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[1]Community Health Centre Zagreb-Centre, Zagreb,
[2]Unit of Clinical Embriology, Department of Gynecology and Obstetrics, University Hospital Centre Zagreb,
[3]Department of Gynecology and Obstetrics, University Hospital Centre Zagreb, School of Medicine University of Zagreb

PRELIMINARY OUTCOME OF ONCOFERTILITY PATIENTS IN CROATIA

Marija Svalina[1], Dorotea Šijak[1], Nina Gelo[2], Gabriela Kirinec[2], Hrvoje Vrčić[3], Marina Šprem Goldštajn [3]

Original scientific paper

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Summary. Oncofertility is a relatively new field of medicine focuses on developing methods to preserve reproductive function in patients diagnosed with cancer. The major technique of fertility preservation includes hormonal stimulation of ovulation, followed by IVF and then cryopreservation of the resulting oocytes or embryos for use at a later date. *Aim.* The primary outcome of this study was to determine efficiency of oncofertility program considering oncological diagnosis and ovarian stimulation protocol. Secondary outcome was to establish possible recommendation for oncofertility program based on ovarian reserve marker, estradiol level and presence of estrogen and progesteron receptors in breast cancer cells. *Materials and methods.* We conducted a retrospective study of 30 female patients (24–41 yrs) with different oncological diagnosis, who attended Human Reproduction Unit**,** at Department of Obstetrics and Gynecology at University Hospital Centre Zagreb, from November 2013 until February 2018. Inclusion criteria were oncological diagnosis, as well as treatment with specific ovarian stimulation protocol. *Results.* We found that patients with malignant disease are predominantly in the group of poor responders. Same protocol yielded a different response through the obtained number of oocytes. Isolated gonadotropins resulted with highest average estradiol level contrary to protocol of isolated aromatase inhibitor, where lowest average estradiol level was obtained. *Discussion.* Ovarian stimulation protocols should be individualized based on time available prior to cancer diagnosis, latency time needed for inclusion into oncofertility protocol as well on fertility status of the patient. *Conclusion.* Further follow-up and alternative protocol may be crucial for female cancer patients, in enabling of remarkable possibility for fertility preservation and improvement of their overall health care.

Introduction

Cancer treatment can cause severe detrimental effects on fertility, that can depend on chemotherapy, radiotherapy, or surgical treatments involved. Women with cancer diagnosis frequently have to deal with the long-term medical and emotional consequences.[1] In 2014 nearly 14.5 million people were diagnosed with cancer worldwide.[2] It is estimated that almost 1 million new cancer cases have occurred among 20–39 year-olds worldwide in 2012, with the disease more frequent among women.[3] Oncofertility is a new, multidisciplinary field of medicine that includes an integrated network of clinical resources that focus on developing methods to preserve reproductive function in patients diagnosed with cancer.[4] The Oncofertility Consortium is initiative created in 2005 in North America designed to assess the reproductive future of young women facing fertility-threatening condition or treatment.[2]

The ideal oncofertility approach would involve a proactive and multi-disciplinary dialogue with the patient about fertility-sparing options and prognosis, provision of readily accessible information, and an established, efficient system of referral to fertility specialists. Cancer diagnosis followed by the quick decision for treatment is often accompanied by a short window of time in which fertility preservation must be managed.[1] It can be challenging for practitioners to facilitate discussions about fertility amidst other critical and life-altering topics.[5]

Oncofertility procedures in women are more challenging than in men, because unlike sperm, the female germ cell (oocyte) is available in limited numbers, degree of maturity depends on the time of the menstrual cycle and oocyte must be retrieved surgically. One fertility preservation technique for this group of patients includes hormonal stimulation of ovulation, followed by IVF and then cryopreservation of the resulting embryos for use at later date. Embryo banking prior to cancer treatment should be the first option for fertility management whenever practical.[4] The primary outcome of this study was to determine efficiency of oncofertility program considering oncological diagnosis and ovarian stimulation protocol.

Materials and methods

We conducted a retrospective study of 30 female patients, aged 24 to 41 years, who have had oncological diagnosis and have been involved in oncofertility program. Data were collected from patients who attended Human Reproduction Unit, at Department of Obstetrics and Gynecology at University Hospital Centre Zagreb, from November 2013 until February 2018.

Inclusion criteria were oncological diagnosis, where we differentiate those with breast cancer and other malignant diseases, as well as treatment with specific ovarian stimulation protocol for achieving a pregnancy. Therefore, all patients were in reproductive age. Exclusion criteria were disruption of ovarian stimulation pro-

tocol of any reason. We searched past medical history and collected data about certain method of assisted reproduction, for patients who met our criteria. Stratification was made using following parameters: oncological diagnosis, ovarian stimulation protocol, number of aspirated oocytes per patient (which was the main criteria for estimation of responders into 4 groups), estradiol level (E2) for each patient and antral follicle count (AFC) as a marker of ovarian reserve. We investigated possible existence of numerous correlations between described parameters.

Stratification upon oncological diagnosis

Patients have been observed based on their oncological diagnosis through 2 groups, those with breast cancer and other malignant diseases (hematologic malignancies, adenocarcinoma of the lungs, cerebellar neuroblastoma and fibular osteosarcoma).

Distribution of ovarian stimulation protocols

As a part of method of assisted reproduction (MAR), different protocols for ovarian stimulation were used depending on individual needs and hormonal status of each patient. That is why we made a specific division on A, which stands for natural menstrual cycle, and B-D protocols, where each protocol consists of certain hormonal inducers or inhibitors.

Type of responder according to total number of aspirated oocytes

Patients have also been divided by total number of aspirated oocytes, into 4 main types of responders: poor responders (less than 3 aspirated oocytes), suboptimal responders (4–9 aspirated oocytes), normoresponders (10–15 aspirated oocytes) and highresponders (more than 15 aspirated oocytes).

Distribution by estradiol level

We collected data about maximal estradiol level, that was established just before aspiration of oocytes, during the implementation of MAR. That gave us valuable information about response to ovarian stimulation protocol during certain method of assisted reproduction and hormonal status of our patients. Also, estradiol levels can potentially be used as a positive predictor of following pregnancy rate.

Ovarian reserve based on antral follicle count (AFC)

Initial antral follicle count, measured on the beginning of treatment and before usage of any ovarian stimulation protocol, led us to ovarian reserve of each patient. AFC was measured for both ovaries and shown as a total number of active follicles.

Final outcome based on number of aspirated oocytes

Number of aspirated oocytes was a leading parameter for estimating efficiency of used ovarian stimulation protocol. Follow-up wasn't conducted after cryopreservation procedure, consequently pregnancy rate was not used as final outcome measure.

Statistical analysis

All collected data was stored and analyzed in form of descriptive statistics, using Excel 2016 (Microsoft, USA), which gave us information about distribution, central tendency and dispersion of certain values. Particular correlations were processed using SPSS v23, obtained variables didn't show normal distribution, and therefore, the nonparametric Mann-Whitney test was used to determine statistical significance of correlations by paired measurements. The adopted statistical significance level was $P<0.05$. All categorical variables were described graphically by pie and combined bar charts and numerically by frequency table, as absolute numbers and percentages.

Results

1. General demographic data

The mean age was 33 years. The age range was 24–41 years. 14 patients were <33 years of age and 16 patients were >= 33 years of age.

Most of the patients have not given birth, except two patients aged 38 and 41 yrs, who had only one preg-

Table 1. Statistical values of observed parameters referring to patients with breast cancer (N=23) and those with other malignancies (N=7)

Tablica 1. Statističke vrijednosti promatranih parametara kod pacijentica s rakom dojke (N=23) i onih s ostalim malignim bolestima (N=7)

Malignancy	Breast cancer		Other malignancies		P^2
	M*	IQR**	M*	IQR **	
Estradiol (pg/mL)	522.0	263.5 – 1087.65	295.5	152.5 – 687	0.496
ER (%)	0	0 – 0	90	70 – 100	
PR (%)	0	0 – 0	60	17.5 – 87.5	
FSH (I.U.)	1012.5	600 – 1425	1293.75	900 – 2062.5	0.26
Aspirated oocytes (n)	6	1.75 – 16.5	5	3 – 7.75	0.739
Time from dg to IVF (days)	360	77.75 – 1520.25	32	23.5 – 60.5	0.022

*M – median value; **P – IQR (25–75); [1]Mann-Whitney test value; [2]p value (<0.05)

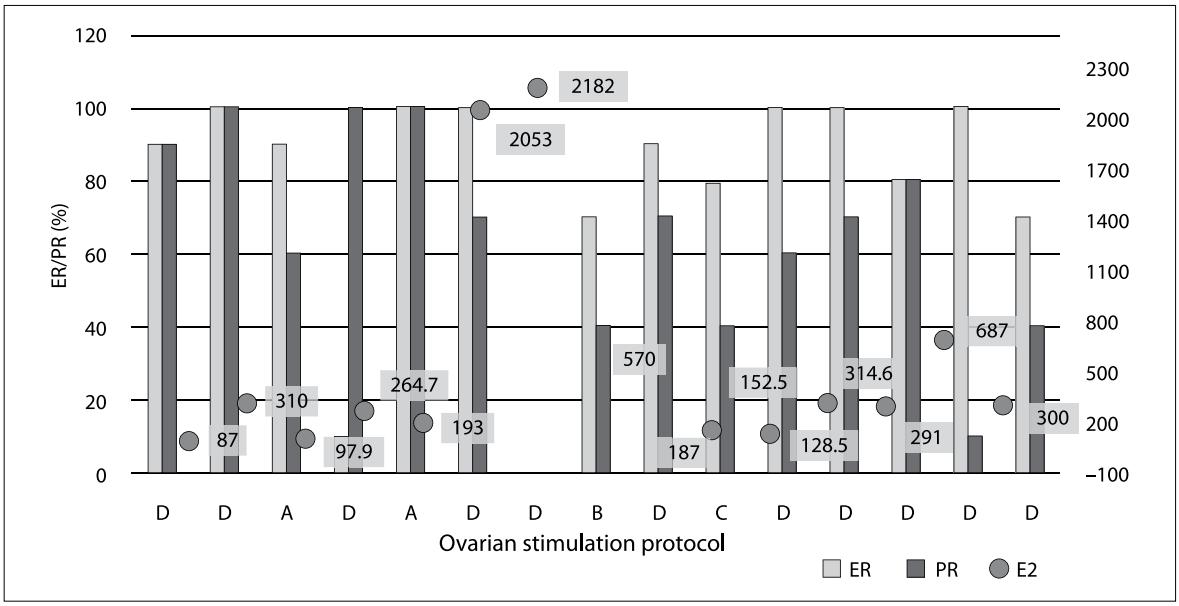

Figure 1. Correlation between E2-ER/PR-ovarian stimulation protocol in patients with breast cancer
Slika 1. Povezanost E2-ER/PR-protokola ovarijske stimulacije u pacijentica s rakom dojke

nancy and one delivery. Additionally, two patients aged 31 and 41 yrs had a miscarriage once.

Average duration of menstrual cycle was 28.74 days (SD 4.51) with average duration of menstrual bleeding for 5.19 days (SD 1.32). Methods of assisted reproduction (MAR) that were used in oncofertility program were oocyte cryopreservation (N=26, 86.7%) and embryo cryopreservation (N=4, 13.3%).

Surgical procedures in oncofertility patients

Most of the patients were treated surgically for breast carcinoma (N= 14; 68%), on the other hand, rest of surgical procedures (conization, LLETZ, hysteroscopic surgery, laparoscopic surgery and cesarean section) were with other surgical indication (N= 7; 32%).

2. Distribution of oncological diagnosis in oncofertility patients

Among oncofertility patients on ovarian stimulation protocol, the most common oncological diagnosis was breast cancer (N=23; 77%). Other malignant diseases (N=7; 23%) included adenocarcinoma of the lungs, cerebellar neuroblastoma, fibular osteosarcoma and hematologic diagnosis, as Non-Hodgkin follicular lymphoma, essential thrombocytosis, thrombophilia and myelodysplastic syndrome.

3. Latency (delay) time from assessment of oncological diagnosis to inclusion into oncofertility program

Median value of latency time from diagnosis of malignant disease to inclusion into oncofertility program was 43.5 days, with minimal time distinction of 11 days and maximal of 4449 days.

4. Distribution of ovarian stimulation protocols in oncofertility patients

We have classified ovarian stimulation protocols based on used agents, into 4 classes A to D. Protocol A is natural menstrual cycle (13.3%; N=4), in protocol B are used only gonadotropins – FSH+LH (23.3%, N=7), protocol C includes isolated aromatase inhibitor, and it is used in only one patient (3.3%), and D, as the most common protocol, refers to combination of aromatase inhibitor + gonadotropins (60.1%, N=18).

5. Correlation between estradiol level, presence of ER/PR and ovarian stimulation protocol in group of patients with breast cancer

Based on presence of hormonal receptors (ER, PR) in breast cancer, we divided patients into four major groups: ER>50%+PR>50%, ER>50%+PR<50%, ER< 50%+PR>50%, ER<50%+PR<50%.

The highest level of E2 (E2=2182 pg/mL) was reached in patient without presence of hormonal receptors (ER 0%, PR 0%) which undergo protocol D (aromatase inhibitor+FSH+LH). Unexpectedly, second highest level of E2 (E2=2053 pg/mL) was achieved in patient with maximal presence (100%) of ER and presence of 70% of PR, which undergo protocol D. On the other hand, the lowest level of E2 (E2=87 pg/mL) was obtained in patient with 90% of both ER and PR, in which protocol D had also been applied.

Coefficient of correlation between ER (%) and estradiol concentration wasn't statistically significant ($r = -0.381$; $P = 0.161$). Similarly, coefficient of correlation between PR (%) and estradiol concentration was near limit of statistical significance ($r = 0.468$; $P = 0.079$).

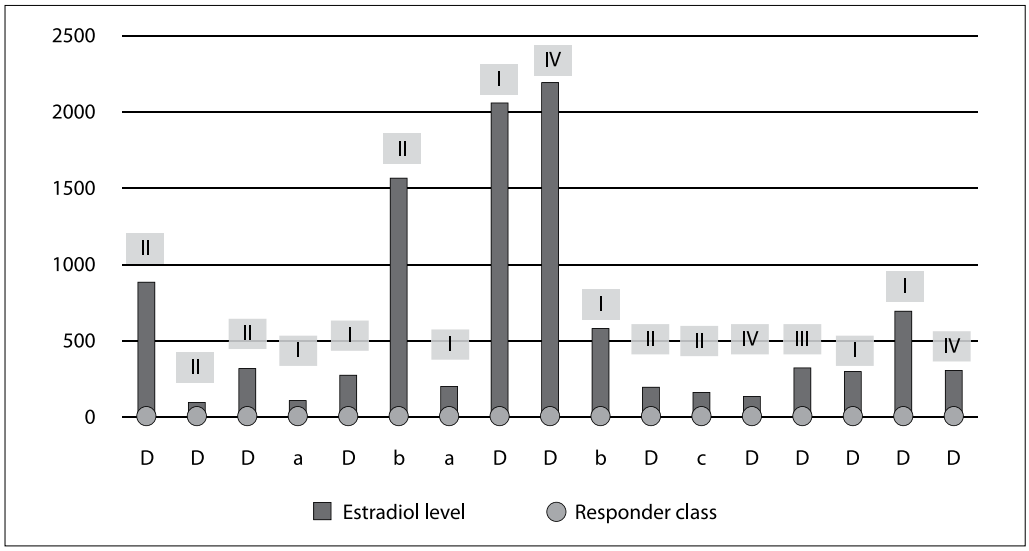

Figure 2. Correlation between ovarian stimulation protocol-E2-type of responder in patients with breast cancer
Slika 2. Povezanost protokola ovarijske stimulacije-E2-tipa respondera u pacijentica s rakom dojke

6. Correlation between type of responder, ovarian stimulation protocol and estradiol level in oncofertility patients

Among patients with breast cancer, 76% responded poor or suboptimal on applied ovarian stimulation protocol, despite of patients with other malignant disease where 42% of them were poor or suboptimal responders.

6.1. Correlation between type of responder and ovarian stimulation protocol in patients with breast cancer

Referring generally on patients with breast cancer, 76.5% of them were in the group of low responders (poor responders+suboptimal responders) and 23.5% of them were normoresponders/highresponders. Considering group of poor responders (I) and suboptimal responders (II) most of the patients undergo protocol D (61,5%), further on there were protocols A and B with 15,4 % and only one patient on protocol C (7,7%). In opposite group, of normoresponders (III) and high responders (IV) all of patients undergo protocol D.

6.2. Correlation between type of responder and ovarian stimulation protocol in patients with other malignant diseases

Considering group of poor responders (I) and suboptimal responders (II) each of patient undergo different protocol (A, B, D). In opposite group of highresponders (IV) both of patients undergo protocol B.

6.3. Average estradiol level per each ovarian stimulation protocol

As expected, average estradiol level was highest in protocol B (isolated gonadotropins) and lowest in protocol C (isolated aromatase inhibitor). In protocol D, which consists of gonadotropins and aromatase inhibitor, we founded second highest average value of estradiol level, possibly associated with their mechanism of action. Finally, protocol A, as natural cycle without any ovarian stimulation agent, resulted with unexpectedly low value of average estradiol level, which can be described by limited sample of only four patients, who showed individual variations.

7. Correlation between type of responder and ovarian reserve (antral follicle count)

Referring to correlation between type of responder and average value of antral follicle count, ovarian reserve based on AFC expectedly followed type of responder; average value of AFC for poor responders was 10.6 and for high responders was 35.7. It has been confirmed that the lowest level of AFC (AFC= 4) was present in patient from the group of poor responders and one of high responders had the highest level of AFC (AFC= 41).

8.1. Correlation between given FSH (I.U.) protocol, aspirated oocytes and estradiol level

Average value of FSH dosage applied through ovarian stimulation protocol was 1489.6 I.U., with minimal dosage of 750 I.U. and maximal dosage of 3300 I.U. Increasement of FSH dosage (I.U.) didn't affect number of aspirated oocytes and obtained etradiol level, as shown in the figure 4.

Discussion

We conducted a retrospective study of 30 female patients, aged 24 to 41 years, who have had different oncological diagnosis and have been involved in oncofertility program. Data were collected from patients who attended Human Reproduction Unit, at Department of

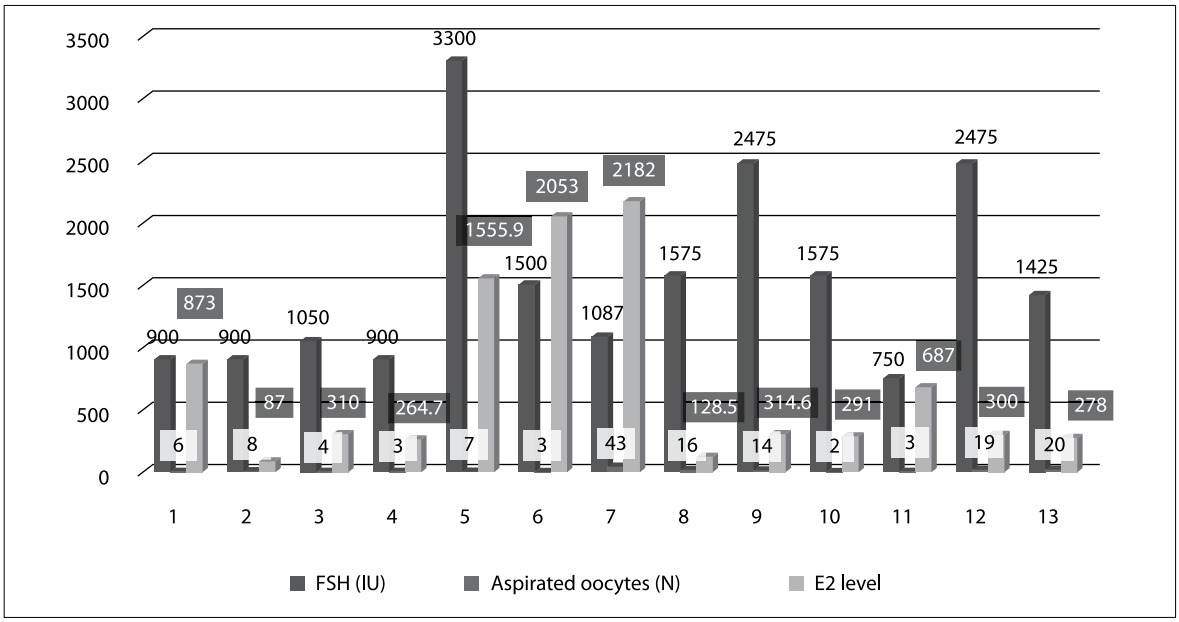

Figure 3. Correlation between FSH protocol, aspirated oocytes and E2
Slika 3. Povezanost FSH protokola, aspiriranih oocita i E2

Obstetrics and Gynecology at University Hospital Centre Zagreb, from November 2013 until February 2018.

Stratification was made using following parameters: oncological diagnosis, protocol for ovarian stimulation, total number of aspirated oocytes per patient (type of responder), estradiol level (E2) for each patient and AFC as a marker of ovarian reserve. Our main objective was to determine efficiency of oncofertility program considering oncological diagnosis and ovarian stimulation protocol.

As we haven't found similar clinical study in Croatia and surrounding regions, we decided to collect data from our country and compare them with other studies around the globe. This is preliminary outcome in oncofertility field in Croatia, with emphasize on number of aspirated oocytes which was taken as a valuable outcome of oncofertility program. Further investigations upon this field are strongly encouraged.

Poor responders are defined as those who produced less than three follicles despite adequate ovarian stimulation, according to Serafini et al. (1988), while Jenkins et al. (1991) have considered four follicles as their cut-off point (7).

The same ovarian stimulation protocol is applied in patients with positive as well as in those with negative receptors (ER, PR), resulting in the same levels of estradiol. Same as in patients with only positive receptors, who were on the same protocol, the lowest estradiol level was obtained.

Patients with breast cancer are predominantly in the group of poor responders. The same used protocol (D) yielded a different response through the obtained number of oocytes, that was further used for determining the type of responder.

Several authors have found that antral follicle count is the best pretreatment predictor of the follicular response to gonadotropin stimulation during ovarian stimulation (9,10). Child et al., using multiple linear regression, found that the AFC was shown to be the most important independent predictor of the numbers of oocytes retrieved (11). In our patients correlation between type of responder and average value of antral follicle count, as an indicator of ovarian reserve, expectedly followed type of responder.

Isolated gonadotropins, in protocol B, resulted with highest average estradiol level contrary to protocol C of isolated aromatase inhibitor, where was obtained lowest average estradiol level. Protocol D combination, of gonadotropins and aromatase inhibitor, produced second highest average value of estradiol, associated with their synergistic mechanism of action. Fatum et al. The co-administration of letrozole and gonadotropins in patients with breast cancer would reduce both the high supraphysiological serum concentrations of estradiol and intratumoral in situ estrogen production. Specific caution is needed in patients with known hormone-receptor-positive breast cancer undergoing ovarian stimulation (6).

Increase in FSH dosage administration, during ovarian stimulation protocol, didn't result in higher estradiol levels not more efficient responder type.

Limitations of our study have been reflected through our outcome where we observed total number of aspirated oocytes, instead of final pregnancy rate, since there was no evidenced data on follow-up of patients after cryopreservation. Other important limitation was disruption of ovarian stimulation protocol caused by any reason, as well as a precision in notation of patients

data, that we have to take with extreme caution. It is important to keep in mind, when patients have been diagnosed with malignant dissease, it is of high-priority to start with treatment as soon as possible. Consequently, the available time for fertility preservation and intervention is limited. Therefore, time window from oncological diagnosis to inclusion into oncofertility program is also considering limitation.

Conclusion

Oncofertility is a relatively new diagnostic therapeutic approach in medicine, which is gradually developing, what is shown through small sample of patients involved in oncofertility program, in a period from 2013–2018. Based on that, further follow-up of oncofertility patient is clearly necessary for declaring of suitable conclusions.

Ovarian stimulation protocols should be individualized based on time available prior to cancer diagnosis, latency time needed for inclusion into oncofertility program as well on fertility status of the patient. Pregnancy outcomes in observed population are still unknown, however previous studies showed promising results. Further follow-up and alternative protocol may be crucial for female cancer patients, in enabling of remarkable possibility for fertility preservation and improvement of their overall health care.

Disclosure statement

The authors declare no conflicts of interest.

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Address for correspondence: Professor Marina Šprem Goldštajn, M.D, Ph.D., Clinical Hospital Centre Zagreb, Department of obstetrics and Gynecology, School of Medicine, University of Zagreb. Petrova ulica 13, 10 000 Zagreb, Croatia.

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[1]Dom zdravlja Zagreb – Centar, Zagreb, Hrvatska, [2]Odjel kliničke embriologije KBC-Zagreb,
[3]Klinika za ženske bolesti i porode KBC-a Zagreb, Medicinski fakultet Sveučilišta u Zagrebu

PRELIMINARNI REZULTATI ONKOFERTILITETNIH PACIJENTICA U REPUBLICI HRVATSKOJ

Marija Svalina[1], Dorotea Šijak[1], Nina Gelo[2], Gabriela Kirinec[2], Hrvoje Vrčić[3], Marina Šprem Goldštajn[3]

Izvorni znanstveni članak

Ključne riječi: Onkofertilitet; ovarijska stimulacija; broj antralnih folikula; tip respondera; estradiol

Sažetak. Liječenje zloćudnih bolesti može imati štetne učinke na fertilitet. Onkofertilitet je relativno novo, multidisciplinarno područje u medicini koje se zasniva na suradnji različitih kliničkih disciplina, a koje se baziraju na razvoju metoda za očuvanje reproduktivne funkcije u pacijenata s malignom bolesti. Glavni način očuvanja fertiliteta uključuje hormonsku stimulaciju ovulacije, uz IVF i krioprezervaciju dobivenih oocita i embrija. *Ciljevi.* Glavni cilj ovog rada je odrediti uspješnost onkofertilitetnog postupka s obzirom na onkološku dijagnozu i protokol ovarijske stimulacije. Dodatni cilj je utvrditi moguće preporuke za onkofertilitetni postupak bazirajući se na AFC, razini estradiola te prisutnosti estrogenskih i progesteronskih receptora u stanicama karcinoma dojke. *Materijali i metode.* U ovoj je analitičkoj studiji obuhvaćeno 30 pacijentica, dobi od 24 do 41 godinu, uključenih u onkofertilitetni program. Podatci su sakupljeni od pacijentica koje su liječene u razdoblju od studenog 2013.godine do veljače 2018. godine na Zavodu za humanu reprodukciju, u Klinici za ženske bolesti i porode, KBC Zagreb. Uključujući kriteriji su bili onkološka dijagnoza te liječenje određenim protokolom ovarijske stimulacije. Isključujući kriterij je prekid protokola ovarijske stimulacije iz bilo kojeg razloga. Klasifikacija pacijentica se temelji na: onkološkoj dijagnozi, protokolu ovarijske stimulacije, broju aspiriranih oocita po pacijentici (4 skupine respondera), razini estradiola te AFC. *Rezultati.* Prema dobivenim podatcima, pacijentice s rakom dojke pretežito su u skupini *poor respondera*. Specifični protokol ovarijske stimulacije nije utjecao na konačnu razinu estradiola u toj skupini pacijentica, neovisno o tipu prisutnog hormonskog receptora. Pacijentice s ostalim malignim oboljenjima su također pretežito u skupini *poor respondera*, neovisno o primjenjenom protokolu ovarijske stimulacije. Primjena istog protokola ovarijske stimulacije rezultirala je drugačijim ishodom, bazirajući se na broju aspiriranih oocita. Protokol u kojemu su korišteni samo gonadotropini rezultirao je najvišom razinom estradiola, suprotno od protokola baziranog samo na inhibitorima aromataze, koji je rezultirao najnižom razinom estradiola. Kombinirani zajedno, gonadotropini i inhibitori aromataze rezultirali su drugom najvišom razinom estradiola. Porast doze FSH u protokolu nije uzrokovao višu razinu estradiola kao niti uspješniji tip respondera. *Zaključak.* Onkofertilitet je relativno novi dijagnostičko – terapijski pristup u medicini koji se postepeno razvija, što je vidljivo i kroz mali uzorak pacijentica uključenih u onkofertilitetni postupak, u periodu od 2013. do 2018. godine. Daljnje praćenje onkofertilitetnih pacijentica je nužno za donošenje preciznijih zaključaka.