Iatrogenic premature ovarian insufficiency

Skalicki, Lucija

Master's thesis / Diplomski rad

2020

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:223002

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Lucija Skalicki

IATROGENIC PREMATURE OVARIAN INSUFFICIENCY

Graduate thesis

Zagreb, 2020

This graduate thesis was made at University Hospial Centre Zagreb, Department of Obstetrics & Gynecology mentored by dr.sc. Maja Banović, dr.med. and was submitted for evaluation in the academic year 2019/2020

ABBREVATIONS

ABVD- doxorubicin, bleomycin, vinblastine and dacarbazine

AFC- antral follicle count

AMH- anti-Mullarian hormone

ASCO- American Society of Clinical Oncology

ATM- ataxia telangiectasia mutated

BEACOPP- bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone

BMD- bone mineral density

BPA- bisphenol A

COC- combined oral contraceptive

COS – controlled ovarian stimulation

CVD- cardiovascular disease

DNA- deoxyribonucleic acid

ESHRE – European Society of Human Reproduction and Embryology

FSH – follicle-stimulating hormone

GnRH – gonadotropin-releasing hormone

hCG – human chorionic gonadotropin

HDL- high-density lipoprotein

HRT- hormone replacement therapy

IVF- in-vitro fertilization

LDL- low-density lipoprotein

LH – luteinizing hormone

POI – premature ovarian insufficiency

ROS- reactive oxygen species

SART – Society for Assisted Reproductive Technology

SERM- selective estrogen receptor modulator

SSRI- selective serotonin reuptake inhibitors

TBI- total body irradiation

WHO- World Health Organization

Contents

Summary

Title: Iatrogenic premature ovarian insufficiency

Author: Lucija Skalicki

Premature ovarian insufficiency (POI) is defined as a transient or complete loss of ovarian function before the age of 40. It can occurs as a result of treatment of certain tumors. Premature ovarian insufficiency induced by a medical treatment is referred to as iatrogenic and its incidence is rising mostly due to successful cancer treatments. A chance of ovarian insufficiency depends on type of a drug, dose of a drug or irradiation as well as the patients' age at the time of the treatment. Damage to the ovaries and POI as a result can be induced by many different mechanisms. Chemotherapy and radiotherapy can cause direct damage to the oocyte DNA or indirect damage via reactive oxygen species (ROS). Alkylating agents are the most harmful chemotherapeutic drugs and are associated with highest incidence of amenorrhea and infertility following chemotherapy. Radiotherapy with doses as low as 2 Gy have been reported to cause POI, therefore many preventive measured such as oophorexy and ovarian shielding have been implemented in younger cancer patients. Surgical procedures can also cause a direct damage of the ovarian tissue, or have an indirect effect through vasculature damage. Clinical effects of ovarian insufficiency are low estrogen levels with many short term and serious long term consequences. For this reason, early diagnosis and immediate management of POI is crucial. Short term effects of estrogen deficiency include vasomotor, urogenital and psychological symptoms. Serious long term consequences include osteoporosis, risk of cardiovascular diseases, neurodegenerative diseases and infertility. Majority of POI patients are advised to take hormone replacement therapy (HRT) to help with short term and long term effects of low estrogen levels. Along with HRT patients are advised to do regular weight bearing exercises and to take vitamin D and calcium supplements daily. Fertility preservation is one of the important issues that these patients have to be advised on.

Key words: iatrogenic, POI, estrogen deficiency, infertility

Sažetak

Naslov: Jatrogena ovarijska insuficijencija

Autor: Lucija Skalicki

Prijevremena ovarijska insuficijencija (POI) definira se kao prijelazni ili potpuni gubitak funkcije jajnika prije dobi od 40 godina. Može se pojaviti spontano ili može biti izazvan različitim čimbenicima. Prijevremena ovarijska insuficijencija kao rezultat liječenja naziva se jaterogenom i njena učestalost raste uglavnom zbog uspješnog liječenja raka. Mogućnost insuficijencije jajnika ovisi o vrsti lijeka, dozi lijeka ili zračenja kao i dobi pacijentice u vrijeme liječenja. Oštećenja jajnika i POI mogu biti uzrokovana različitim mehanizmima. Kemoterapija i radioterapija mogu uzrokovati izravno oštećenje DNK oocita ili neizravno oštećenje putem slobodnih radikala. Alkilirajući citostatici su najštetniji kemoterapijski lijekovi i povezani su s najvećom učestalošću amenoreje i neplodnosti nakon kemoterapije. Zabilježeno je da radioterapija u dozi od 2 Gy uzrokuje POI, stoga su kod mnogih mlađih pacijentica s rakom provedene preventivne mjere poput kirurške transpozicije jajnika izvan polja zračenja i zaštite jajnika štitnikom. Kirurški zahvati također mogu uzrokovati izravno oštećenje tkiva jajnika ili imati neizravan učinak kroz oštećenje vaskulature. Klinički učinci insuficijencije jajnika su niska razina estrogena s mnogim kratkoročnim i ozbiljnim dugoročnim posljedicama. Iz tog razloga, rana dijagnoza i obrada POI pacijenata su od velike važnosti. Kratkoročni učinci nedostatka estrogena uključuju vazomotorne, urogenitalne te psihološke simptome. Ozbiljne dugoročne posljedice uključuju osteoporozu, rizik od kardiovaskularnih bolesti, neurodegenerativne bolesti i neplodnost. Većini bolesnica kojima je dijagnosticirani POI preporučuje se hormonska nadomjesna terapija (HRT) kako bi se pomoglo u kratkoročnim i dugoročnim učincima niskih razina estrogena. Zajedno s HRT-om, pacijentima se preporučuje redovito vježbanje s utezima i svakodnevno uzimanje dodataka vitamina D i kalcija. Očuvanje plodnosti jedna je od važnih tema o kojoj je potrebno savjetovati ove pacijentice.

Ključne riječi: jatrogeni, POI, nedostatak estrogena, neplodnost

1 Introduction

Iatrogenic premature ovarian insufficiency (POI) is one of the possible negative consequences in young women undergoing cancer treatment or procedures effecting genital organs. It is characterized by irregular or completely absent menstrual cycles before the age of 40 years and low estrogen levels that can lead to many long term consequences such as osteoporosis, infertility and increased risk of cardiovascular diseases (1). The incidence of POI in general is around 1 percent of women under the age of 40 years (2). The exact incidence of iatrogenic POI is not known; however it is surely increasing with better cancer treatment outcomes and higher survival rate. Considering the increasing incidence and serious consequences of iatrogenic POI that can be prevented, this topic should be discussed more frequently. Diagnosis of POI can have a significantly negative impact on psychological wellbeing and quality of life in young women. Majority of patients do not feel comfortable discussing this matter with their physician and are not aware that it can be managed with appropriate therapy. Women should be referred to their reproductive endocrinologist as soon as possible after the diagnosis has been established to start with the treatment plan. Before undergoing any type of cancer treatment, patients should be informed about POI and all of its possible consequences. Patients should especially be advised on risk factors that can easily be modified with simple lifestyle changes such as quitting smoking. Infertility is often the most devastating consequence for young women and having emotional support from the physician is of high importance. All patients should be presented with fertility preserving options prior to a required treatment if there is a reasonable risk of POI.

2 Premature ovarian insufficiency

2.1 Physiology of the ovary

In early embryonic life, primordial germ cells start to divide and migrate from the yolk sac to the outer surface of the ovary. Once they reach germinal epithelium, they migrate to the ovarian cortex and become oogonia or primordial ova. Each oognoia surrounds itself with a

single layer of granulosa cells and becomes primary oocyte. The ovum surrounded by a single layer of granulosa cells is called primordial follicle. Primary oocyte begins the first meiotic division around fifth month of fetal life and stays in this stage of meiosis until puberty. At birth, ovary contains around 1 to 2 million primary oocytes arrested in first meiotic division (3) (4).

At the start of puberty, ovaries have only about 300,000 oocytes remaining to mature. Before the onset of puberty, hypothalamus starts to release GnRH and acts on the pituitary gland to start to release gonadotropins- luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadotropins stimulate production of estrogen and progesterone in the ovary. Negative and positive feedback mechanisms of these steroid hormones on the pituitary gland lead to oscillations of the hypothalamic-pituitary-ovarian system throughout the month and regulated female monthly sexual cycle. Every month, 6-12 primary follicles undergo accelerated growth under the influence of FSH. Only one follicle fully matures and continues to grow until ovulation, while the remaining follicles undergo atresia. During female reproductive life only 400 to 500 primordial follicles mature and undergo ovulation (4).

Around the age of 40 to 50 years, only a few primordial follicles are left with ability to mature and ovulate. Menstrual cycles become irregular and finally cease completely after a few months to years leading to menopause. Menopause is defined as amenorrhea for more than 12 months (4). As the amount of primordial follicles decreases, so does the level of estrogen. This leads to the loss of negative feedback of estrogen on the pituitary resulting in high levels of FSH.

2.2 Definition

Primary ovarian insufficiency (POI) is defined as a continuous decline or loss of ovarian function before the age of 40 (5). Iatrogenic premature ovarian insufficiency refers to a POI induced by surgical, medicamental, or treatments with physical agents. It is characterized by oligomenorrhea or amenorrhea, decreased levels of steroid sex hormones and increased levels of gonadotropins. According to ESHRE guidelines, diagnosis of POI requires amenorrhea lasting for at least 4 months after a treatment and FSH levels > 25 IU/L on two occasions at least 4 weeks apart (6). Previously it was referred to as “premature ovarian failure” or “premature menopause” however these expressions were soon replaced with POI.

Many clinicians agreed that the term insufficiency is a more suitable description of this disorder since it includes continuation of events rather than a single event. The terms “failure” and “premature menopause” were also found to be more distressing for the patient (2).

2.3 Incidence

According to many sources, 1 percent of women will develop POI before the age of 40. (5) (7) (8). The incidence in women aged 18-25 years is 1:10,000 and in women aged 25-30 years is 1:1000 (8). The incidence of iatrogenic POI is not known, uncertain and it varies among different countries. New Zealand database from 2015 showed that 37 percent of women diagnosed with POI had iatrogenic etiology, 25 percent idiopathic, 19 percent autoimmune and 19 percent genetic etiology (2). A Swedish study showed that out of 1,9 percent of women diagnosed with POI, 0,2 percent had iatrogenic etiology and 1,7 percent had spontaneous POI (9) (10). The incidence has has significantly increased over the years and is constantly growing, as more women are being treated for cancer with gonadotoxic agents with a higher survival rate (7).

3 Etiology

POI is a complex and poorly understood process with multiple etiologies. It can be either iatrogenic or can occur spontaneously. Etiology of spontaneous POI is idiopathic in 90 percent. Other causes of spontaneous POI are genetic causes, autoimmune causes, metabolic and infections (8). The incidence of iatrogenic POI has increased with more successful cancer treatments as it can occur as a result of chemotherapy, radiotherapy, surgical procedures directly or inflammatory conditions after surgical procedures. According to Duru Shah et al. amenorrhea caused by chemotherapy or radiotherapy is reversible if only larger maturing follicles are destroyed and irreversible if primordial follicles are affected and destroyed in the process (11).

POI can occur during, immediately after, or months to years following a cancer treatment. The American Society of Clinical Oncology (ASCO) guidelines have divided the

risk of premature amenorrhea in women treated with modern chemotherapy and radiotherapy into five categories:

High risk group, where >80 percent of women develop premature amenorrhea after receiving the treatment.

Intermediate risk, where 20 to 80 percent of women develop premature amenorrhea following the treatment.

Low risk where < 20 percent develop premature amenorrhea.

Very low risk with no effect on menstrual cycle.

Unknown categories (12).

3.1 Chemotherapy

Chemotherapeutic drugs, along with radiotherapy, are the most common cause of toxin-induced premature ovarian failure. Although number one priority in cancer patients is undoubtedly to maximize the cure rate, medical professionals nowadays are giving a lot of attention to chemotherapy side effects and different ways to minimize them. This is especially applicable to younger patients where the goal is to preserve fertility while maximizing the probability of the cure. When talking about chemotherapy induced POI, one must remember that most treatment guidelines use multidrug approach, therefore it is more appropriate to talk about the consequences of drug regimens rather than a single drug (13).

3.1.1 Mechanism of action

Chemotherapeutic agents act on different cell types within the ovary. Some drugs act directly on the oocyte and cause damage to its DNA, while others act on stromal cells. Both cell types are sensitive, and can be damaged by chemotherapy, but majority of anticancer drugs act on dividing cells and effect follicular development more than oocyte itself. This is supported by the fact that many women develop amenorrhea during the treatment, with menstrual cycle and fertility returning months to years after chemotherapy (13). Dividing

cells are sensitive and can be altered even with chemotherapeutic agents which are thought to have low toxicity on primordial follicles.

The main mechanism of chemotherapy-induced loss of primordial follicles is through apoptotic death (14). Chemotherapy drugs can cause various types of DNA damage within the oocyte, with double-stranded DNA breaks being the most damaging one. The damage activates the ataxia-telangiectasia mutated (ATM)-mediated DNA repair pathway to try to repair the breakage. Cells with sufficient DNA repair ability can survive, while other ones are lost by apoptotic death pathway. This results in a reduced ovarian reserve. Damage to stromal cells of the ovary is mostly through vascular effects and focal fibrosis of the ovarian cortex (14). Studies have shown that some chemotherapeutic agents such as doxorubicin can cause spasm of the ovarian blood vessels and as a result, reduction in the ovarian blood flow (14) (15). Vascular injury was previously thought to act primarily on growing follicles which require sufficient blood flow, but newer studies have concluded that primordial follicles depend on adequate vascularization as well; therefore showing that chemotherapy can indirectly reduce ovarian reserve through this process. Chemotherapy also influences ovarian endocrine function and leads to impaired steroidogenesis (14).

3.1.2 Individual chemotherapeutic agents

The effect of drugs and the degree of ovarian failure depends on patients age when receiving the treatment, dose and type of the drug (13). Some chemotherapeutic agents cause temporary amenorrhea, with return of the menstrual cycle months to years after the treatment, while other agents can cause permanent ovarian failure.

Alkylating agents, such as cyclophosphamide, are the most harmful group of chemotherapeutic drugs and have the most potent gonadotoxic effect (13). Cyclophosphamide is the first known chemotherapeutic drug to cause amenorrhea in humans (16). It is used in many cancer treatment regimens, particularly in childhood malignancies. Only limited numbers of studies have been done on humans to test the exact effect of cyclophosphamide; however animal studies showed direct damage to primordial follicles in mouse and in growing human follicles studied in vitro after administration of this drug (15). It acts on both resting and dividing cells. Active metabolite of cyclophosphamide causes cross-links with DNA and thereby inhibits DNA synthesis and function, affecting dividing cells. Double stranded DNA

breaks cause death of the oocyte by apoptosis (14). As a result, regiments containing cyclophosphamide have the highest incidence of prolonged amenorrhea (>6 months) and highest risk for infertility. In general, younger women are less affected, probably due to the fact that they have more remaining primordial follicles compared to older women. There is no certain threshold for the safe dose of these agents, however study done on breast cancer patients showed that in women over the age of 40 years, amenorrhea occurred after 5,2g of cyclophosphamide, and in younger women after 9,5g (17).

Another group of drugs which is associated with intermediate risk for infertility and are in general thought to be damaging to the ovaries are platinum-based compounds. Cisplatin is usually received as part of the multidrug regimen, so it is difficult to determine how toxic it actually is to the ovary (15). Its mechanism of injury is similar to alkylating agents, by forming DNA cross-links that lead to DNA breakage during replication (14). Exposure to cisplatin also causes decrease in antioxidant enzyme activity and increase in ROS (15). Cisplatin is always included in the treatment protocol for ovarian and cervical cancers, which are one of the most common malignancies in women of reproductive age. They are known to be effective and superior to other treatment regimens in aggressive ovarian cancers; explaining their wide usage despite toxic effects. Most women who receive three to four doses of platinum based agents recover their normal ovarian function over a period of time, even though they are rated as gonadotoxic (18).

Doxorubicin, an anthracycline antibiotic has been studied in the past few years as it is known to cause damage to the ovary, even though is it currently considered as an agent with low risk of POI (19). It is widely used in many cancer treatments including breast, lung and gastric cancer (16). Other than the fact that it causes apoptotic cell death in primordial follicles, it also induces chromosomal fragmentation, and fragmentation of the cytoplasm into apoptotic bodies (19). Doxorubicin acts by inhibiting nuclear enzyme topoisomerase II which prevents twisting of the DNA during replication, resulting in accumulation of DNA fragments and cell death (16). Study done with human ovarian tissue cultured with doxorubicin have shown that doxorubicin can cause reduced vascular density, compared to controls cultured with normal saline (14).

3.1.3 Chemotherapeutic regimens

Breast cancer is one of the most common malignancies in reproductive age group. There are a few chemotherapeutic regimens to treat early-stage breast cancer; doxorubicin plus cyclophosphamide regimen is considered less gonado-toxic than cyclophosphamide, methotrexate and 5-fluorouracil (13). Preferred treatment for Hodgkin lymphoma in younger women is a combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) because it has a lower incidence of POI than BEACOPP regimen that includes bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (13).

3.2 Radiotherapy

Radiotherapy is an important component in management of many malignancies. Today it is used in almost every patient with gynaecological malignancies, breast cancer and Hodgkin lymphoma. The goal of radiation is to target cancer cells; however damage to the normal tissue within the radiation field is almost inevitable. Ovaries are very sensitive to irradiation and both oocyte and stroma can be damaged in the process (13). Doses as low as 2 Gy have been reported to cause damage to the oocyte and result in POI (20). For the adequate treatment of majority of malignancies, higher doses of irradiation are needed to achieve the treatment goal. Premature ovarian insufficiency, subfertility and fertility often follow the treatment (21). It is thought to be more toxic than chemotherapy due to the fact that it is more damaging to the oocyte in comparison to chemotherapy, where majority of agents affect growing follicles rather than oocyte itself (21).

3.2.1 Mechanism of injury

Irradiation primarily causes injury to the oocyte, through direct and indirect damage to the DNA. Although little information is known about the effects of radiotherapy on stroma of the ovary, it is thought to cause damage to the vasculature, resulting in atrophy and fibrosis (20). Indirect DNA damage is caused when ionizing radiation enters the body and interacts with water molecules, splits them and releases reactive oxygen species (ROS). Reactive oxygen species react with DNA and interfere with thymine nucleic acid, creating mutations.

The cell cannot continue cell division or transcription until mutation is repaired. Ionizing radiation also induces direct damage to the DNA by causing single and double stranded DNA breaks. DNA repair mechanisms are initiated and work well until damage is accumulated, overcomes the repair mechanisms, and apoptosis of the cell occurs (22) (23).

3.2.2 Types of irradiation and doses

Ovaries are exposed to gonadotoxic effects of irradiation when treating pelvic or abdominal malignancies in majority of cases. Craniospinal irradiation for CNS malignancies or total body irradiation (TBI) is also associated with ovarian failure depending on the dose and radiation fields (24). Ovarian failure has been reported in 97 percent of patients receiving abdominal radiation and 90 percent of patients receiving TBI (25). The extent of ovarian injury produced by ionizing radiation depends on patients age, treatment dose and radiation field (25). 2 Gy represents the dose at which half of the oocytes in humans (LD50) are lost (25). According to Wallace et.al., permanent ovarian failure with radiotherapy is estimated with 18.4 Gy at the age of 10 years, 16.5 Gy at the age of 20 years and 14.3 Gy at the age of 30 years in 97.5 percent of women (13).

3.2.3 Preventive measures before radiotherapy

Protecting the ovaries from harmful effects of irradiation is especially important in infants, children and young adults. Every treatment should include a detailed plan to ensure minimal surrounding tissue damage. Ovarian protection can be accomplished with pharmacological or non-pharmacological intervention. Non-pharmacological protection includes either a lead shield that is placed precisely or oophoropexy (20) (25). Oophoropexy is a laparoscopic transpositioning of ovaries out of the radiation field. Before considering this technique, it is important to exclude the possible ovarian metastases, especially in gynaecological malignancies. Patients should be aware of the fact that oophorexy is not always successful in protecting the ovaries due to radiation scatter and efficacy of this procedure is controversial (12). This procedure does not protect the ovaries from gonadotoxic effects of chemotherapy and it should be avoided if the patient has to undergo both chemotherapy and radiotherapy. Women are often unable to conceive naturally after oophoropexy and require assisted reproductive technology (20). Pharmacological protection can be prophylactic, used before the damage to the tissue occurred, or treatment that acts on

radiation-induced fibrosis. Prophylactic therapy can be used before the start of radiotherapy or shortly after the beginning of the treatment. These drugs were tested on animal models, which showed that sphingosine-1-phosphate (S1P), tamoxifen and growth hormone can have protective properties on ovarian reserve by inhibiting apoptosis. Amifostine, in its active form, causes scavenge of free radicals and in that way protects DNA from radiation damage (20) (22). Copper superoxide dismutase and manganese superoxide dismutase are thought to have anti fibrotic properties and are used after the treatment to reduce fibroses of the ovarian stroma (20).

3.3 Surgical procedures

Surgical procedures can result in the development of POI, either directly with removal of both ovaries or during other procedures done in pelvis that may damage the ovarian blood supply (9). There is a risk for developing POI after surgery for both benign conditions and cancer of the female reproductive system.

3.3.1 Oophorectomy

Bilateral oophorectomy is a surgical removal of both ovaries. Most common indications for this procedure are bilateral abscess, ovarian cancer, endometrial cancer, fallopian tube cancer or in most cases, as a prophylaxis for ovarian cancer in those with BRCA1 and BRCA2 genes. Surgically induced menopause causes abrupt decrease in endogenous sex steroids and sudden onset of severe menopausal symptoms that require exogenous steroids for symptom relief (26). In contrary, naturally occurring menopause or spontaneous POI have gradual onset of symptoms since ovaries continue to produce some amount of testosterone which is converted to estrogen in the periphery (26). In addition to menopause and sexual dysfunction, studies have linked prophylactic oophorectomy with numerous health problems including cardiovascular diseases and premature death.

Unilateral oophorectomy is usually indicated when treating ovarian torsion, tumors, rupture or endometriomas. Studies have shown that the mean age of menopause in

premenopausal women who underwent unilateral oophorectomy was 49.5 years, which is 1.8 years earlier than naturally occurring menopause at 51.3 years (27). Younger age at unilateral oophorectomy resulted in younger age of menopause. By removing one of the ovaries, one would expect a 50 percent decrease in ovarian reserve and earlier menopause. However, the moderate decrease in age of menopause by 1.8 is not well understood. It is thought to occur due to compensatory increase in follicular recruitment leading to earlier exhaustion of ovarian reserve and therefore earlier menopause. Two other studies done on more than 23 000 women in Japan and Norway also concluded earlier age of menopause in women after unilateral oophorectomy compared to women with both ovaries. (28) (29).

3.3.2 Hysterectomy

Association between surgical removal of the uterus and premature menopause has been studied for years, yet this question still remains unanswered due to many limitations in the available studies. Some have shown that hysterectomy without oophorectomy does not influence the age of menopause, while others concluded the opposite (30) (31). A cohort study by Farquhar et al. concluded that hysterectomy is associated with premature menopause and women who underwent hysterectomy reached menopause 3.7 years earlier than the control group (32). The exact mechanism of how hysterectomy can cause POI is not known however several hypotheses exist. The main mechanism that is thought to be responsible for premature menopause is the damage to the ovarian blood supply during surgery. This is supported by several studies that show decreased ovarian blood flow after hysterectomy. Another possible explanation is that the underlying condition that is an indication for hysterectomy is responsible for premature menopause and not the surgery itself. This is supported by the fact that the most common indications for hysterectomy are conditions that are associated with increased risk for POI (33). Hysterectomy in combination with unilateral oophorectomy is thought to cause even earlier onset of menopause than isolated hysterectomy (32).

3.3.3 Cystectomy

Ovarian cysts are fluid containing sacs that develop on the ovaries. They are common and are usually benign in nature. Cystectomy, usually done laparoscopically, is indicated if there is a chance of malignancy or if the cyst is causing symptoms. Endometriomas and dermoid cysts are the ones that most commonly require surgical intervention. The risk of POI is thought to be dependent on the size of the cyst, nature of the cyst and number of cysts present (34). Surgical technique is important when considering the risk of POI in these patients. There are many studies reviewing different approaches and the degree of ovarian injury after the procedure. Laparoscopic cystectomy is the gold standard procedure and is thought to be better than cyst ablation or drainage. Studies have also showed that laparoscopic electrocoagulation for hemostasis after cystectomy is more destructive to the ovarian tissue compared to suturing (35). Latest research from 2018 suggests stripping technique and ablation as first line treatment for fertility preservation in these patients, while other studies have demonstrated stripping to be associated with higher risk of POI (36). Ovarian endometriomas often require removal which can affect considerably the ovarian reserve. Women suffering from ovarian endometriosis in general have a lower mean age of menopause, however, recent studies support the fact that surgery for this condition lowers the mean age even more, and carries a high risk for POI. This is especially the case in bilateral endometriomas where mean age of menopause is around 42 years (35). Studies have found non-endometriotic cysts to be easier to remove with a minimal loss of the ovarian reserve, compared to endometriomas. Lower AMH levels were reported following surgeries for endometriomas compared to other cysts. Long-term follow up is especially important in these patients since the onset of POI can be 6 to 10 years after cystectomy (37).

3.3.4 Salpingectomy

Salpingectomy is a surgical excision of one or both fallopian tubes. Unilateral or bilateral salpingectomy, without oophorectomy, is a procedure done usually in case of ectopic pregnancy, hydrosalpynx or pyosalpinx (38). Salpingectomy is also indicated in some ovarian cancers, especially epithelial ovarian cancers which are thought to arise from fallopian tube tissue. Bilateral salpingectomy is often proposed as a preventive measure for ovarian cancer in women undergoing hysterectomy for benign conditions. This type of surgery could potentially cause damage to the ovarian vasculature and cause POI since ovarian and tubal arterial anastomosis in mesosalpinx lie in close proximity (39). Whether salpingectomy

affects ovarian reserve is very controversial. Recent cohort study done in 2018 reported an increased risk of menopausal symptoms one year after hysterectomy with bilateral salpingectomy compared to isolated hysterectomy. (40) The accuracy of this data is arguable as evaluation of menopausal symptoms alone does not provide strong evidence. One further point is that a benign hysterectomy is usually done in perimeopausal women that might experience naturally occurring menopause shortly after the procedure (41). A study done by Chan et al. compared the function of both ovaries after unilateral salpingectomy. Women were evaluated after either laparoscopy or laparotomy by evaluating ovarian stroma blood flow with 3D Doppler ultrasonography, AFC and ovarian volume. Results showed impaired ovarian function on the operated side after laparoscopic unilateral salpingectomy compared to non-operated sides. (42). Recent studies done in 2017 and 2019 suggest that laparoscopic salpingectomy does not have any short term effect on AMH and ovarian reserve; however to determine long term effects, further investigations are needed (38) (39).

3.4 Other causes

Many bacterial and viral pathogens have been suggested as a potential cause of oophoritis and POI in women. Some of the pathogens include mumps, varicella, malaria and cytomegalovirus (8). This etiology should be considered if patient's history suggests any risk factors and if other, more common causes, have been excluded.

Environmental toxins are a serious concern for humans nowadays. They can influence female reproductive system via three different mechanisms. They can act as endocrine disruptors, induce oxidative stress or cause epigenetic modifications (43).

Phthalates are compounds used in plastics manufacture and are potent endocrine disruptors. They are stable compounds and stay in the environment for several years in house dust, food or water (44). These compounds find their way into our body through inhalation, ingestion or through the skin. Studies have associated phthalates with increased incidence of POI and infertility by disruption of folliculogenesis and steroidogenesis (43).

Bisphenol A (BPA) is a compound found in plastic food packaging. It is also an endocrine disruptor and it acts by mimicking estrogen and binding to estrogen receptors. It is

found in 90 percent of urine samples and high urine BPA has been associated with decreased AFC and ovarian reserve (43).

Pesticides are substances used in agriculture to control pests. They remain in environment for several years and can be found in food and water. They act as endocrine disruptors altering ovarian function. Study done on 219 women found association between earlier onset of menopause and increased levels of organochlorines in blood (43).

Cigarette smoking has also been linked to POI, earlier age of menopause and infertility. Many studies concluded that mean age of menopause in smokers is earlier than in non-smokers. Risk of POI depends on period and quantity of smoking (45). Polycyclic hydrocarbons are the most studied chemicals in cigarette smoke and are thought to be responsible for the toxic effect of cigarette smoke on the ovaries (11). They act on the ovary by binding receptors on granulosa cells and activating pro-apoptotic genes. In one study, smokers had decreased AFC and AMH levels and increased FSH levels. Results correlated with number of pack years. (46).

4 Consequences of POI

4.1 Short term consequences

Short term consequences of POI are mostly due to the sudden drop in estrogen levels. They include vasomotor symptoms such as hot flushes or night sweats, palpitations, headache, urgent or stress incontinence and psychological problems including irritability, insomnia and difficulty concentrating (1). Hot flushes are common and majority of POI patients experience them. They are usually described as a sudden onset of heat sensation affecting the face, neck and chest. Genital pain due to vaginal dryness is another common symptom that can affect the quality of life (47)

4.2 Long term consequences

4.2.1 Osteoporosis

According to the World Health Organization (WHO), osteoporosis is defined as bone mineral density (BMD) less than 2.5 standard deviations or more below average value for young females (48). Peak bone mass is reached around the age of 30 years. Estrogen deficiency before this age leads to the decreased peak bone mass and estrogen deficiency after this age results in the accelerated bone loss. Both of these scenarios result in a higher risk of fractures (49). It is a well-known fact that low levels of estrogen can influence bone mass and cause osteoporosis. Bone mineral density was found to be decreased in both spinal skeleton and femoral neck in POI patients in several studies (1). Osteoporosis can occur in patients with both spontaneous and iatrogenic POI. A study done on 49 breast cancer patients found a decreased BMD by 7.7 percent in lumbar spine and 4.6 percent in the neck of the femur of premenopausal women who developed POI following chemotherapy (50). Osteoporosis can occur as a consequence of chemotherapy through several different mechanisms: with development of POI due to chemotherapy, by cancers direct effect on the bone, by the effect of chemotherapy itself on bone density or by low calcium and vitamin D intake throughout chemotherapy treatment (50). Decreased levels of estrogen due to POI can cause increased osteoclast activity and result in the increased bone reabsorption. Even though osteoblast activity also increases, bone reabsorption is greater than bone formation and the end result is bone loss (50). Several studies have shown that the risk of fracture in women with POI is significantly reduced by HRT (50). Hormone replacement therapy is effective for the prevention of fractures if introduced before the age of 60 years or within few years after the diagnosis of POI (51). Early initiation of HRT after the diagnosis and long-term continuation showed a reduction in the risk of non-spine fractures. A study done in POI patients taking HRT for 3 years showed no difference in BMD of lumbar spine and femoral neck between those patients and control group of women who reached menopause naturally. Along with HRT, these patients should include weight-bearing exercises, 1,000 to 2,000 IU of vitamin D3 and calcium into their daily routine to support bone health (49).

4.2.2 Cardiovascular diseases

Cardiovascular disease (CVD) is the main reason for mortality in POI patients (1). Women who experience menopause before the age of 45 years are known to be at the higher risk for the ischemic heart disease, atherosclerosis and angina compared to premenopausal women and women who reach menopause after the age of 50 years (49). Estrogen is known to play an important role in protection from possible ischemic heart disease and stroke through many effects. It improves mitochondrial function and decreases oxidative stress in cells, causes vasodilatation, decreases fibrosis and stimulates angiogenesis (52). These patients have significantly lower circulating levels of estrogen and carry a risk of earlier onset of CVD. Risk increases with earlier onset of POI and additional risk factors such as abnormal lipid profile, metabolic syndrome or endothelial dysfunction. Women suffering from POI show significantly higher levels of triglycerides and low-density lipoprotein (LDL) cholesterol and lower high-density lipoprotein (HDL) cholesterol levels (53). Smoking was also found to be an important additional factor. Bilateral oophorectomy carries a high risk for CVD in young women and is in general associated with increased mortality rate. Women that enter menopause before the age of 40 are also at a two-fold increased risk for stroke.

4.2.3 Infertility

Infertility is one of the most prevalent long term consequences of iatrogenic POI and to many women it is the most devastating one. The course of POI in unpredictable and ovulation can reoccur at any moment after the cancer treatment, unless complete sterility has been reached during therapy (49). Chance for spontaneous conception in POI patients in general is known to be between 5 and 10 percent (1), depending on many factors. Amenorrhea presenting alone is inaccurate to assess ovarian function in these patients; women can have regular menstrual cycles but decreased ovarian reserve and therefore low chance of pregnancy. Most important biochemical markers used in clinical practice are anti-Mullerian hormone (AMH) serum levels and FSH serum levels (54).

AMH is a glycoprotein produced by granulosa cells of preantral and early antral follicles. It regulates primordial follicle recruitment and its levels are an excellent representation of the size of the primordial follicle pool (55). Low levels of this hormone indicate low ovarian reserve. AMH is a marker with good sensitivity and specificity and it is used for predicting the risk of amenorrhea after chemotherapy. It is a practical test for women

that are early diagnosed with cancer and require urgent treatment, since its values can be obtained at any day of the menstrual cycle (14).

FSH serum levels, obtained in early follicular phase of the cycle are used in clinical practice as an ovarian reserve test, along with other markers. Higher FSH levels indicate compromised ovarian reserve and accompanied with amenorrhea in younger women suggest POI. Isolated estradiol levels are of little value, but can help in the interpretation of FSH levels.

Antral follicle count (AFC) is a number of antral follicles on both ovaries measured by a transvaginal ultrasound in the early follicular phase. It represents the number of remaining primordial follicles (56). Low AFC on days 2 to 3 of a menstrual cycle is highly specific in predicting a low ovarian reserve (13).

4.2.4 Neurodegenerative diseases

Women in menopause are more prone to cognitive disturbances and dementia in general. Patients experiencing menopause earlier than normal are especially prone due the fact that younger brain is thought to be more vulnerable to estrogen deficiency (1). POI patients have shown worse results in cognitive and verbal memory tests in various studies (1). Surgical procedures causing POI have especially been connected to neurological dysfunction due to the rapid decline of estrogen levels. Bilateral oophorectomy was found to be associated with higher incidence of Alzheimer's disease, cognitive decline, anxiety, depression and Parkinson's disease (49). Estrogen replacement therapy in post-menopausal women reduce the incidence of dementia, especially when started early in menopause (49) (57).

4.2.5 Disrupted sexual function and psychological stress

Many women experience unpleasant side effect after chemotherapy, radiotherapy or surgical procedures that result in sexual dysfunction, low estrogen levels due to ovarian insufficiency. Most common symptoms include loss of libido, vaginal dryness, anorgasmia and dyspareunia (50). Apart from physical disturbances, psychological well-being is also affected, especially in younger women. Anxiety, depression and low self-esteem are the most commonly reported mood disturbances in POI patients. Majority of women do not feel

comfortable discussing this matter with their physician, however when asked, 90 percent will report at least one of these problems (58). Interestingly, one study reported a higher incidence of depression among POI patients than in Turner syndrome patients, suggesting that sudden diagnosis in adulthood is more devastating than diagnosis established in childhood (49). Chemotherapy and oophorectomy have been reported to cause sexual dysfunction more than other treatment types, due to the abrupt decrease in serum androgen levels after the treatment (58). Almost 60 percent of breast cancer patients treated with chemotherapy reported vaginal dryness, dyspareunia or difficulty reaching orgasm even years after the treatment (58). Hysterectomy with bilateral oophorectomy causes abrupt onset of symptoms and has a higher incidence of hypoactive sexual desire disorder. Vaginal lubricants are sometimes not adequate, and local therapy with vaginal estrogen is needed in these patients (59).

5 Management of POI

Currently there is no proven therapy to restore ovarian function after surgery, chemotherapy or radiotherapy. The management of POI consists of three different parts: fertility preservation, prevention of long term consequences caused by low estrogen levels and psychological and emotional support for the patient (11).

5.1 Hormone replacement therapy

Properly selecting the therapy in women with POI is of great importance to improve overall life quality, reduce serious long-term consequences and minimize risk of mortality. The goal of HRT is to restore normal levels of estrogen according to age. Hormone replacement therapy (HRT) and combined oral contraceptive (COC) are two options for POI treatment. Either one of these options is recommended for all POI patients to use from the time of diagnosis until the normal age of menopause (59) (60). Oral or transdermal HRT is recommended as first-line treatment in POI. Therapy is initiated according to the age group and according to the fact is the patient has the uterus. If the patient has not reached puberty yet, puberty induction around the age of 12 to 13 years is needed. It is done with minimal doses of estrogen taken either orally or with a transdermal patch. Dose is increased every 6 to

12 months until the breakthrough bleeding occurs (49). In patients with intact uterus, progestin should be added to the therapy for endometrial protection. Transdermal route is preferred over oral route since it mimics the physiology of natural estrogen better and it avoids the first-pass effect of the liver. Along with transdermal patch, vaginal ring should also be implemented to act locally and reduce vaginal atrophy. Despite low chances of spontaneous pregnancy in POI patients, COC are recommended for patients that also require protection from unwanted pregnancy. Combined oral contraceptives have some unfavourable effects on coagulation factors, lipid profile and blood pressure. Therefore, HRT is considered a better choice of therapy compared to COC. (49).

5.1.1 Hormone replacement therapy in hormone- sensitive cancers

In patients with a history of hormone-sensitive breast cancer HRT is considered unsafe (61). These patients are at risk for cancer recurrence or new cancer occurrence after the treatment with HRT. The effects and safety of other therapies such as selective serotonin reuptake inhibitors (SSRI), clonidine or gabapentin are uncertain and still under research (62). The key goal in this group of patients is to focus on prevention and treatment with local therapy. Vaginal moisturizers, weak vaginal estrogen creams or selective estrogen receptor modulators (SERMs) such as tamoxifen should be introduced to manage urogenital atrophy. Education regarding healthy lifestyle to reduce the risk for CVD should also be a part of prevention along with vitamin D and calcium supplements to minimize the risk of osteoporosis (49) (62). Recent studies suggest that HRT may be associated with development and prognosis of ovarian malignancies. Estrogen and progesterone receptor expression was examined in borderline ovarian tumors and ovarian carcinomas. No definitive assumption can be made by investigating receptor expression alone, however results showed no correlation between increased estorgen or progesterone receptor expression and overall survival in women with ovarian carcinoma. (63).

5.2 Fertility preservation

Fertility preservation options for cancer patients depend on many factors- patients age, diagnosis, type of treatment, metastatic potential of cancer and if the patients has a partner at the time of diagnosis (12). There are two ways to approach family planning in cancer patients. Preventive measures can be done before the beginning of treatment with ovarian suppression, transpositioning of the ovaries outside of radiation field prior to radiotherapy, shielding of the ovaries and oocyte/embryo cryopreservation or ovarian tissue cryopreservation which is still under research (64). As mentioned earlier, 5 to 10 percent of POI patients manage to conceive naturally after the treatment (1).

5.2.1 Ovarian suppression with GnRH agonists

Ovarian suppression with GnRH agonist has been proven to reduce the risk of POI, however it is not established if it has any effect on fertility. Despite that, some studies claim to have higher pregnancy rate in those patients that received GnRH agonists prior to chemotherapy (65). It is especially popular in developing countries since it is not as expensive as other fertility preserving procedures. GnRH agonists bind to receptors and initially cause an increased release of FSH and LH. After about one week, these receptors become downregulated and pituitary gland is releasing less gonadotropin (66). Although the exact mechanism of ovarian protection by GnRH agonists is still not fully understood, it is thought that toxicity from chemotherapy has a higher effect on the ovaries if they are in active state. Hypogonadotropic state is thought to causes less primordial follicles to enter differentiation stage where follicles are more vulnerable to chemotherapeutics (66). Although there are some medical benefits from GnRH agonists, American Society of Clinical Oncology (ASCO) guidelines suggest that there are no sufficient evidence on the effect of these agents on fertility preservation. They also emphasis the possible unwanted side effects and interactions on response to chemotherapy in estrogen-sensitive cancers (64). It should be considered only in cases when other fertility preserving options are not possible and in cases with hormone negative cancers.

5.2.2 Oocyte or embryo cryopreservation

Controlled ovarian stimulation (COS) is the first step in oocyte and embryo cryopreservation. Ovarian stimulation includes stimulation of follicular development with exogenous gonadotropins, prevention of spontaneous ovulation with either GnRH agonists or antagonists and triggering of oocyte maturation prior to oocyte retrieval with human chorionic gonadotropin (hCG) (67) (68).

Ovarian stimulation prior to oocyte or embryo cryopreservation can have a potential harmful effect in women with hormone sensitive cancer (69). There is still inadequate data on short-term and long-term effects of increase hormone levels on the cancer reoccurrence. Modified protocols with aromatase inhibitors (Letrozole) in breast cancer patients have shown successful reduction of estradiol levels during COS; however safety of these protocols is still not known. Short-term follow ups did not show compromised survival rates in those patients, but long term follow up is needed to assess the risk. (70) (71) (72).

In patients who do have a partner, in-vitro fertilization is done with embryo cryopreservation. Pregnancy rate with this method depends on the number of embryos transferred and age of the female partner when embryos were created. According to Society for Reproductive Technology (SART) database, women under the age of 35 years have a 35.6 percent chance of a live birth after embryo transfer while women over the age of 42 years have only 13.9 percent chance of a live birth (73). Oocyte cryopreservation includes harvesting and freezing unfertilized eggs with vitrification method after ovarian stimulation. Vitrification is a method of very fast freezing in less than one second that leaves embryo in vitrified state (74). Oocyte cryopreservation is suitable for women without a partner or in those with ethical objections for embryo cryopreservation (12). Number of oocytes that are needed for a good chance of pregnancy depends primarily on women's age at the time of oocyte cryopreservation. A study done in 2006 concluded that an average number of oocytes needed for clinical pregnancy in 32 year old patient is 22 (75). Recent studies from 2016 have shown that 10 oocytes are needed for a 69 percent chance for pregnancy in 35 year old women. This number decreases to only 50 percent chance of pregnancy in 37 year old women (76).

5.2.3 Ovarian tissues cryopreservation

Freezing of the ovarian tissue and reimplantation after the cancer treatment is still under research. Ovarian tissue is laparoscopically removed, frozen and implanted back after cancer treatment is completed (12). Ovarian tissue autotransplantation can be done with orthotopic transplantation, where tissue is transplanted into its original anatomical location or with heterotopic transplantation where tissue can be transplanted into various sites in the body. In heterotopic transplantation, IVF is needed to conceive. (77) The benefit of this method is that it does not require ovarian stimulation compared to embryo or oocyte cryopreservation and therefore patients do not have to delay the start of the treatment (64). Potential restoring of endocrine function along with fertility preservation is another benefit (64). Studies have shown that about 25 percent of primordial follicles are initially lost during this process; therefore this method is thought to be useless in women over the age of 40 years, since they already have a reduced ovarian reserve (12).

5.2.4 Oocyte donation

Oocyte donation along with in-vitro fertilization (IVF) is proven to be the most successful technique with the highest pregnancy rate in POI patients. Pregnancy success is around 40 to 50 percent per cycle (11). The main reason for high pregnancy success is donor's age. Highest live birth rates have been reported with younger donors aged between 30 and 34. (78) The outcomes of this method depend on uterine and endometrial quality after the cancer treatment (11).

6 Conclusion

As a result of a higher cancer cure rate, incidence of iatrogenic POI is increasing each year. Iatrogenic premature ovarian insufficiency affects young women and increases their risk for osteoporosis, cardiovascular diseases, infertility and other serious consequences. Once the diagnosis of POI has been made, proper therapy should be introduced by a reproductive endocrinology and infertility specialist. Fertility preservation issues should be discussed with patients before the beginning of treatment to ensure they understand all the fertility options as well as possible physical and psychological consequences of POI. Psychologic counseling should also be offered to all patients because emotional distress is common following the diagnosis of POI. Physicians should consider using less toxic chemotherapy if it does not interfere with treatment success and consider some of the protective measures before radiotherapy or surgery. Women suffering from iatrogenic POI should be evaluated at least annually.

7. Acknowledgements

I would like to thank my mentor, dr.sc. Maja Banović, dr.med. for her support, mentorship and expert advice that helped me significantly during process of writing my final thesis .I would also like to thank my Family and friends for their constant support during the past 6 years and especially during these last challenging months of my studies.

8 References

1. Podfigurna-Stopa A, Czyzyk A, Grymowicz M, Smolarczyk R, Katulski K, Czajkowski K, Meczekalski B. Premature ovarian insufficiency: the context of long-term effects. Journal of endocrinological investigation. 2016 Sep 1;39(9):983-90.
2. Fenton AJ. Premature ovarian insufficiency: Pathogenesis and management. Journal of mid-life health. 2015 Oct;6(4):147.
3. Welt CK, Crowley Jr WF. Ovarian development and failure (menopause) in normal women. UpToDate, Oct. 2015.
4. Hall JE. Guyton and Hall textbook of medical physiology e-Book. Elsevier Health Sciences; 2010 Jul 19.
5. Cox L, Liu JH. Primary ovarian insufficiency: an update. International journal of women's health. 2014;6:235.
6. Guidelines on the management of premature ovarian insufficiency (Internet). 2015 Dec (Citated 2020 June 26) Available from: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Management-of-premature-ovarian-insufficiency
7. Spath MA, Braat DD. Iatrogenic and non-iatrogenic causes of female fertility loss that may indicate fertility preservation. Acta obstetricia et gynecologica Scandinavica. 2019 May;98(5):559-62.
8. Rudnicka E, Kruszewska J, Klicka K, Kowalczyk J, Grymowicz M, Skórska J, Pięta W, Smolarczyk R. Premature ovarian insufficiency–aetiopathology, epidemiology, and diagnostic evaluation. Przeglad menopauzalny= Menopause review. 2018 Sep;17(3):105.
9. Lagergren K, Hammar M, Nedstrand E, Bladh M, Sydsjö G. The prevalence of primary ovarian insufficiency in Sweden; a national register study. BMC women's health. 2018 Dec 1;18(1):175.
10. Franasiak JM, Scott RT. Demographics of cancer in the reproductive age female. InCancer and Fertility 2016 (pp. 11-19). Humana Press, Cham.
11. Nagarajan N. Duru Shah, Navneet Magon. Premature Ovarian Failure. Current Progress in Obstetrics & Gynaecology. Volume 2:24-36

12. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. Journal of clinical oncology. 2006 Jun 20;24(18):2917-31.
13. Corrine K Welt CK, Shapiro CL. Ovarian failure due to anticancer drugs and radiation. In: UpToDate, Post TW editor: UpToDate
14. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future oncology. 2016 Oct;12(19):2333-44.
15. Spears N, Lopes F, Stefansdottir A, Rossi V, De Felici M, Anderson RA, Klinger FG. Ovarian damage from chemotherapy and current approaches to its protection. Human reproduction update. 2019 Nov 5;25(6):673-93.
16. Spears N, Lopes F, Stefansdottir A, Rossi V, De Felici M, Anderson RA, Klinger FG. Ovarian damage from chemotherapy and current approaches to its protection. Human reproduction update. 2019 Nov 5;25(6):673-93.
17. Koyama H, Wada T, Nishizawa Y, Iwanaga T, Aoki Y, Terasawa T, Kosaki G, Yamamoto T, Wada A. Cyclophosphamide-induced ovarian failure and its therapeutic significance in patients with breast cancer. Cancer. 1977 Apr;39(4):1403-9.
18. Gershenson DM, Pappo AS, Dizon DS, Barss VA. Treatment of malignant germ cell tumors of the ovary. UpToDate
19. Roness H, Kashi O, Meirow D. Prevention of chemotherapy-induced ovarian damage. Fertility and sterility. 2016 Jan 1;105(1):20-9.
20. Duncan FE, Kimler BF, Briley SM. Combating radiation therapy-induced damage to the ovarian environment. Future Oncology. 2016 Jul 1;12(14):1687-90.
21. Bradley KA, McHaffie DR, Mundt AJ, Dizon DS. Treatment-related toxicity from the use of radiation therapy for gynecologic malignancies. Uptodate. Waltham, MA: Wolters-Kluwer. 2018.
22. Stroud JS, Mutch D, Rader J, Powell M, Thaker PH, Grigsby PW. Effects of cancer treatment on ovarian function. Fertility and sterility. 2009 Aug 1;92(2):417-27.
23. Hubenak JR, Zhang Q, Branch CD, Kronowitz SJ. Mechanisms of injury to normal tissue after radiotherapy: a review. Plastic and reconstructive surgery. 2014 Jan;133(1):49e.
24. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Human reproduction update. 2001 Nov 1;7(6):535-43.

25. Kimler BF, Briley SM, Johnson BW, Armstrong AG, Jasti S, Duncan FE. Radiation-induced ovarian follicle loss occurs without overt stromal changes. Reproduction. 2018 Jun 1;155(6):553-62.
26. Hendrix SL. Bilateral oophorectomy and premature menopause. The American journal of medicine. 2005 Dec 19;118(12):131-5.
27. Rosendahl M, Simonsen MK, Kjer JJ. The influence of unilateral oophorectomy on the age of menopause. Climacteric. 2017 Nov 2;20(6):540-4.
28. Bjelland EK, Wilkosz P, Tanbo TG, Eskild A. Is unilateral oophorectomy associated with age at menopause? A population study (the HUNT2 Survey). Human reproduction. 2014 Feb 18;29(4):835-41.
29. Yasui T, Hayashi K, Mizunuma H, Kubota T, Aso T, Matsumura Y, Lee JS, Suzuki S. Factors associated with premature ovarian failure, early menopause and earlier onset of menopause in Japanese women. Maturitas. 2012 Jul 1;72(3):249-55.
30. Atay V, Ceyhan T, Baser I, Gungor S, Goktolga Ü, Muhcu M. Hysterectomy with preservation of both ovaries does not result in premature ovarian failure. Journal of international medical research. 2007 May;35(3):416-21.
31. Ahn EH, Song CH, Kim JY, Park KH, Bai SW, Lee JS, Kwon JY. Effect of Hysterectomy on conserved Ovarian function. Korean Journal of Obstetrics & Gynecology. 2001 Sep 1;44(9):1691-5.
32. Farquhar CM, Sadler L, Harvey SA, Stewart AW. The association of hysterectomy and menopause: a prospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2005 Jul;112(7):956-62.
33. Moorman PG, Myers ER, Schildkraut JM, Iversen ES, Wang F, Warren N. Effect of hysterectomy with ovarian preservation on ovarian function. Obstetrics and gynecology. 2011 Dec;118(6):1271.
34. Amooee S, Gharib M, Ravanfar P. Comparison of anti-mullerian hormone level in non-endometriotic benign ovarian cyst before and after laparoscopic cystectomy. Iranian journal of reproductive medicine. 2015 Mar;13(3):149
35. Sahin C, Akdemir A, Ergenoglu AM, Ozgurel B, Yeniel AO, Taskiran D, Sendag F. Which should be the preferred technique during laparoscopic ovarian cystectomy: Hemostatic sutures or bipolar electrocoagulation? A Randomized controlled prospective study of long-term ovarian reserve. Reproductive Sciences. 2017 Mar;24(3):393-9.

36. Donnez J, García-Solares J, Dolmans MM. Ovarian endometriosis and fertility preservation: a challenge in 2018. Minerva ginecologica. 2018 Aug;70(4):408-14.
37. Takae S, Kawamura K, Sato Y, Nishijima C, Yoshioka N, Sugishita Y, Horage Y, Tanaka M, Ishizuka B, Suzuki N. Analysis of late-onset ovarian insufficiency after ovarian surgery: retrospective study with 75 patients of post-surgical ovarian insufficiency. PLoS One. 2014 May 23;9(5):e98174.
38. Mohamed AA, Yosef AH, James C, Al-Hussaini TK, Bedaiwy MA, Amer SA. Ovarian reserve after salpingectomy: a systematic review and meta-analysis. Acta obstetricia et gynecologica Scandinavica. 2017 Jul;96(7):795-803.
39. Huang D, Zhu Y, Chen J, Zhang S. Effect of modified laparoscopic salpingectomy on ovarian reserve: Changes in the serum antimüllerian hormone levels. Laparoscopic, Endoscopic and Robotic Surgery. 2019 Mar 1;2(1):8-11.
40. Collins E, Strandell A, Granåsen G, Idahl A. Menopausal symptoms and surgical complications after opportunistic bilateral salpingectomy, a register-based cohort study. American journal of obstetrics and gynecology. 2019 Jan 1;220(1):85-e1.
41. van Lieshout LA, Steenbeek MP, De Hullu JA, Vos MC, Houterman S, Wilkinson J, Piek JM. Hysterectomy with salpingectomy versus hysterectomy alone. The Cochrane Database of Systematic Reviews. 2017 Nov;2017(11).
42. Chan CC, Ng EH, Li CF, Ho PC. Impaired ovarian blood flow and reduced antral follicle count following laparoscopic salpingectomy for ectopic pregnancy. Human reproduction. 2003 Oct 1;18(10):2175-80.
43. Vabre P, Gatimel N, Moreau J, Gayrard V, Picard-Hagen N, Parinaud J, Leandri RD. Environmental pollutants, a possible etiology for premature ovarian insufficiency: a narrative review of animal and human data. Environmental Health. 2017 Dec;16(1):37.
44. Zhang XF, Zhang LJ, Li L, Feng YN, Chen B, Ma JM, Huynh E, Shi QH, De Felici M, Shen W. Diethylhexyl phthalate exposure impairs follicular development and affects oocyte maturation in the mouse. Environmental and molecular mutagenesis. 2013 Jun;54(5):354-61.
45. Yang HJ, Suh PS, Kim SJ, Lee SY. Effects of smoking on menopausal age: results from the Korea National Health and nutrition examination survey, 2007 to 2012. Journal of Preventive Medicine and Public Health. 2015 Jul;48(4):216.
46. Plante BJ, Cooper GS, Baird DD, Steiner AZ. The impact of smoking on antimüllerian hormone levels in women aged 38 to 50 years. Menopause (New York, NY). 2010 May;17(3):571.

47. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. Obstetrics and Gynecology Clinics. 2011 Sep 1;38(3):489-501
48. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. European journal of rheumatology. 2017 Mar;4(1):46.
49. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertility and sterility. 2016 Dec 1;106(7):1588-99.
50. Molina JR, Barton DL, Loprinzi CL. Chemotherapy-induced ovarian failure. Drug Safety. 2005 May 1;28(5):401-16.
51. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Przeglad menopauzalny= Menopause review. 2014 Sep;13(4):213.
52. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biology of sex differences. 2017 Dec;8(1):33.
53. Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. Menopause (New York, NY). 2012 Oct;19(10):1081-7.
54. Jirge PR. Ovarian reserve tests. Journal of human reproductive sciences. 2011 Sep;4(3):108.
55. Kuohung W, Hornstein MD, Barbieri RL, Barss VA. Evaluation of female infertility. UpToDate, Waltham, MA. Accessed Jan. 2016.
56. Agarwal A, Verma A, Agarwal S, Shukla RC, Jain M, Srivastava A. Antral follicle count in normal (fertility-proven) and infertile Indian women. The Indian journal of radiology & imaging. 2014 Jul;24(3):297.
57. Kumar N, Manesh I. Premature ovarian insufficiency: Aetiology and long-term consequences. Women Health Open J. 2017;3(2):45-58.
58. Maciejewska-Jeske M, Szeliga A, Męczekalski B. Consequences of premature ovarian insufficiency on women's sexual health. Przeglad menopauzalny= Menopause review. 2018 Sep;17(3):127.
59. Machura P, Grymowicz M, Rudnicka E, Pięta W, Calik-Ksepka A, Skórska J, Smolarczyk R. Premature ovarian insufficiency–hormone replacement therapy and

management of long-term consequences. Przeglad menopauzalny= Menopause review. 2018 Sep;17(3):135.

60. Webber L, Anderson RA, Davies M, Janse F, Vermeulen N. HRT for women with premature ovarian insufficiency: a comprehensive review. Human Reproduction Open. 2017;2017(2).
61. Deli T, Orosz M, Jakab A. Hormone replacement therapy in cancer survivors–review of the literature. Pathology & Oncology Research. 2019 Jan 8:1-6.
62. Deniz G, Antoine C, Liebens F, Carly B, Pastijn A, Rozenberg S. Treatment of premature menopause in breast cancer patients. Acta chirurgica Belgica. 2007 Jan 1;107(3):263-6.
63. Sallum LF, Sarian LO, Lucci De Angelo Andrade L, Vassallo J, Soares FA, Pinto GA, Ferreira PA, Derchain S. Survival of women with ovarian carcinomas and borderline tumors is not affected by estrogen and progesterone receptor status. Journal of gynecologic oncology. 2013 Apr 1;24(2):167-76.
64. Pinelli S, Basile S. Fertility preservation: current and future perspectives for oncologic patients at risk for iatrogenic premature ovarian insufficiency. BioMed research international. 2018;2018.
65. Poggio F, Lambertini M, Bighin C, Conte B, Blondeaux E, D'Alonzo A, Dellepiane C, Buzzatti G, Molinelli C, Boccardo F, Del Mastro L. Potential mechanisms of ovarian protection with gonadotropin-releasing hormone agonist in breast cancer patients: A Review. Clinical Medicine Insights: Reproductive Health. 2019 Jul;13:1179558119864584.
66. Abdel-Razeq H. Gonadotropin-releasing hormone agonists during chemotherapy for ovarian function and fertility preservation for patients with early-stage breast cancer. Cancer management and research. 2019;11:4273.
67. Gallos ID, Eapen A, Price MJ, Sunkara SK, Macklon NS, Bhattacharya S, Khalaf Y, Tobias A, Deeks JJ, Rajkhowa M, Coomarasamy A. Controlled ovarian stimulation protocols for assisted reproduction: a network meta-analysis. The Cochrane Database of Systematic Reviews. 2017 Mar;2017(3).
68. Dittrich R, Lotz L, Mueller A, Hoffmann I, Wachter DL, Amann KU, Beckmann MW, Hildebrandt T. Oncofertility: combination of ovarian stimulation with subsequent ovarian tissue extraction on the day of oocyte retrieval. Reproductive Biology and Endocrinology. 2013 Dec 1;11(1):19.

69. Mahajan N. Fertility preservation in female cancer patients: An overview. Journal of human reproductive sciences. 2015 Jan;8(1):3.
70. Muñoz E, González N, Muñoz L, Aguilar J, Velasco JA. Ovarian stimulation in patients with breast cancer. ecancermedicalscience. 2015;9.
71. Cavagna F, Pontes A, Cavagna M, Dzik A, Donadio NF, Portela R, Nagai MT, Gebrim LH. Specific protocols of controlled ovarian stimulation for oocyte cryopreservation in breast cancer patients. Current Oncology. 2018 Dec;25(6):e527.
72. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. Journal of Clinical Oncology. 2008 Jun 1;26(16):2630-5.
73. The Oncofertility Consortium: Chance of pregnancy after embryo cryopreservation (Internet) 2012 March (citated: 2020 June 26) Available from: http://oncofertility.northwestern.edu/resources/chance-pregnancy-after-embryo-cryopreservation#sart
74. Kuwayama M, Vajta G, Kato O, Leibo SP. Highly efficient vitrification method for cryopreservation of human oocytes. Reproductive biomedicine online. 2005 Jan 1;11(3):300-8.
75. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. Fertility and sterility. 2006 Jul 1;86(1):70-80.
76. Cobo A, García-Velasco JA, Coello A, Domingo J, Pellicer A, Remohí J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertility and sterility. 2016 Mar 1;105(3):755-64.
77. Demeestere I, Simon P, Emiliani S, Delbaere A, Englert Y. Orthotopic and heterotopic ovarian tissue transplantation. Human Reproduction Update. 2009 Nov 1;15(6):649-65.
78. Wang YA, Farquhar C, Sullivan EA. Donor age is a major determinant of success of oocyte donation/recipient programme. Human Reproduction. 2012 Jan 1;27(1):118-25.

9 Biography

I was born in Zagreb, on February 4th 1995. After elementary school I finished a Classical Gymnasium in Zagreb, and started university at the University of Zagreb, Faculty of Chemical Engineering and Technology where I studied chemical engineering for a year. After a year I decided to go into Medicine, and enrolled into the University of Zagreb, School of Medicine in 2014, where I am currently a 5th year medical student. I was a student demonstrator at the department of Pathophysiology in the year 2017/2018. I was also a student demonstrator for the course "History taking and physical examination" in the year 2019/2020. My additional medical experience includes September 2018 where I attended a clerkship of four weeks in the field of cardiovascular surgery at Texas Medical Centre in Houston, USA, and 4weeks at Cambridge University, UK doing a clerkship in Gynaecology and Obstetrics. Outside of medicine, I am fluent English language at the level of C1/C2, Italian at B1, and French language at A2 level.