radiation on growth plates or to iatrogenic growth hormone deficiency, as the irradiation field includes the pituitary gland [65]. As published data support the hypothesis that the final stature attained by otherwise healthy patients with pubertal delay may fall below the predicted potential [66,67], postponing pubertal induction may result in an additional worsening of the stature attained at the end of growth.

Furthermore, as HSCT has become the standard-of-care of a growing body of genetically heterogeneous non-oncological conditions (hemoglobinopathies, primary immunodeficiencies and inborn errors of metabolism), the timing of pubertal induction and the route of administration should be also tailored according to patient's clinical and cognitive baseline *status*.

There is agreement that pubertal induction should be carried out over period of 2 to 3 years, but a shorter induction can be taken into account in girls diagnosed with POI late, after the age of 13 years.

Table 2 lists the criteria to be taken into account when establishing timing, starting dose and formulation for pubertal induction in pre/peripubertal patients.

Either oral or transdermal 17βE and oral EE have been described as potentially fitting choices in terms of pubertal induction in girls. EE has been historically used for this purpose mostly in the United Kingdom but not in other Countries, and data about its safety and efficacy are therefore limited.

In patients with Turner syndrome, several studies demonstrated a suboptimal uterine development in patients treated with EE for pubertal induction [68,69]. Conversely, transdermal 17βE has shown better results in terms of uterine parameters [45,46] On the other hand, conflicting outcomes have been reported about the effectiveness of oral 17βE in achieving a complete development of uterine volume, with some supporting the hypothesis of a good response and others advising against its use in this specific setting [70–72].

Given the known detrimental effects of pelvic RT on uterine maturation [73], the choice of the most effective HT for pubertal induction becomes pivotal in irradiated patients. Though infertility is a frequent outcome in patients with POI, progresses in assisted reproductive technologies (*i.e.* fertility preservation and oocyte donation) should lead clinicians to focus on this issue, as a remarkably increased number of miscarriages have been reported in irradiated patients with a suboptimal uterine development [74].

Cancer survivors present with an increased risk of low BMD, mostly as a consequence of cancer-related treatments undertaken in childhood (high-doses of corticosteroids, total body irradiation, tyrosine-kinase inhibitors). As the bone mass peak is exploited during adolescence, the relative effects of each single HT agent used for pubertal induction should be taken into account. In a randomized controlled trial comparing 17βE and EE, Crofton and colleagues raised some concerns about the poor efficacy of the latter in improving BMD during and at the end of pubertal induction, with 17βE being remarkably more effective [32].

Several Authors demonstrated that patients treated with HSCT are exposed to a higher risk of developing metabolic syndrome [75,76]. Studies assessing the metabolic impact of HT in women have shown the positive impact of 17βE on the lipid profile, with a demonstrated reduction of LDL and concomitant increase in HDL levels [53]. Conversely, EE has been shown to negatively affect mean blood pressure and insulin tolerance [51].

Furthermore, in the specific subset of CAYA cancer survivors, a therapeutic route that avoids the “hepatic first-passage effect” should be pursued. Liver focal nodular hyperplasia (FNH) is an incidental finding frequently reported in these patients, with an estimated incidence remarkably higher than the general population. As HT plays a potential contributory effect on the onset of this condition [77], the use of transdermal 17βE may be associated with a reduction of its incidence, though no specific trials have been carried out so far. In addition, also patients with chronic iatrogenic hepatic toxicity may benefit from the avoidance of “hepatic first-passage effect” and transdermal route could be preferred in these cases.

Finally, oral EE is known to decrease serum insulin-like growth factor-I (IGF−I) levels, probably because of a direct effect on hepatic synthesis [78]. Though no data about its effects on growth are available, this effect may raise an issue in the management of growth hormone (GH) deficient patients. Childhood cancer survivors experience GH deficiency as a consequence of the treatments undertaken and IGF-I is a useful guide in the process of titration and subsequent monitoring of the dose of recombinant Human GH administered. The use of transdermal 17βE does not affect IGF-I levels [79] and is therefore more suitable for the management of patients diagnosed with both GH deficiency and POI.

For all the reasons above, we strongly recommend that transdermal 17βE is listed as the first choice among the drugs used to induce puberty in the specific setting of cancer survivor girls. Oral 17βE should be administered only whether a contraindication for transdermal route exists (poor compliance, chronic skin GvHD that may affect estradiol

Table 3
Suggested dosages to induce puberty with different estrogens formulations and route of administration – abbreviations: 17βE - 17β-estradiol.

Time elapsed after pubertal induction start	Transdermal 17βE Patches releasing 25 μg of 17βE daily	Oral 17βE 1–2 mg tablets	Oral ethinylestradiol 10 μg tablets	17βE transdermal gel Pump dispensing a metered dose of 0.5 mg of estradiol at each activation
0–6 months	1/8 of a patch all week; alternatively, 1/4 of a patch left *in situ* for 3–4 days per week.	0.5 mg every other day	5 μg every other day	–
6–12 months	1/4 of a patch every week 7/7 days	0.5 mg every other day	5 μg every other day	–
12–18 months	1/2 of a patch for 3–4 days, 1/4 of a patch for the remaining 3–4 days every week	0.5 mg daily	5 μg daily	–
18–24 months	1/2 of a patch every week 7/7 days	0.5 mg and 1 mg every other day	5 μg and 10 μg every other day	0.5 mg every other day
> 24 months	1 full patch every week 7/7 days	1 mg daily	10 μg daily	0.5 mg daily

absorption or local reaction to patches).

In addition, the availability of cuttable matrix patches of 17βE suits the need of low starting doses in order to mimic the physiological slow progression of puberty in healthy girls.

Irrespectively of body weight, pubertal induction commonly starts with progressively increasing fractions of 25 micrograms matrix patches, available in most Countries. Our suggestion, as reported in Table 3, is to start with 1/8 of patch, to be applied on dry and clean skin continuously and left *in situ*. The patch should be changed as indicated (once or twice a week, according to the specific instructions provided for each brand). Alternatively, the same dose can be yielded by applying ¼ of patch for only 3 sequential days every week.

Estrogen doses should be increased not earlier than 6-monthly over a period of 24 months, as suggested by analyses comparing the mean estradiol levels achieved during induction and circulating estradiol concentrations in healthy girls [80]. Both periodical clinical assessment of the secondary sexual features achieved and ultrasonographic evaluation of uterine volume and morphology may guide the clinician in managing dose escalation.

In patients for whom anti-neoplastic treatment was undertaken after the onset of pubertal signs and who therefore experienced a pubertal arrest, estrogens may be started at somewhat higher doses and escalated more rapidly [81]. In these patients, baseline ultrasonographic assessment can be useful to estimate the estrogen induction dose, with more estrogenized pictures deserving higher starting dosages.

When transdermal 17βE is contraindicated or not tolerated, dose equivalences with different formulations are reported in Table 3.

Two to three years after the start of pubertal induction, breakthrough bleeding occurs and progestin has to be added to the estrogens for endometrial protection and to achieve regular withdrawal bleeding. A sonographic evaluation could be advised at this point, in order to demonstrate a proper endometrial thickness before prescribing progestin.

MP, administered orally at a dose of 100–200 mg daily for 12–14 every 28 days, is the first choice due to its physiological and safe profile, as previously widely discussed [9]. MPA 5–10 mg daily or Norethisterone 5 mg daily administered 12–14 every 28 days represent alternatives whenever MP is contraindicated or poorly tolerated [9].

Progestins can be also administered transdermally, as in some Countries combined patches of 17βE and progestogens are available for either continuous or sequential administration.

5.2. Hormone therapy in young post-pubertal patients

HT is indicated in all post-pubertal girls and women with a clinical and biochemical picture of POI. The present paragraph is focused both on post-pubertal patients for whom pharmacological induction of puberty had been previously undertaken due to pubertal arrest and adolescents and young women who achieved menarche spontaneously but who experienced premature menopause later on, in the setting of iatrogenic POI.

In order to customize treatment options and to increase the compliance to therapy, patient's individual needs and preferences, such as route of administration, request of contraception and desire of withdrawal bleeding must be taken into account. In addition, patient's specific contraindication to HT and metabolic risk factors should be carefully considered, especially in cancer survivors and transplanted patients who are known to be at higher risk of metabolic syndrome and often present with treatment-related complications [76] (Table 2).

Fig. 1 shows the decisional process that should be undertaken when tailoring treatment decisions on the basis of patient's specific needs. Table 4 summarizes the suggested treatment protocol for HT in post-pubertal patients with iatrogenic POI.

If no contraception is requested, HRT *via* 17βE-based transdermal patches or vaginal gel should be strongly recommended as a first line approach.

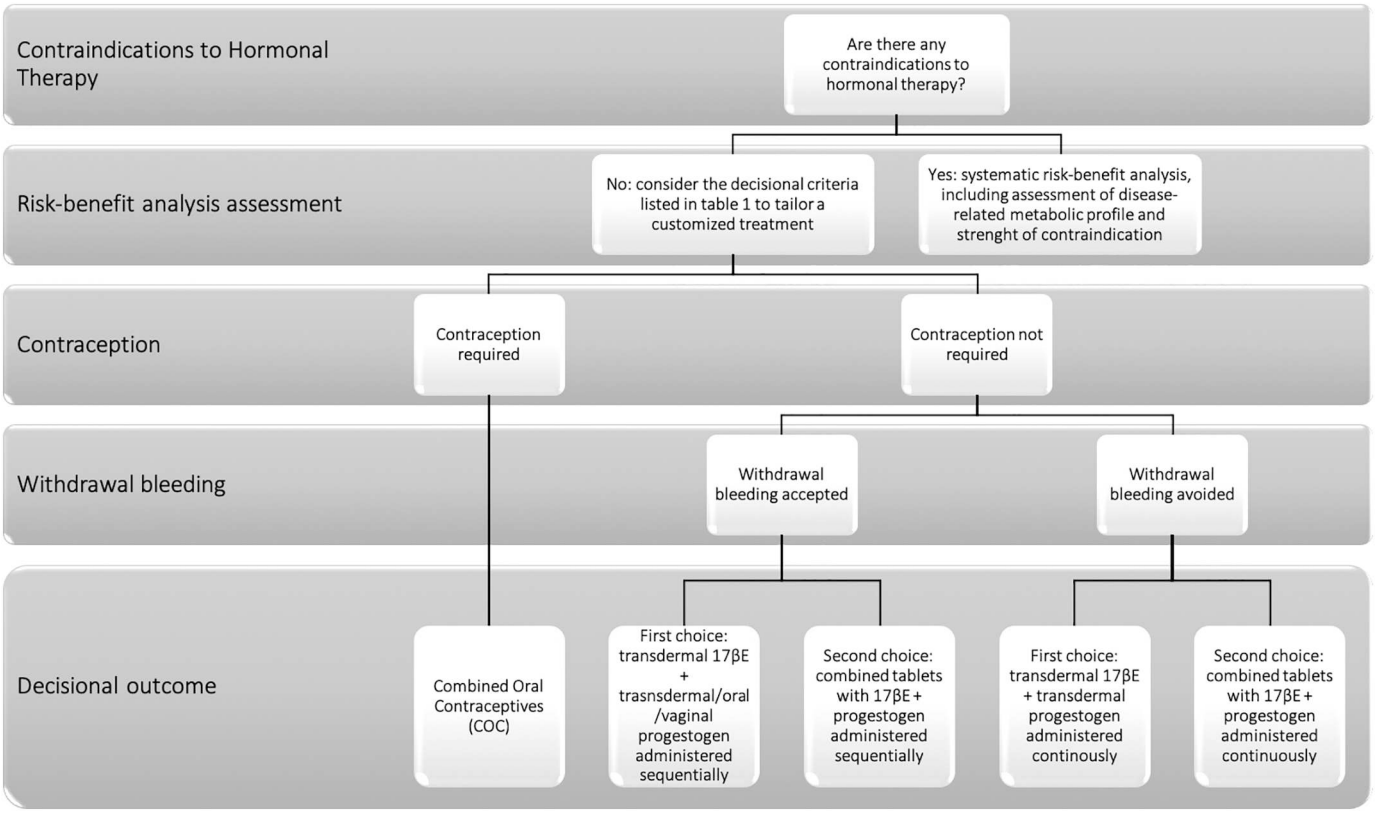

Fig. 1. Decisional algorithm for undertaking hormonal therapy in post-pubertal adolescents/ young adult women with iatrogenic POI – Abbreviations: 17βE: 17β-estradiol. COC: Combined Oral Contraceptives.

Firstly, though no studies have systematically investigated the potential advantages of 17βE in young girls with iatrogenic POI, the higher cardiovascular risk experienced by cancer survivors [82,83] should be looked at as a pivotal criticism when customizing HT recommendations for this selected cohort and strengthens the indication of 17βE-based transdermal/vaginal HRT as the first treatment choice (*see previous paragraphs*). In addition, as already widely discussed, the avoidance of the "first-line hepatic effect" and the demonstrated better profile of transdermal estrogens on bone mass accrual further support this approach in a population at increased risk of developing liver FNH

Table 4
Systematical approach to hormonal therapy in post-pubertal adolescents and young women with iatrogenic premature ovarian insufficiency: overall proposal for a pragmatical treatment protocol. Abbreviations: 17βE - 17βEstradiol; MP – micronized progesterone; MPA - medroxyprogesterone acetate.

Contraception not required	Withdrawal bleeding accepted	First choice: 17βE administered transdermally	Transdermal 17βE + transdermal progestin - sequential combined patches: Patches of 17βE alone administered for 2 weeks, followed by patches of combined 17βE and progestin for 2 additional weeks; 4-weeks courses restarted without interruptions. Example: Patches releasing 50 μg of 17βE daily for 2 weeks, followed by patches releasing 50 μg of 17βE and 10 μg of levonorgestrel daily for 2 additional weeks. Transdermal 17βE + oral/vaginal progestin: Transdermal 17βE administered continuously and oral/vaginal progestin administered for 12–14 every 28 days. Example: Patches releasing 50 μg of 17βE daily administered continuously for 28 days; add oral progestin (*i.e.* MP 200 mg daily or MPA 10 mg daily) or vaginal progestin (*i.e.* MP 200 mg daily) for 12–14 every 28 days.
		Second choice: 17βE administered orally	Oral 17βE + progestin – Sequential combined tablets: Tablets of 17βE alone administered for 14 days, followed by tablets containing both 17βE and progestin for 12–14 days; 4-weeks courses restarted without interruptions. Example: Tablets containing 17βE alone (1–2 mg daily) for 2 weeks, followed by tablets containing both 17βE (1–2 mg daily) and dydrogesterone (10 mg daily) for 2 additional weeks.
	Avoiding of withdrawal bleeding required	First choice: 17βE administered transdermally	Combined patches containing 17βE and progestin administered continuously without interruptions. Example: Patches releasing 50 μg of 17βE and 7 μg of levonorgestrel daily administered continuously without interruptions.
		Second choice: 17βE administered orally	Combined tablets containing 17βE and progestin administered continuously. Example: Tablets containing 1–2 mg of 17βE and 5 mg of dydrogesterone (or 2 mg of dienogest) administered continuously without interruptions.
Contraception required	First choice: 17βE-based combined oral contraceptives. - 17βE + acetate nomegestrol - 17βE + dienogest Second choice: ethinylestradiol-based combined oral contraceptives.		

and low BMD.

In post-pubertal adolescent/young adult childhood cancer survivors with POI, 17βE can be administered either transdermally *via* patches releasing 50 to 100 μg 24 hourly (to be changed twice a week or weekly according to the specific instructions provided for each brand), or *via* vaginal gel, with doses ranging from 0.5 to 1 mg daily.

In order to improve compliance to treatment, we recommend the use of combined 17βE and progestin patches as a first choice (*i.e.* 17βE + levonorgestrel, available in different Countries). Both sequential combined (17βE administered continuously and progestogen administered cyclically for 2 every 4 weeks) and continuous combined (17βE and progestogen administered continuously) patches are available, respectively inducing or avoiding withdrawal bleeding, as *per* patient's request.

If combined 17βE and progestin patches are not available, transdermal 17βE can be administered continuously and oral (or vaginal) progestin can be added cyclically for 12–14 every 28 days. Adult doses of oral progestin depend on the doses of estrogen administered. Sequential regimens require 200 mg of oral (or vaginal) MP for 12–14 every 28 days or 10 mg of MPA for 12–14 days per month, or 10 mg of dydrogesterone for 12–14 days per month. Continuous regimens require a minimum of 1 mg of oral norethisterone, 2.5 mg of oral MPA and 5 mg of oral dydrogesterone daily.

Among progestins, MP is the first choice; indeed recent studies have reported that, if taken with cyclical administration, MP is associated with a lower risk of cardiovascular disease and venous thromboembolism and it determines endometrial protection (*see previous paragraphs)* [33]. Second choices are MPA, dydrogesterone or norethisterone.

Systematic analyses have demonstrated that patients with iatrogenic POI may suffer from diminished *libido* or impaired sexual function as a consequence of low circulating testosterone levels [84]. As a consequence, progestins with an anti-androgenic effect could worsen hypoandrogenism and should be therefore avoided in this specific cohort of patients.

When transdermal administration is contraindicated (*i.e.* diffuse cutaneous disorders, such as chronic skin GvHD) or refused by the patient, the second choice of treatment should be represented by oral 17βE, administered at adult doses of 1–2 mg daily. Combined oral HRT containing 1–2 mg of 17βE and progestin are available in several Countries (i.e 17βE + dydrogesterone, 17βE + MPA). Again, both sequential combined and continuous combined formulations are available (See Table 4 for additional details).

The dose of 17βE should be adjusted according to each woman's tolerance and feeling of wellbeing.

HRT in cancer survivors with POI should be continued until the average age of spontaneous menopause (45–55 years). Afterwards, the decision to stop or continue HRT must be weighed on individual risks, family history, personal feelings and relevance of menopausal symptoms. Lower post-menopausal doses of HRT have been associated with an advantageous risks-benefit ratio [29].

When either the request for contraception or its better social acceptance leads the clinician to prescribe COC instead of HRT, the specific choice should be guided by a risk assessment as set out by the Faculty of Sexual & Reproductive Healthcare [85]. As already debated, 17βE-based COC could be preferred to pills containing EE, though no double-blinded studies have systematically compared these two formulations yet.

Finally, it is worthy of remark that women who undergo TBI as conditioning for bone marrow transplantation or women who survived Hodgkin lymphoma show an increased incidence of breast cancer [86,87]. A strict follow-up is fundamental in patients on treatment with HT, and a reasonable approach includes promotion of breast self-examination and annual imaging from the age of 25 years onwards [86]. In young patients, like those included in the present analysis, high density breast tissue may affect the diagnostic accuracy of screening mammography. Breast MRI has been proved to remarkably increase the early detection of cancer in young patients with negative mammography and should therefore be taken into account when assessing high-risk young women [88].

6. Conclusions

Survivors after cancer and/or HSCT occurring during childhood or adolescence are nowadays up to 0.5% of the general population, thanks to the advances in cancer treatment allowing progressively increased survival.

Young women with iatrogenic POI are at major risk of subsequent onset of late effects due to chronic estrogen deprivation. The shared skills of gynecologists, pediatricians, endocrinologists, dietitians and psychologists are crucial to provide adequate long-term follow-up and improve the quality of life of these patients. The protocol hereby presented, resulting from the collaboration of a multidisciplinary team, may help the clinician in tailoring hormonal therapy according to patient's medical and psychological needs, in order to maximize safety, efficacy and *compliance* to treatment.

7. Future considerations

Given the outstanding improvements in pediatric oncology during the last decades, cancer survivorship-related burden of long-term effects represents a new world-wide challenge. In addition, HSCT has become the standard-of-care of a growing body of non-malignant disorders. As a consequence, tailored patient- and disease-specific protocols dealing with the management of pubertal induction and HT in patients with POI due to different indications should represent the focus of future analyses.

In addition, due to the increasing awareness of the detrimental role played by traditional chemotherapeutic agents on ovarian function, less gonadotoxic treatment protocols and drugs have been developed. As a consequence, systematic multidisciplinary teamwork involving endocrinologists, gynecologists and oncologists will become pivotal to tailor the most suitable diagnostic and therapeutic approach to patients treated with new-generation antineoplastic agents.

Practice points

- More than in otherwise healthy patients, young cancer survivors and transplanted patients with ovarian insufficiency should be regarded as a highly peculiar cohort; thus, hormonal therapy should be carefully tailored according to patient's individual needs and comorbidities.
- Unless contraception is regarded as a paramount, transdermal 17βEstradiol-based hormonal replacement therapy should represent the first choice in terms of safety profile in patients with cancer-related late effects.
- Combined oral contraceptives should be prescribed only in patients deeming contraception as a priority.
- Favorite route of administration, desire of avoiding periodical withdrawal bleeding and the hormonal treatment undertaken for pubertal induction are some of the additional criteria that clinicians should take into account when choosing among the available formulations.

Research agenda

- A double-blind randomized study comparing combined oral contraceptives *versus* 17βEstradiol-based transdermal hormonal replacement therapy in a selected cohort of young cancer survivors with iatrogenic POI could finally either confirm or reject the hypothesis of a safer and most effective profile of the latter drawn from the elder population.
- The effectiveness and safety profile of micronized progesterone in

the setting of hormonal replacement therapy in patients with iatrogenic POI still needs to be defined.
- The suggested age for starting pubertal induction is drawn from studies performed on patients with Turner syndrome, but the most suitable age in girls with iatrogenic ovarian insufficiency still needs to be clarified.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution (CRediT author statement)

Alessandro Cattoni: Conceptualization, Methodology, Writing – original draft preparation, review and editing, Supervision, Project administration.

Francesca Parissone: Conceptualization, Methodology, Writing – review and editing.

Irene Porcari: Writing – original draft preparation, Resources.

Silvia Molinari: Writing – original draft preparation, Resources.

Nicoletta Masera: Writing – review and editing.

Massimo Franchi: Writing – review and editing.

Cesaro Simone: Writing – review and editing.

Gaudino Rossella: Writing – review and editing.

Paolo Passoni: Writing – review and editing.

Adriana Balduzzi: Conceptualization, Methodology, Writing – review and editing, Supervision.

Declaration of Competing Interest

The Authors declare no conflict of interest.

Appendix 1

CED can be calculated according to the following equation:

CED (mg/m^2) = 1.0 x (cumulative cyclophosphamide dose [mg/m^2]) + 0.244 x (cumulative ifosfamide dose [mg/m^2]) + 0.857 x (cumulative procarbazine dose [mg/m^2]) + 14.286 x (cumulative chlorambucil dose [mg/m^2]) + 15.0 x (cumulative carmustine dose [mg/m^2]) + 16.0 x (cumulative lomustine dose [mg/m^2]) + 40 x (cumulative melphalan dose [mg/m^2]) + 50 x (cumulative Thiotepa dose [mg/m^2]) + 100 x (cumulative nitrogen mustard dose [mg/m^2]) + 8.823 x (cumulative busulfan dose [mg/m^2].

References

[1] ACOG Committee Opinion No. 747: gynecologic issues in children and adolescent Cancer patients and survivors. Obstet. Gynecol. 2018;132(2):e67–77.
[2] Howlader N, Noone A, Krapcho M, Miller D, Bishop K, Kosary C, et al. SEER Cancer Statistics Review (CSR). Natl Cancer Inst 1975-2014:2017.
[3] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J. Clin. 2017;67(1):7–30.
[4] Olsen JH, Möller T, Anderson H, Langmark F, Sankila R, Tryggvadóttír L, et al. Lifelong Cancer incidence in 47 697 patients treated for childhood Cancer in the Nordic countries. JNCI J Natl Cancer Inst 2009;101(11):806–13.
[5] Meadows AT. Pediatric cancer survivors: past history and future challenges. Curr. Probl. Cancer 2003;27(3):112–26.
[6] Wallace WHB, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol 2005;62(3):738–44.
[7] van Dorp W, Haupt R, Anderson RA, Mulder RL, van den Heuvel-Eibrink MM, van Dulmen-den Broeder E, et al. Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult Cancer: a review. J. Clin. Oncol. 2018;36(21):2169–80.
[8] Levine JM, Whitton JA, Ginsberg JP, Green DM, Leisenring WM, Stovall M, et al. Nonsurgical premature menopause and reproductive implications in survivors of childhood cancer: a report from the childhood Cancer survivor study. Cancer 2018;124(5):1044–52.
[9] Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, et al. ESHRE guideline: management of women with premature ovarian insufficiency. Hum. Reprod. 2016;31(5):926–37.
[10] van Dorp W, Mulder RL, Kremer LCM, Hudson MM, van den Heuvel-Eibrink MM, van den Berg MH, et al. Recommendations for premature ovarian insufficiency surveillance for female survivors of childhood, adolescent, and young adult Cancer: a report from the international late effects of childhood Cancer guideline harmonization Group in Collaboration with the PanCareSurFup consortium. J. Clin. Oncol. 2016;34(28):3440–50.
[11] Green DM, Nolan VG, Goodman PJ, Whitton JA, Srivastava D, Leisenring WM, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the childhood cancer survivor study. Pediatr. Blood Cancer 2014;61(1):53–67.
[12] Green DM, Nolan VG, Srivastava DK, Leisenring W, Neglia JP, Sklar CA, et al. Quantifying alkylating agent exposure: evaluation of the cyclophosphamide equivalent dose—a report from the childhood Cancer survivor study. J. Clin. Oncol. 2011;29(15):9547.
[13] Chemaitilly W, Li Z, Huang S, Ness KK, Clark KL, Green DM, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude lifetime cohort study. J. Clin. Oncol. 2015;33(5):492–500.
[14] Byrne J, Fears TR, Gail MH, Pee D, Connelly RR, Austin DF, et al. Early menopause in long-term survivors of cancer during adolescence. Am. J. Obstet. Gynecol. 1992;166(3):788–93.
[15] Chiarelli AM, Marrett LD, Darlington G. Early menopause and infertility in females after treatment for childhood Cancer diagnosed in 1964-1988 in Ontario. Canada Am J Epidemiol 1999;150(3):245–54.
[16] Sanders J, Hawley J, Levy W, Gooley T, Buckner C, Deeg H, et al. Pregnancies following high-dose cyclophosphamide with or without high- dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996;87(7):3045–52.
[17] Sarafoglou K, Boulad F, Gillio A, Sklar C. Gonadal function after bone marrow transplantation for acute leukemia during childhood. J. Pediatr. 1997;130(2):210–6.
[18] Chatterjee R, Goldstone AH. Gonadal damage and effects on fertility in adult patients with haematological malignancy undergoing stem cell transplantation. Bone Marrow Transplant. 1996;17(1):5–11.
[19] Jadoul P, Anckaert E, Dewandeleer A, Steffens M, Dolmans M-M, Vermylen C, et al. Clinical and biologic evaluation of ovarian function in women treated by bone marrow transplantation for various indications during childhood or adolescence. Fertil. Steril. 2011;96(1):126–33.
[20] Nelson LM. Primary ovarian insufficiency. N. Engl. J. Med. 2009;360(6):606–14.
[21] No Committee Opinion. 605: primary ovarian insufficiency in adolescents and young women. Obstet. Gynecol. 2014;124(1):193–7.
[22] López-Ibor B, Schwartz AD. Gonadal failure following busulfan therapy in an adolescent girl. Am J Pediatr Hematol Oncol 1986;8(1):85–7.
[23] Giorgiani G, Bozzola M, Cisternino M, Locatelli F, Gambarana D, Bonetti F, et al. Gonadal function in adolescents receiving different conditioning regimens for bone marrow transplantation. Bone Marrow Transplant. 1991;8. Suppl 1:53.
[24] Michel G, Socié G, Gebhard F, Bernaudin F, Thuret I, Vannier JP, et al. Late effects of allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: the impact of conditioning regimen without total-body irradiation–a report from the Société Française de Greffe de Moelle. J. Clin. Oncol. 1997;15(6):2238–46.
[25] Singhal S, Powles R, Treleaven J, Horton C, Swansbury GJ, Mehta J. Melphalan alone prior to allogeneic bone marrow transplantation from HLA-identical sibling donors for hematologic malignancies: alloengraftment with potential preservation of fertility in women. Bone Marrow Transplant. 1996;18(6):1049–55.
[26] Nakano H, Ashizawa M, Akahoshi Y, Ugai T, Wada H, Yamasaki R, et al. Assessment of the ovarian reserve with anti-Müllerian hormone in women who underwent allogeneic hematopoietic stem cell transplantation using reduced-intensity conditioning regimens or myeloablative regimens with ovarian shielding. Int. J. Hematol. 2016;104(1):110–6.
[27] Gussi I. Speroff Leon, Fritz Marc A, editors. Clinical Gynecologic Endocrinology and Infertility. 7th ed.1(2). Publisher: Lippincot Williams Wilkins. Book Review Acta Endocrinologica (Buc); 2005. p. 240.
[28] Chetkowski RJ, Meldrum DR, Steingold KA, Randle D, Lu JK, Eggena P, et al. Biologic effects of transdermal estradiol. N. Engl. J. Med. 1986;314(25):1615–20.
[29] Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil. Steril. 2016;106(7):1588–99.
[30] Maclaran K, Panay N. Current concepts in premature ovarian insufficiency. Womens Health (Lond) 2015;11(2):169–82.
[31] Langrish JP, Mills NL, Bath LE, Warner P, Webb DJ, Kelnar CJ, et al. Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. Hypertension 2009;53(5):805–11.
[32] Crofton PM, Evans N, Bath LE, Warner P, Whitehead TJ, Critchley HOD, et al. Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. Clin. Endocrinol. 2010;73(6):707–14.
[33] Gibbons WE, Moyer DL, Lobo RA, Roy S, Mishell DR. Biochemical and histologic effects of sequential estrogen/progestin therapy on the endometrium of postmenopausal women. Am. J. Obstet. Gynecol. 1986;154(2):456–61.
[34] Bjarnason K, Cerin Å, Lindgren R, Weber T. Adverse endometrial effects during long cycle hormone replacement therapy. Maturitas 1999;32(3):161–70.
[35] Sitruk-Ware R. Progestogens in hormonal replacement therapy: new molecules, risks, and benefits. Menopause 2002;9(1):6–15.
[36] Sitruk-Ware R. Pharmacological profile of progestins. Maturitas

2004;47(4):277–83.
[37] Mueck AO. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Climacteric 2012;15(sup1):11–7.
[38] Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women. Circulation 2007;115(7):840–5.
[39] Kupferminc MJ, Lessing JB, Amit A, Yovel I, David MP, Peyser MR. A prospective randomized trial of human chorionic gonadotrophin or dydrogesterone support following in-vitro fertilization and embryo transfer. Hum. Reprod. 1990;5(3):271–3.
[40] No Committee Opinion. 698 summary: hormone therapy in primary ovarian insufficiency. Obstet. Gynecol. 2017;129(5):963–4.
[41] Bidet M, Bachelot A, Bissauge E, Golmard JL, Gricourt S, Dulon J, et al. Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. J. Clin. Endocrinol. Metab. 2011;96(12):3864–72.
[42] Fruzzetti F, Trémollieres F, Bitzer J. An overview of the development of combined oral contraceptives containing estradiol: focus on estradiol valerate/dienogest. Gynecol. Endocrinol. 2012;28(5):400–8.
[43] Stanczyk FZ, Archer DF, Bhavnani BR. Ethinyl estradiol and 17β-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment. Contraception 2013;87(6):706–27.
[44] Jensen JT. Evaluation of a new estradiol oral contraceptive: estradiol valerate and dienogest. Expert. Opin. Pharmacother. 2010;11(7):1147–57.
[45] Petitti DB. Hormonal contraceptives and arterial thrombosis — not risk-free but safe enough. N. Engl. J. Med. 2012;366(24):2316–8.
[46] Dinger J, Do Minh T, Heinemann K. Impact of estrogen type on cardiovascular safety of combined oral contraceptives. Contraception 2016;94(4):328–39.
[47] Gaussem P, Alhenc-Gelas M, Thomas J-L, Bachelot-Loza C, Remones V, Dali Ali F, et al. Haemostatic effects of a new combined oral contraceptive, nomegestrol acetate/17β-estradiol, compared with those of levonorgestrel/ethinyl estradiol. Thromb. Haemost. 2011;105(3):560–7.
[48] Scarabin P-Y, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet 2003;362(9382):428–32.
[49] Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 2008;336(7655):1227–31.
[50] Mohammed K, Abu Dabrh AM, Benkhadra K, Al Nofal A, Carranza Leon BG, Prokop LJ, et al. Oral vs transdermal estrogen therapy and vascular events: a systematic review and meta-analysis. J. Clin. Endocrinol. Metab. 2015;100(11):4012–20.
[51] Stegeman BH, Raps M, Helmerhorst FM, Vos HL, van Vliet HAAM, Rosendaal FR, et al. Effect of ethinylestradiol dose and progestagen in combined oral contraceptives on plasma sex hormone-binding globulin levels in premenopausal women. J. Thromb. Haemost. 2013;11(1):203–5.
[52] Machura P, Grymowicz M, Rudnicka E, Pięta W, Calik-Ksepka A, Skórska J, et al. Premature ovarian insufficiency – hormone replacement therapy and management of long-term consequences. Menopausal Rev 2018;17(3):135–8.
[53] Taboada M, Santen R, Lima J, Hossain J, Singh R, Klein KO, et al. Pharmacokinetics and pharmacodynamics of Oral and transdermal 17β estradiol in girls with turner syndrome. J. Clin. Endocrinol. Metab. 2011;96(11):3502–10.
[54] Theintz G, Buchs B, Rizzoli R, Slosman D, Clavien H, Sizonenko PC, et al. Longitudinal monitoring of bone mass accumulation in healthy adolescents: evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. J. Clin. Endocrinol. Metab. 1992;75(4):1060–5.
[55] Leite-Silva P, Bedone A, Pinto-Neto AM, Costa JV, Costa-Paiva L. Factors associated with bone density in young women with karyotypically normal spontaneous premature ovarian failure. Arch. Gynecol. Obstet. 2009;280(2):177–81.
[56] Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone replacement therapy versus the combined Oral contraceptive pill in premature ovarian failure: a randomized controlled trial of the effects on bone mineral density. J. Clin. Endocrinol. Metab. 2016;101(9):3497–505.
[57] Zacharin M. Disorders of ovarian function in childhood and adolescence: evolving needs of the growing child. An endocrine perspective. BJOG 2010;117(2):156–62.
[58] McCabe MJ, Bancalari RE, Dattani MT. Diagnosis and evaluation of hypogonadism. Pediatr. Endocrinol. Rev. 2014;11(Suppl. 2):214–29.
[59] Sabatier JP, Guaydier-Souquières G, Laroche D, Benmalek A, Fournier L, Guillon-Metz F, et al. Bone mineral acquisition during adolescence and early adulthood: a study in 574 healthy females 10–24 years of age. Osteoporos. Int. 1996;6(2):141–8.
[60] Cleemann L, Holm K, Fallentin E, Skouby SO, Smedegaard H, Møller N, et al. Uterus and ovaries in girls and young women with turner syndrome evaluated by ultrasound and magnetic resonance imaging. Clin. Endocrinol. 2011;74(6):756–61.
[61] de Muinck Keizer-Schrama SMPF. Introduction and Management of Puberty in girls. Horm Res Paediatr 2007;68(5):80–3.
[62] Donaldson M, Kriström B, Ankarberg-Lindgren C, Verlinde S, Van Alfen-Van Der Velden J, Gawlik A, et al. Optimal pubertal induction in girls with turner syndrome using either Oral or transdermal estradiol: a proposed modern strategy. Horm Res Paediatr 2019;91(3):153–63.
[63] Matthews D, Bath L, Högler W, Mason A, Smyth A, Skae M. Hormone supplementation for pubertal induction in girls. Arch. Dis. Child. 2017;102(10):975–80.
[64] Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with turner syndrome: proceedings from the 2016 Cincinnati international turner syndrome meeting. Eur. J. Endocrinol. 2017;177(3):G1–70.
[65] Rodari G, Cattoni A, Albanese A. Final height in growth hormone-deficient childhood cancer survivors after growth hormone therapy. J. Endocrinol. Investig. 2020;43(2):209–17. Available from: https://doi.org/10.1007/s40618-019-01102-w.
[66] Poyrazoglu Ş, Günöz H, Darendeliler F, Saka N, Bundak R, Baş F. Constitutional delay of growth and puberty: from presentation to final height. J. Pediatr. Endocrinol. Metab. 2005;18(2) Available from: https://www.degruyter.com/view/j/jpem.2005.18.2/jpem.2005.18.2.171/jpem.2005.18.2.171.xml.
[67] Sperlich M, Butenandt O, Schwarz HP. Final height and predicted height in boys with untreated constitutional growth delay. Eur. J. Pediatr. 1995;154(8):627–32. Available from: https://doi.org/10.1007/BF02079065.
[68] Quigley CA, Wan X, Garg S, Kowal K, Cutler GB, Ross JL. Effects of low-dose estrogen replacement during childhood on pubertal development and gonadotropin concentrations in patients with turner syndrome: results of a randomized, double-blind, placebo-controlled clinical trial. J. Clin. Endocrinol. Metab. 2014;99(9):E1754–64.
[69] Paterson WF, Hollman AS, Donaldson MDC. Poor uterine development in turner syndrome with oral oestrogen therapy. Clin. Endocrinol. 2002;56(3):359–65.
[70] Bannink EMN, Van Sassen C, Van Buuren S, De Jong FH, Lequin M, Mulder PGH, et al. Puberty induction in turner syndrome: results of oestrogen treatment on development of secondary sexual characteristics, uterine dimensions and serum hormone levels. Clin. Endocrinol. 2009;70(2):265–73.
[71] Snajderova M, Mardesic T, Lebl J, Gerzova H, Teslik L, Zapletalova J. The uterine length in women with turner syndrome reflects the Postmenarcheal daily estrogen dose. Horm Res Paediatr 2003;60(4):198–204.
[72] McDonnell CM, Coleman L, Zacharin MR. A 3-year prospective study to assess uterine growth in girls with Turner's syndrome by pelvic ultrasound. Clin. Endocrinol. 2003;58(4):446–50.
[73] van de Loo LEXM, van den Berg MH, Overbeek A, van Dijk M, Damen L, Lambalk CB, et al. Uterine function, pregnancy complications, and pregnancy outcomes among female childhood cancer survivors. Fertil. Steril. 2019;111(2):372–80.
[74] Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female Cancer patients. Int J Radiat Oncol 2009;73(5):1304–12.
[75] Ragbourne SC, Crook MA. Metabolic syndrome in long-term survivors of hematopoietic stem-cell transplantation. Clin Lymphoma Myeloma Leuk 2017;17(6):340–6.
[76] Bielorai B, Weintraub Y, Hutt D, Hemi R, Kanety H, Modan-Moses D, et al. The metabolic syndrome and its components in pediatric survivors of allogeneic hematopoietic stem cell transplantation. Clin. Transpl. 2017;31(3):e12903.
[77] Cattoni A, Rovelli A, Prunotto G, Bonanomi S, Invernizzi P, Perego R, et al. Hepatic focal nodular hyperplasia after pediatric hematopoietic stem cell transplantation: The impact of hormonal replacement therapy and iron overload. Pediatr. Blood Cancer 2020;67(4).
[78] Kalantaridou SN, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, et al. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. J. Clin. Endocrinol. Metab. 2004;89(8):3907–13.
[79] Phelan N, Conway SH, Llahana S, Conway GS. Quantification of the adverse effect of ethinylestradiol containing oral contraceptive pills when used in conjunction with growth hormone replacement in routine practice. Clin. Endocrinol. 2012;76(5):729–33.
[80] Ankarberg-Lindgren C. Nocturnal application of transdermal estradiol patches produces levels of estradiol that mimic those seen at the onset of spontaneous puberty in girls. J. Clin. Endocrinol. Metab. 2001;86(7):3039–44.
[81] Davenport ML. Approach to the patient with turner syndrome. J. Clin. Endocrinol. Metab. 2010;95(4):1487–95.
[82] Felicetti F, D'Ascenzo F, Moretti C, Corrias A, Omedè P, Marra WG, et al. Prevalence of cardiovascular risk factors in long-term survivors of childhood cancer: 16 years follow up from a prospective registry. Eur. J. Prev. Cardiol. 2015;22(6):762–70.
[83] Scott Baker K, Ness KK, Steinberger J, Carter A, Francisco L, Burns LJ, et al. Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. Blood. 2007;109(4):1765–72.
[84] Janse F, Tanahatoe SJ, Eijkemans MJC, Fauser BCJM. Testosterone concentrations, using different assays, in different types of ovarian insufficiency: a systematic review and meta-analysis. Hum. Reprod. Update 2012;18(4):405–19.
[85] Faculty of Sexual and Reproductive Healthcare. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2009). 2009.
[86] Mulder RL, Kremer LCM, Hudson MM, Bhatia S, Landier W, Levitt G, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the international late effects of childhood Cancer guideline harmonization group. Lancet Oncol. 2013;14(13):e621–9.
[87] Friedman DL, Constine LS. Late effects of treatment for Hodgkin lymphoma. J. Natl. Compr. Cancer Netw. 2006;4(3):249–57.
[88] Bakker MF, de Lange SV, Pijnappel RM, Mann RM, Peeters PHM, Monninkhof EM, et al. Supplemental MRI screening for women with extremely dense breast tissue. N. Engl. J. Med. 2019;381(22):2091–102. Available from: https://doi.org/10.1056/NEJMoa1903986.