



NINTH INTERNATIONAL
CONFERENCE ON RADIATION
IN VARIOUS FIELDS OF RESEARCH

June 14-18, 2021 | Hunguest Hotel Sun Resort | Herceg Novi | Montenegro

CASE OF *OVARIAN CANCER AFTER IN-VITRO
FERTILIZATION.*

FORENSIC MEDICAL MALPRACTICE.
CLINICAL CASE AND DATA REVIEW

AUTHORS: R. HADJIEV^{1*}, M. TANKOVA¹, M. TAUSHANOVA², L. DAMYANOV³

1 – MULTIFUNCTIONAL HOSPITAL FOR ACTIVE TREATMENT 'LOZENETZ', DEPARTMENT OF FORENSIC MEDICINE, SOFIA, BULGARIA

2 – UNIVERSITY HOSPITAL 'TSARITSA YOANNA – ISUL', DEPARTMENT OF ONCOLOGY, SOFIA, BULGARIA

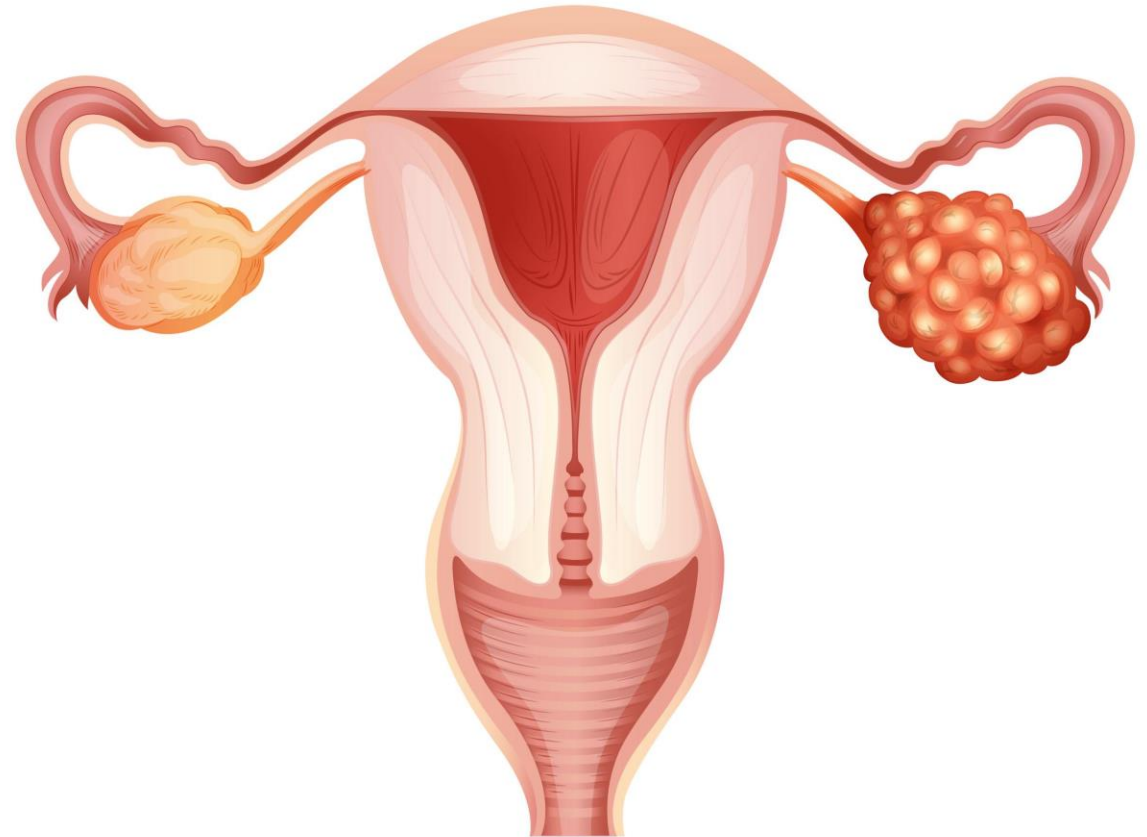
3 – HEALTH CENTER FOR HUMAN REPRODUCTION, SOFIA, BULGARIA



OVARIAN CANCER

Ovarian cancer is a **leading cause of death amongst women.**

It accounts for more deaths than any other cancer of the female reproductive system.



Source: Pintas & Mullins, Available Types of Treatment for Ovarian Cancer



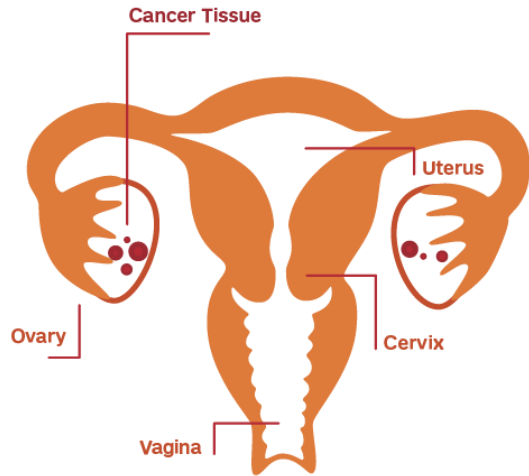
RISK FACTORS FOR OVARIAN CANCER

- ✓ **Extreme hormonal stimulation;**
- ✓ **In-vitro fertilization (IVF);**
- ✓ **Family history of cancer;**
- ✓ **Genetic mutations (BRCA-1 & BRCA-2 genes);**
- ✓ Pregnancy after 35 years;
- ✓ Lack of pregnancy;
- ✓ Early menarche;
- ✓ Late onset of menopause;
- ✓ Oral contraceptives;
- ✓ Hormone therapy after menopause;
- ✓ Obesity, etc.



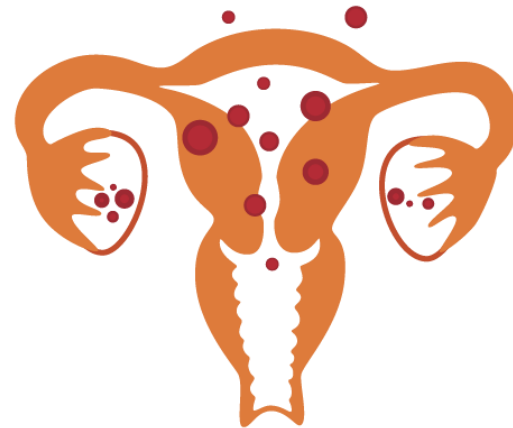
OVARIAN CANCER STAGING

Stage 1



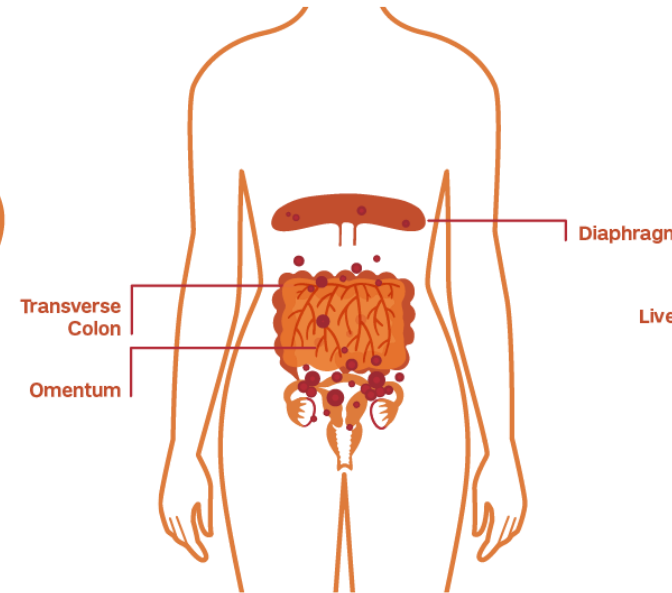
Cancer is found in one or both ovaries.

Stage 2



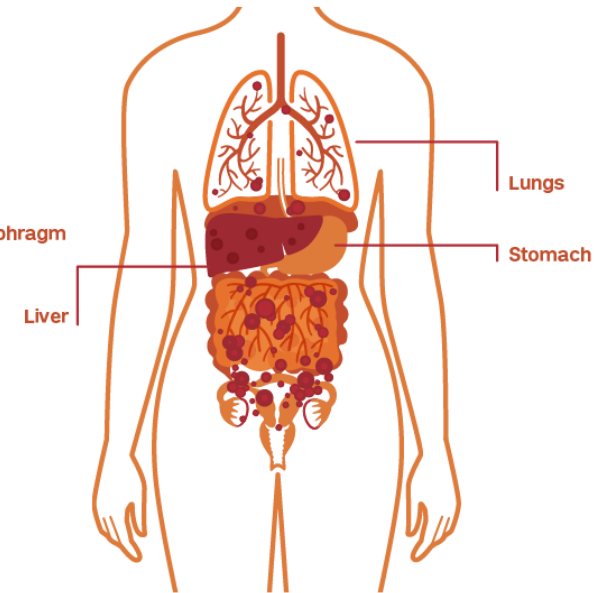
Cancerous cells have spread from the ovaries to other parts of the pelvis, such as the fallopian tubes or uterus.

Stage 3



Cancerous cells have spread outside the pelvis to the nearby lymph nodes, diaphragm, intestines, or liver.

Stage 4



The cancer has spread beyond the abdomen, such as to the lungs or spleen.



IN-VITRO FERTILIZATION (IVF)

In-vitro fertilization procedures (IVF) are a part of the **assisted reproductive technologies (ART)**. IVF includes:

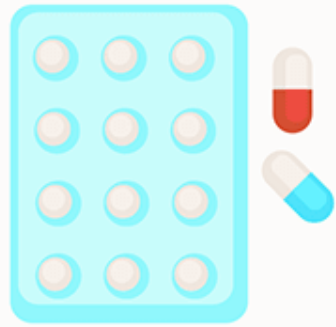
1. *Stimulation of the ovaries to obtain several eggs;*
2. *Follicular puncture to retrieve the eggs;*
3. *Fertilization of the eggs outside the body;*
4. *Implanting the eggs in the woman's body.*



IVF is used to treat infertility in women with different health conditions.

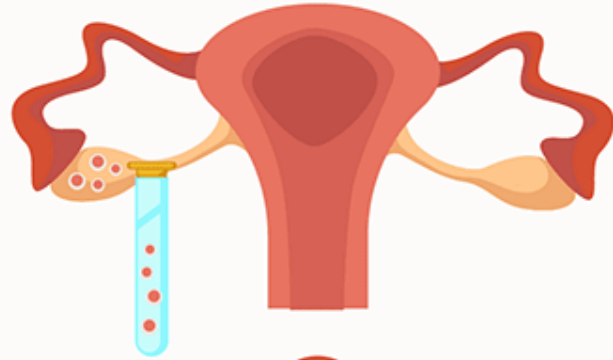


IN-VITRO FERTILIZATION (IVF) PROCEDURE



1

OVARIAN
HYPERSTIMULATION



2

EGG
RETRIEVAL



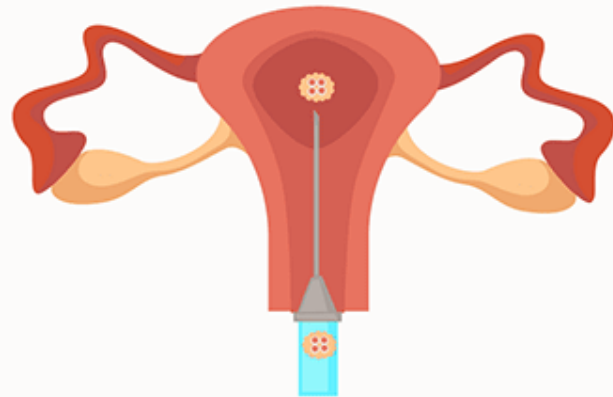
3

SPERM
PREPARATION



4

CO-INCUBATION



5

EMBRYO
TRANSFER



6

PREGNANCY

Source: In Vitro Fertilization (IVF): Side Effects and Risks, Laurel Fertility Care



HYPER STIMULATION & CARCINOGENESIS

There are known cases of **cystic and malignant formations in the ovaries**, as well as **Ovarian hyper stimulation syndrome**, after IVF procedures due to the usage of *ovulation stimulating drugs* such as gonadotropins, SERM (Selective estrogen receptor modulators), Clomiphene Citrate, etc.

There is a theory that ***hyper stimulation with the purpose of provoking repeated ovulations lead to malignant transformation of the ovarian parenchyma.***



CASE REPORT



A **45-year-old woman** with *no family history of cancer*, with almost diminished ovarian reserve started **IVF procedures** with the first two attempts being unsuccessful.

The subsequent IVF attempt was successful and embryo transfer was completed. The patient had a normal pregnancy and delivery at 39 weeks of gestation of a healthy fetus via Cesarean section.

The doses of the **hormone medications** that were used – *Merional* (**highly purified Human Menopausal Gonadotrophin (HMG)**) and *Cetrotide* (***Cetrorelix Acetate***), do not exceed the recommended values.



CASE REPORT



Three months later, during a gynecological ultrasound examination, formations were found (*unilocular cysts*) as follows:

✓ **30.5 mm in the right ovary & 20.0 mm in the left ovary.**

Tumor markers testing:

- ROMA (Risk of Ovarian Malignancy Algorithm) – **12.36%** (ref. <11.4%);
- Ca-125 – **37.34** (ref. <35);
- HE4 – 61.8 (ref. <70).



CASE REPORT



Therapy with ***Dufaston (Dydrogesterone)*** 2x1 tab. was prescribed with the assumption that the ovarian cysts indicate Luteinized unruptured follicle (LUF) syndrome.

After another 3 months, during a gynecological ultrasound examination it was established that **the formations persisted**:

✓ **49.0 mm in the right ovary & 15.0 mm in the left ovary.**

Regulon (Ethinylestradiol/ Desogestrel) 1x1 tab. was included in the therapy.



CASE REPORT



Half a year later, the patient was hospitalized because of a **sudden bloating** and **pain in the lower abdomen**.

Ultrasound diagnostics revealed **a formation** measuring **25 cm/ 15 cm**, with heterogeneous echogenic content, occupying almost the entire abdominal cavity.

The tumor markers indicated as follows:

- Ca-125 – **38.54** (ref. <35);
- HE4 – **106.3** (ref. <70).



CASE REPORT



A **total hysterectomy with bilateral tumor adnexectomy** was performed.

During the surgery **two formations were found:**

- ✓ A solid formation **from the right ovary** with dimensions **25 cm/ 25 cm;**
- ✓ a solid formation **from the left ovary** with dimensions **5 cm/ 5 cm.**

Histological examination confirmed the diagnosis:

- **Malignant Mixed Müllerian Tumor**, FIGO IB, pT1bNxMx.



CASE REPORT



Adjuvant chemotherapy was prescribed: *six courses of Carboplatin AUC 6 + Paclitaxel 175 mg/m²* with an interval of 21 days between the courses.

With the disease progression after first-line chemotherapy *Ifosfamide 1,500mg/m² + Etoposide 100mg/m³* 1-3 days was prescribed.

A BRCA-1 and BRCA-2 genetic mutation test was performed, and the result was **negative**.



CASE REPORT



In this particular clinical case, in addition to the development of ovarian cancer, an object of interest is *the delayed diagnosis of the malignant process (ovarian cancer)*, respectively its untimely staging and treatment.

Lack of regular ultrasound and tumor markers examinations as well as the neglected data from the already performed ones are an omission of the physician.



CONCLUSION

Each IVF procedure needs to be tailored to the individual patient with regards to the specific health conditions.

It is a necessity for a ***detailed medical history of inherited oncological diseases*** to be established, as well as for ***genetic testing of BRCA-1 and BRCA-2 mutations*** to be performed.

The **strict and regular disease control** is important if pathological changes are confirmed. It is a mandatory condition for implementing a good clinical practice.



CONCLUSION

IVF procedures should be performed by physicians who are highly qualified in the field.

Each clinical case should be managed particularly and in considering to the patient's individual needs and preferences. This ensures reliability for the absence of medical malpractice and an unfavorable outcome for the patients.



REFERENCES

1. D Farhud D, Zokaei S, Keykhaei M, Zarif Yeganeh M. (2019). *Strong Evidences of the Ovarian Carcinoma Risk in Women after IVF Treatment: A Review Article*. 48(12):2124-2132. [Iran J Public Health] [PubMed]
2. Mohan S Kamath, Abha Maheshwari, Siladitya Bhattacharya, Kar Yee Lor, Ahmed Gibreel. (2017). *Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization*. 11(11):CD008528 [PubMed]
3. Mochtar MH, Danhof NA, Ayeleke RO, Van der Veen F, van Wely M. (2017). *Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles*. 5(5):CD005070 [PubMed]
4. Pacchiarotti A, Selman H, Valeri C, Napoletano S, Sbracia M, Antonini G, Biagiotti G, Pacchiarotti A. (2016). *Ovarian Stimulation Protocol in IVF: An Up-to-Date Review of the Literature*. 17(4):303-15. [PubMed]



REFERENCES

5. Del Pup L, Peccatori FA, Levi-Setti PE, Codacci-Pisanelli G, Patrizio P. (2018). *Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors*. 22(22):8042-8059. [PubMed]
6. Rizzuto I, Behrens RF, Smith LA. (2013). *Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility*. 2013(8):CD008215. [PubMed]
7. Zafeiriou S, Loutradis D, Michalas S. (2018). *The role of gonadotropins in follicular development and their use in ovulation induction protocols for assisted reproduction*. 5(2):157-67 [PubMed]
8. Zhao J, Li Y, Zhang Q, Wang Y. (2015). *Does ovarian stimulation for IVF increase gynaecological cancer risk? A systematic review and meta-analysis*. 31(1):20-9. [PubMed]



REFERENCES

9. Siristatidis C, Sergentanis TN, Kanavidis P, Trivella M, Sotiraki M, Mavromatis I, Psaltopoulou T, Skalkidou A, Petridou ET. (2013). *Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer--a systematic review and meta-analysis*. 19(2):105-23. [PubMed]
10. Tsafrir A, Lerner-Geva L, Zaslavsky-Paltiel I, Laufer N, Simon A, Einav S, Eldar-Geva T, Holzer H, Gal M, Hirsh-Yechezkel G. (2020). *Cancer in IVF patients treated at age 40 years and older: long term follow-up*.40(3):369-373. [PubMed]
11. Vassard D, Schmidt L, Glazer CH, Lyng Forman J, Kamper-Jørgensen M, Pinborg A. (2019). *Assisted reproductive technology treatment and risk of ovarian cancer-a nationwide population-based cohort study*. 34(11):2290-2296. [PubMed]



REFERENCES

12. Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. (2013). *In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk*. 128(2):260-4. [PubMed]
 13. A Venn 1, L Watson, J Lumley, G Giles, C King, D Healy. (1995). *Breast and ovarian cancer incidence after infertility and in vitro fertilization*. 346(8981):995-1000. [PubMed].
-

THANK YOU
FOR YOUR ATTENTION!