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OVULATION INDUCTION AGENTS AND OVARIAN CANCER

INDUKTORJI OVULACIJE IN RAK JAJČNIKA

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Abstract – Background. *Ovarian cancer is the most frequent cause of death among gynecologic malignancies. Epidemiological data show that environmental, hormonal and genetic factors are etiologically significant. Beside the already known risk factors, ovulation induction agents have been reported as risk factors in literature since 1986. Over the last two decades, ovulation induction agents have been widely used in various assisted reproduction techniques (ART). This study focused on the question whether in patients receiving ovulation induction agents the risk for developing pathologic processes on the ovaries was higher than in those not receiving them, and whether they were related to the dose and type of ovulation induction agent.*

Methods. *In a prospective study 380 subjects were enrolled. The study group consisted of 280 women who had undergone an ART procedure three or more times. The control group consisted of 120 infertile women, never included in an ART procedure. All the enrolled subjects underwent the same examinations: a detailed gynecological history was taken, pelvic examination and vaginal ultrasound were performed, and a blood sample for tumour marker CA 125 determination was taken. Statistical analysis was done using Chi-square test, t test and logistic regression.*

Results. *Ultrasound examination revealed pathology on the genital tract in 136 women in the study group and in 60 women in the control group. Differences in the incidence of ovarian, tubal and uterine pathology were not statistically significant. The analysis of the medical records showed that the incidence of ovarian pathology was significantly higher in the study than in the control group ($p < 0.05$). We found no correlation between the incidence of ovarian pathology and type or dose of ovulation induction agent. Increased CA 125 levels were found in 12 women. In none of the women neither malignant nor borderline malignant disease was found.*

Conclusions. *Although the analysis of the data from medical history showed statistically higher incidence of ovarian pathology in the study than in the control group, clinical, ultrasound and biochemical examinations of the current health status showed no difference between the groups. Also, no correlation between ovarian pathology and type or dose of ovulation induction agent was found. We believe that the risk of ovarian malignancy due to ovulation induction agents is very small. For definitive answers large prospective studies are required.*

Ključne besede: *neplodnost; oploditev z biomedicinsko pomočjo; induktorji ovulacije; rak jajčnika*

Izvleček – Izhodišča. *Rak jajčnika je najpogostejši vzrok smrti med ginekološkimi malignimi obolenji. Epidemiološki podatki kažejo, da so etiološko pomembni dejavniki okolja, hormonski in genetski dejavniki. Ob že znanih dejavnikih se od leta 1986 v literaturi omenjajo tudi induktorji ovulacije (IO), ki se zadnji dve desetletji veliko uporabljajo v postopkih oploditve z biomedicinsko pomočjo (OBMP). Temelj naše raziskave je bilo vprašanje, ali je pri bolnicah, ki so dobivale IO, tveganje za nastanek patoloških procesov na jajčnikih večje kot pri bolnicah, ki IO niso dobivale, ter ali so ti odvisni od odmerka ali vrste IO.*

Metode. *V prospektivno študijo smo vključili 380 preiskovank. Študijsko skupino je sestavljalo 260 preiskovank, ki so bile v postopke OBMP vključene tri- in večkrat. Kontrolno skupino je sestavljalo 120 neplodnih preiskovank, ki v te postopke še niso bile vključene. Pri vseh preiskovankah smo opravili usmerjeno ginekološko anamnezo, ginekološki pregled, vaginalni ultrazvočni pregled ter odvzeli kri za tumorski marker CA 125. Statistično analizo rezultatov smo naredili s Studentovim t-testom, χ^2 testom ter logistično regresijo.*

Rezultati. *Z ultrazvočnim pregledom smo patološke procese na rodilih ugotovili pri 136 preiskovankah iz študijske skupine in 60 preiskovankah iz kontrolne skupine. Razlika v pogostnosti patoloških procesov na jajčnikih, jajcevodih in maternici ni bila statistično pomembna. Ko smo poleg ultrazvočnega izvida upoštevali tudi podatke o prejšnjih patoloških procesih, ki so nam bili na voljo iz popisov preiskovank, smo dobili naslednje rezultate: v skupini preiskovank, ki so že imele opravljene postopke OBMP, smo ugotovili statistično pomembno več patoloških procesov na jajčnikih kot v skupini, ki teh postopkov še ni imela ($p < 0,05$). Nismo ugotovili povezave med pogostnostjo patoloških procesov na jajčnikih in določeno vrsto oziroma odmerkom IO. Patološko vrednost CA 125 smo ugotovili pri 12 preiskovankah. Nismo ugotovili malignega ali mejno malignega procesa na jajčnikih.*

Zaključki. *Čeprav so imele ženske v študijski skupini v anamnezi pomembno več patoloških procesov na jajčnikih in jajcevodih kot ženske v kontrolni skupini, z ultrazvočnimi, kliničnimi in biokemičnimi preiskavami sedanjega zdravstvenega stanja med obema skupinama nismo ugotovili razlik. Prav tako nismo ugotovili povezave med pogostnostjo patoloških procesov na jajčnikih, ter vrsto ali odmerkom induktorjev ovulacije. Menimo, da je tveganje za nastanek raka jajčnika zaradi uporabe IO majhno. Za dokončne odgovore bodo potrebne velike prospektivne študije.*

Introduction

The issue of ovarian carcenogenesis related to ovulation induction agents is important for various reasons:
– Ovarian cancer is the most frequent cause of death among gynecologic malignancies.
– Ovulation induction agents have been increasingly used in infertility treatment.
– Some authors have correlated the development of ovarian cancer with ovulation induction agents.

Ovarian cancer

In the last decade the incidence of ovarian cancer has not increased significantly (1), but neither has its early detection. In spite of advances in knowledge and in diagnostic methods, a reliable screening test for ovarian cancer has not been made available yet. For its unspecific signs and symptoms, the disease has a bad prognosis, since 70% of the cases are detected in advanced stages (2). Little is known of biological nature of the disease, especially of the pace of its progress (3), and of etiology. Three main groups of etiological factors are genetic, hormonal and environmental (2). Numerous studies investigate individual reproductive factors and their influence on the risk for developing ovarian cancer. The risk is reduced by pregnancy, breast-feeding, and hormonal contraceptives. There are two hypotheses on the effect of reproductive factors on the risk of ovarian cancer.
Ovulation hypothesis was set by Fathalla in 1971. The repeated trauma of the epithelium, caused by ovulation, is quickly healed due to intensive cell replication and reparation (4). During reparation the so-called inclusion cysts, surrounded by epithelial cells, are formed. Due to quick division a mistake in recombinant DNA may occur in epithelial cells, which leads to malignant transformation (5).
Gonadotropin hypothesis. Stadel and Cramer (6, 7) pointed out that elevated gonadotropin concentrations affect the development of ovarian neoplasm either directly or indirectly. After the epithelial inclusion cyst has been formed, the epithelium is no longer separated from the follicular fluid with connective tissue (8) and becomes exposed to intraovarian steroids (9). It has been found that high doses of steroids in vitro stimulate cancerous ovarian cells as they have estrogen receptors on their surface. High gonadotropin levels affect the epithelial inclusion cysts via their affect on steroidogenesis (10, 11). These protective factors are supposed to function through lower number of ovulations, and through affecting the gonadotropin levels. The risk is increased by infertility and by nulliparity.
– Infertility is a risk factor independent of nulliparity (6). Many studies have found correlations between incapacity to conceive and ovarian cancer (12–15), the risk of ovarian cancer in infertile nulliparas thus being 1.8–6.5-times higher than in the women who have not tried to conceive yet (13).
– Nulliparity in itself increases the risk of ovarian cancer by 1.5–2 times (16).

Infertility treatment

According to the data provided by the World Health Organization (WHO) (17) about 10% of couples in developed countries are faced with infertility problems. The causes related to infertility are environmental factors, sexually transmitted diseases and postponed childbearing. The advances in science and new technologies such as laparoscopy, hysteroscopy, microsurgical techniques, have essentially contributed to improved diagnosis and treatment of infertility. Also, over the last few decades the use of drugs for interfering with the natural process of ovulation has increased: induction of ovulation, stimulation of ovulation and monitored ovarian hyperstimulation – ovulation-induction agents. Clomiphene citrate has been on the market since 1967, human menopausal gonadotropins since 1969. In the USA these drugs are estimated to be taken by 2 million women (12, 18). In vitro fertilization, first efficiently performed in 1977 resulting in delivery of a healthy baby girl, Louise Brown, the first test-tube baby in 1978, represents a truly revolutionary milestone. The increasing use of ovulation induction agents over many years has led to discussions of their potentially increasing risk of ovarian cancer.

Infertility treatment and cancer

First reports on ovulation induction agents as a risk factor of ovarian cancer date back to 1982 (19, 20). Ten years later Whittemore and co-workers (12) published the results of 12 retrospective controlled studies performed in the USA between 1956 and 1986, which aimed at finding a correlation between ovarian cancer and reproductive characteristics. Three of the analysed studies provided information on the use of ovulation induction agents. The risk of infertile patients, treated with ovulation induction agents, was by 2.8-times higher for developing invasive ovarian cancer, and 4-times higher for developing borderline malignant tumours (4 cases) than in fertile women. Infertile women who were treated by ovulation induction agents and conceived did not have a significantly higher risk of ovarian cancer (1.4-times). However, those infertile women who were treated and never conceived had a 27-times higher risk for ovarian cancer (12 cases found). Her report was received with variable responses and much criticism (incomplete data on the type and dose of ovulation induction agent, badly chosen control group (21).
Two years later a similar study was published by Rossing and co-workers (22) who found that the risk of invasive ovarian cancer and borderline malignant tumours was increased only with clomiphene citrate taken for more than 12 months. The risk was increased by 11.1-times in comparison with infertile women not receiving ovulation induction agents. It should be stressed that this increased risk was the same in patients with or without ovarian pathology and regardless of whether they were nulli- or multiparas.
Shushan and co-workers (23) did not find a statistically significant correlation between ovulation induction agents and invasive ovarian cancer, whereas borderline malignant tumours were statistically more often found in women receiving ovulation induction agents (3.52-times). The use of human menopausal gonadotropins (HMG) alone or in combination with other ovulation induction agents increased this risk for further 9.38-times, regardless of the duration of use. None of the reports published after 1994 found a correlation between invasive ovarian cancer and ovulation induction agents (14, 16, 24). In the study on 30,000 women, published in 1999, Venn and co-workers (25) did not find an increased risk of ovarian cancer in women receiving ovulation induction agents. There were short term increased risks of ovarian and breast cancer (1 year after the procedure), but the overall expected incidence was not increased. They found that the risk of ovarian cancer was increased in women with unexplained infertility in comparison with fertile women. Over 80 case reports have been published on the correlation between ovulation induction agents and ovarian malignancies (8, 9); in over one half of the cases borderline malignant tumours, which represent 10–15% of ovarian neoplasms, were found (23). In four reports a statistically significant increased risk of borderline malignant tumours after the use of ovulation induction agents was found (12, 22, 23, 25).

Over the last two decades various ovulation induction agents have been used at the Department of Obstetrics and Gynecology in Ljubljana (18). Monitored ovarian hyperstimulation has been used since the introduction of in vitro fertilization-embryo transfer (IVF-ET) in 1983. Between 1984 and the end of 1997, 4539 infertile couples were included in the IVF-ET programme, 302 new couples in 1997. In the same period, the number of cycles was 12,238. Approximately 2000 babies have been born following IVF procedure, of which almost 1000 in the last 4 years. These numbers provide definite evidence of the widespread use of ovulation induction agents in our institution.

Patients and methods

In the period 1996–1998 we performed a prospective study in which we included 380 women: 260 in the study and 120 in the control group. The aim of the study was to contribute to the pool of knowledge on potential effects of ovulation induction agents on ovarian cancer. We hypothesized that the incidence of benign, borderline malignant and malignant processes on the ovaries would be significantly higher in the study group of patients with a high number of previous IVF cycles than in the control group. We aimed at finding whether the women in the study group who had received ovulation induction agents had a higher incidence of pathological changes on the ovaries than the women who had not received this treatment, whether there was a correlation between pathological processes and type and/or dose of ovulation induction agent and to find characteristics of the population in the compared groups.

The inclusion criteria for the study group were 3 or more IVF procedures for primary or secondary infertility, the last procedure performed at least 1 year prior to enrolment; the patient had to be a permanent resident of Slovenia.

The control group consisted of women referred to the Department for infertility workup and had not received more than 6 cycles of oral contraceptives.

The patients were taken medical history, pelvic and vaginal ultrasound examinations were made, and a blood sample was taken for determination of serum marker CA 125. When the findings were pathological, an invasive procedure was performed (hysteroscopy, laparoscopy).

Statistical analysis was done using Chi-square test, and t-test was used to compare non-parametric variables. To find the effect of the type and dose of ovulation induction agent on pathological processes on the ovaries, logistic regression was used.

Results

The mean age of patients in the study group (n = 260) was 38.4 years; the mean duration of infertility was 8.7 years. The mean age of patients in the control group (n = 120) was 30.0 years; the mean duration of infertility was 3.2 years. The mean patient age and the mean duration of infertility differed significantly between the groups ($p < 0.001$). Tubal factor was the cause of infertility in 75.7% of the study group patients and in 34.2% of the control group patients, the difference being statistically significant ($p < 0.05$). The number of pregnancies (prior to ART procedure in the study and before diagnostic procedures in the control group) did not differ significantly between the groups.

In the study group ART resulted in 128 pregnancies that ended in 11 ectopics, 54 spontaneous abortions and 63 deliveries. Ultrasound revealed pathological changes on the genital tract in 136 women in the study and in 60 women in the control group. Regarding pathological processes on the ovaries the difference between the groups was almost statistically significant ($p = 0.06$) (Tab. 1).

Tab. 1. *Patients with pathology on ovaries, tubes and uterus found by vaginal ultrasound.*

Tab. 1. *Preiskovanke z ultrazvočno ugotovljenimi patološkimi procesi na jajčnikih, jajcevodih in maternici.*

Pathological changes on Patološki procesi	Study group Študijska skupina	Control group Kontrolna skupina	p
ovaries / jajčnikov	72 (27.7 %)	28 (23.3 %)	NS
tubes / jajcevodov	23 (8.8 %)	4 (3.3 %)	p = 0.06
uterus / maternice	41 (15.8 %)	24 (20.0 %)	NS

NS –not statistically significant
NS – statistično neznačilno

Due to pathological ultrasound findings, 59 women from the study group and 38 women from the control group were asked for a follow-up visit. Invasive procedure was required in 17 women from the study group and in 10 women from the control group (Tab. 2).

Tab. 2. *Pathological changes on ovaries and other parts of genital tract, found on ultrasound, requiring invasive procedures.*

Tab. 2. *Ultrazvočno ugotovljeni patološki procesi na jajčnikih in ostali patološki procesi na rodilih, zaradi katerih je bil potreben invazivni poseg.*

Pathological changes on Patološki procesi	Study group Študijska skupina	Control group Kontrolna skupina
ovaries / jajčnikov	6 (35.3%)	9 (34.6%)
other / ostalo	11 (64.7%)	17 (65.4%)

The difference in the number of procedures performed for ultrasound findings of pathological processes on the genital tract was statistically significant ($p < 0.001$) between the groups, yet the number of invasive procedures required for pathological processes on the ovaries did not differ significantly between the groups. The comparison of history data of pathological processes on the genital tract, showed a significantly higher rate of ovarian pathology in the study than in the control group (Tab. 3), taking into consideration totally or partially removed ovaries and tubes.

Tab. 3. *Pathological findings on ovaries.*

Tab. 3. *Patološki procesi na jajčnikih.*

	Study group Študijska skupina	Control group Kontrolna skupina	p
Before study Pred raziskavo	28 (10.7%)	4 (3.4%)	p < 0.05
During study Med raziskavo	72 (27.7%)	28 (23.4%)	NS
Total Skupaj	100 (28.4%)	32 (26.7%)	p < 0.05

Serum marker CA 125 level was increased (above 35 U/ml) in 12 women: in 9 from the study and in 3 from the control group. Control values were normal in 7 women, in 4 they remained increased, and in 2 even on the second follow-up visit. These two women underwent laparoscopy, which did not show neither borderline nor malignant disease. The study group women had had mean 5.4 ART attempts performed, the last one 3.4 years prior to our study. The number of ART attempts did not correlate with the incidence of ovarian pathology. The doses of drugs administered in the ART attempts are shown in Table 4. Neither any of the enumerated drug nor their combi-

nation was chosen for the predictive logistic model of ovarian pathology.

Tab. 4. *Doses of ovulation inductor agents.*

Tab. 4. *Odmerki zdravil.*

	Dose (X ± SD) Odmerek (X ± SD)	Highest-lowest dose Najmanjši – največji odmerek
Clomid (g)	2.8 ± 2.6	0.5–15
Metrodin HP (amp)	30.2 ± 19.1	13–87
Pergonal (amp)	102.6 ± 65.1	23–432
GF/RH (IU)	113.2 ± 78.1	12–108
Suprefact (ml)	15.1 ± 7.2	5.5–44

Suprefact – GnRH analog
GF – growth factor (RH – rastni faktor)

Human menopausal gonadotropin was administered to all study group women. The relationship between the dose and ovarian pathology is shown in Figure 1, demonstrating no effect of the doses on the incidence of pathology.

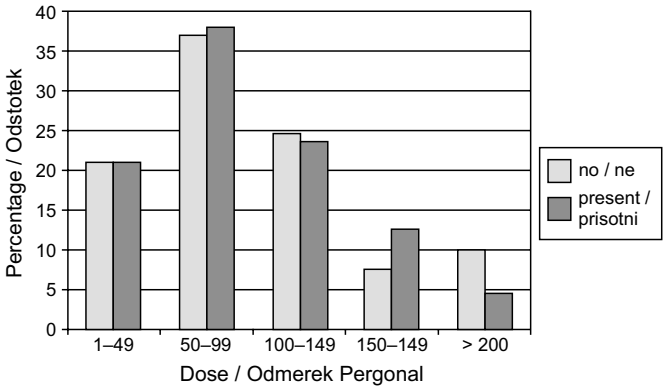

Fig.1. *Relationship between the dose of human menopausal gonadotropin and pathological findings on ovaries.*

Sl. 1. *Odnos med odmerkom humanega menopavznega gonadotropina in prisotnostjo patoloških procesov na jajčnikih.*

Discussion

From the inclusion criteria set for the study and control group we expected certain characteristics to differ significantly between the groups. The study group women were by mean 8 years older and had been receiving infertility treatment for 5 years longer than the control group women. Comparison between the groups showed that the current treatment of infertility is less expectative, the mean age at the first ovarian stimulation being 27 years.

The fact that in the control group there were significantly fewer cases of tubal infertility than in the study group reflects the wider range of indications considered nowadays for this type of treatment at our Department. Improvement of diagnostic and therapeutical procedures has lead to the changed indications for ART procedures; in the past the prevailing indication was tubal factor of infertility, whereas nowadays over 40 % of couples are included in ART procedures for male or combined infertility. Prior to an ART procedure ovarian stimulation can be prescribed alongside with sexual intercourse. Besides, some patients had had ovarian stimulation administered for subsequent intrauterine insemination. From the records we obtained the data on the use of clomiphene citrate, often prescribed by the general practitioner; nowadays it is on the average prescribed 4-times, whereas in the past it was prescribed 9-times. Due to the inclusion criteria for the study group (high number of procedures), the success rate was lower than was the average of the last 10 years. The pregnancy rate was 37 %, 49 % of pregnancies ended in a delivery. The comparison of the incidence of benign, borderline malignant and malignant changes on the ovaries showed no statistically significant differences between the groups. The most frequent pathology were polycystic ovaries, less frequent were cystic and solid changes on the ovaries. It should be emphasized that prior to this study (medical history), ovarian pathology was significantly more frequent in the study group ($p < 0.05$). Ovarian pathology was classified as partly or totally removed ovaries. There are more possible explanations for this fact: benign processes may have occurred under the influence of ovulation induction agents in ART procedures, they were present already before the introduction of ART procedures, but were not recognized during reconstructive procedures on the ovaries, but most likely it is due to the fact that conservative surgical treatment was more often an exception than a rule in the past. Among pathological changes the most frequent was hydrosalpinx**.** Its high incidence in the study group may partly explain low success rate and high abortion rate in ART procedures. Among uterine pathologies, the most frequent were congenital malformations. It is surprising that their incidence was almost the same in both groups, although the study group patients had had all diagnostic procedures made prior to ART. Additionally to advances in the diagnosis, the approach to treatment has also changed: over these last few years their influence on the occurrence of preterm delivery has been proven (26). Pathologic levels of serum marker CA 125 was found in 12 study group patients; in 7 of them ultrasound revealed the changes that, according to literature (27), can increase its level. The remaining 5 patients were followed until the finding was normal or they had to undergo an invasive diagnostic procedure. The quantitative correlation between the rate of pathological processes and each drug, as well as the dose used showed that none of the agents could be included into the predictive logistic model. Most authors have obtained similar results, with the exception of the studies by Rossing (22) and Shushan (23). Over the last 30 years the incidence of ovarian cancer has not changed significantly, in spite of a wider use of ovarian stimulating agents in this period, which does not imply their cancerogenous effect (28). It is important to note that it is only now that most receivers of ovulation induction agents are reaching the age in which the ovarian cancer incidence is the highest (29). Most authors are still striving to elucidate the mechanism through which ovulation induction agents trigger ovarian cancer. None of the above mentioned theories explain the correlation in its totality. It is possible that the repeated trauma itself, caused by ovarian aspiration in ART procedures, is harmful. Besides the mechanical activity, the natural events in the ovary are interrupted, since on ovarian aspiration, granulosa cells are aspirated as well, which prevents luteinization and the formation of the corpus luteum. It is very likely that the combination of events leads to malignant transformation. Some authors are of the opinion that a relation between ovulation induction agents and the development of borderline malignant diseases is more likely (12, 22, 23, 25), since their incidence has been increasing since 1970 (12). In Israel, for example, their incidence doubled between 1985 and 1993, which is ascribed to a wider use of ovulation induction agents (30). Further, it has not been found yet, whether a borderline malignant tumour becomes malignant or not (23). Borderline malignant tumours are supposed to be extremely dependent on hormones. Very often estrogen receptors are found on their surface (30). Infertility may be a sign of an occult cancer (31), or they can both originate from a genetic anomaly. Thus, close female relatives of infertile women, who had not conceived despite a treatment, are supposed to be at increased risk for the development of can-

cer (32). We are well aware that we did not find an ideal control group in this study. Actually, this would be a group of women matched by age, reproductive characteristics, and by cause of infertility without being ever included in an ART procedure. In practice, however, this is impossible to achieve, or, if it were, it would not be ethically justified. The control group could also consist of a group of women, receiving an ART treatment due to partner's infertility. In this way, we could differentiate between the effect of infertility itself and cause of infertility drugs on the development of cancer.

Conclusions

The records showed that the study group patients had significantly more benign pathologic processes on the ovaries than the control group women. However, clinical and ultrasound examinations at the time of the study did not show significant differences. Additionally, no correlation was found between the incidence of ovarian pathology and the type/dose of ovulation induction agent. In the study group no malignant or borderline malignant ovarian disease was found. Thus, we think the risk of ovarian cancer in ovulation induction agent users is low.

In spite of only a few studies that have found a correlation between ovarian cancer and the use of ovulation induction agent, the causal correlation cannot be stated. The problem is objectivization, since ovarian cancer is relatively rare, and even rarer in connection with the use of ovulation induction agent. Numerous factors have been recognized to affect the basic risk (30). Further prospective studies on a large number of cases are required to find a causal relation between ovulation induction agents and invasive/borderline malignant cancer. Until the results are made known, a rational use of ovulation induction agents is recommended and thorough information to the patient on potential risks should be provided. Besides, it would be reasonable to continuously follow the patients receiving ovulation induction agents, especially those having a hereditary predisposition.

We should not forget that the natural cycle is a promising option.

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