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Risk of ovarian cancer in women using ovarian induction protocols for infertility treatment.

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ABSTRACT

Abstract: *Cancer is rapidly becoming a major cause of morbidity and mortality worldwide, & Infertility has been found to be an important risk factor for ovarian cancer. However, the association between infertility drugs and ovarian cancer needs to be addressed with consideration of other factors such as age, body mass index, parity, genetic factors (i.e. family history for ovarian cancer), and etiology of the infertility, along with longer follow - up times*

Aim of the study:*To rule out or to prove that; the ovulation induction in infertility treatments and can cause ovarian cancer .*

Design: *Retrospective randomized study*

Setting: *Data were obtained from the patient records of those who were diagnosed as ovarian problem, which indicate surgical intervention, at lamis hospital for infertility & Gyn. Misurata -libya. From January 1, 2017 to December 31, 2023. (seven years). Our study contained 110 patients operated with ovarian tumors & 3608 patients treated for infertility by ovulation induction drugs & icsi .*

Results: *The age range of patients with ovarian tumors in our study was from 24 to 72 years, and the highest incidence of ovarian tumors was seen between 46 to 60 years. Most of the patients were at postmenopaus. More than half of the patient with ovarian pathology (58.2%) were multiparous; while nulliparous & patients delivered up to three kids were 8.2% & 33.6% consecutively. The main complain that the patient with ovarian pathology presented with abnormal vaginal bleeding (38.2%) ,lower abdominal pain (26.4%), abnormal vaginal discharge (23.6%) & pelvic mass (21.8%), Some patients were with more than one complains. Only two patient out of 110 included at this study , received ovulation induction drugs (1.8%), while 98.2% of patient with ovarian pathology they never use any drugs for ovarian stimulation. Out of (110) patient there 38 patient were their diagnosis confirmed by histopathology as ovarian cancer of different types, tow patients were received ovulation induction drugs.*

Only one of them with history of icsi & ovum retrieval (1/3608) I.e. 0.027%, she also had family history of breast cancer.(3608 are the number of cases done ovum retrieval for icsi at lamis infertility clinic at the period from January 2017 up to December 2023.)

***Conclusions**: Although ,the question of whether ovarian stimulation increases the incidence of ovarian cancer, as an independent factor remains unanswered , We confirmed that ovulation induction drugs as treatment of infertility & ovum retrieval for icsi are not a risk factors for ovarian cancer, and we observed no increase incidence of ovarian cancer , Further larger studies are recommended to confirm such findings*

Keywords: Subfertility, Fertility drugs, ovarian cancer, intracytoplasmic sperm injection (icsi).

Introduction:

Subfertility has been defined as failure to conceive after frequent unprotected sexual intercourse for one year in the absence of known causes of subfertility (19). The prevalence of subfertility in Western societies ranges from 3% to 33% (7).

Drugs to stimulate ovulation have been used to treat subfertility since the early 1960s Fertility drugs are used during the follicular phase of the menstrual cycle to increase the serum concentration of gonadotrophins, with the aim of promoting maturation of multiple follicles and consequently multiple ovulations. Commonly used ovulation induction agents include:

1. anti oestrogens, such as clomiphene citrate;
2. tamoxifen, a selective oestrogen receptor modulator (SERM);
3. human menopausal gonadotrophin (urinary HMG. H.P), which contains follicle stimulating hormone (FSH) and luteinizing hormone;
4. human chorionic gonadotrophin (HCG);
5. gonadotrophin releasing hormone agonist (GnRH AG); (6) gonadotrophin releasing hormone antagonist (GnRH A);
6. purified FSH;(urinary & recumbent).
7. letrozole, which is a third generation aromatase inhibitor (8,9,10).

These hormones are used either alone or in combination depending on the cause of infertility and the protocol used. In our center (Lamis IVF center) we use non pituitary down regulation HP HMG protocol for ovulation induction .In addition, other fertility drugs used in most regimens of assisted reproductive technologies, such as in vitro fertilisation (IVF &ICSI), include progesteron to support the luteal phase of the menstrual cycle (19).

For isolated anovulatory infertility, letrozole and clomiphene citrate alone or in combination with metformin are currently preferred drugs (26).

There is uncertainty about the safety of these drugs and their potential risk of causing cancer. Moreover, it has already been shown that infertility itself increases the risk of ovarian cancer.(11)

The most significant risk factors for ovarian cancer is inherited genetic mutation in one of two genes: breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2) . other Risk factors for cancer ovary include: having a multiple pregnancy or birth (twins, triplets or more) ,ovarian hyper stimulation syndrome ,having an ectopic pregnancy ., possible

birth defects (these are rare and research is still ongoing).

Aim of the study:

To prove that; the ovulation induction in infertility treatments and its complication can cause ovarian cancer .

Design:

Retrospective randomized study

Setting:

Data were obtained from the patient records of those who were diagnosed as ovarian disease. which indicate surgical intervention ,at lamis hospital for infirtility & Gyneacology Misurata -libya. from January 1, 2017 to December 31,

2023(seven years).Our study contained 110 patients operated for ovarian tumors .& 3608 patients treated for infirtlity by ovulation induction drugs for ICSI

Different parameters were recorded for each patient specifically, including age, city ,parity ,infertility ,ovulation induction drugs, ovum retrieval for icsi & type of ovarian pathology.

Results:

Distribution of the patient with ovarian pathology according to age group

Age group	15-30yrs	31-45yrs	46-60yrs	≥61yrs	Total
No	6	17	70	17	110
%	5,5%	15.5%	63.6%	15.5%	100%

The age range of patients with ovarian tumors in our study was from 24 to 72 years,(the median =48years) and the highest incidence of ovarian tumors seen were between 46 to 60 years. The most of the patients were in postmenopausal period . On the other hand, there were no patients less than 21 years old.

Distribution of the patient with ovarian pathology according to parity:

No of delivery	Nullipara	P1-p3	≤4
No	9	37	44 total (110)
%	8.2%	33,6%	58.2%

More than half of the patient with ovarian pathology (58.2%) were multiparous , while nulliparous & who delivered up to three kids were 8.2% & 33.6% consecutively.

Distribution of the patient with ovarian pathology according to complain of the patients:

Complain	Pain	p/v bleeding abnormal	Abnormal vaginal discharge	Pelvic mass	total
No	29	44	46	44	110
%	26.4%	38,2%	23,6%	21,8%	

The main complain that the patient with ovarian pathology presented with were abnormal vaginal bleeding (38.2%) ,lower abdominal pain (26.4%), abnormal vaginal discharge (23.6%) & pelvic mass (21.8%), Some pt present with more than one complain.

Distribution of the patient with ovarian pathology according to receiving infertility treatment & ovarian stimulation drugs:

	Infertility drugs	No drugs	Total
No	2	101	110
%	1.8%	98.2%	

Only two patient out of 110 included at this study , received ovulation induction drugs (1.8%), while 98.2% of patient with ovarian pathology they never use any drugs for ovarian stimulation.

Distribution of the patient according to type of ovarian pathology:

Pathology	Benign	Malignant	Total
No	72	38	110
%	65.5%	34.5%	

Out of (110) patient there 38 patient were their diagnosed & confirmed by histopathology as ovarian cancer of different types, only two patients were received ovulation induction drugs. Only one of them with history of icsi & ovum retrieval (1/3608) I.e. 0.027%, (prevalence of 0.8%) this patient had family history of breast cancer.(3608 are the number of cases done ovum retrieval for icsi at lamis infertility clinic at the period from January 2017 up to December 2023.)

Discussion:

Ovarian cancer is a relatively rare outcome; it occurs most often late in life - many years after normal childbearing age or completion of fertility therapy. Furthermore, Studies in Benghazi Libya area showed that ovarian cancer cases represented 13% (1). there is uncertainty over the role of various drugs because limited information is available on their different potential effects. Fertility medication stimulates multiple oocytes so there is simultaneous maturation and ovulation during a single cycle. This serves to increase the mechanical trauma and the number of epithelial inclusions in the surface epithelium of the ovary (11). It has been estimated that a single cycle of ovulation induction in preparation for IVF can be equivalent to two years of normal menstrual cycles, in terms of the number of follicles produced and the oestrogen concentrations achieved (3). However, some epidemiological studies contradict this link (16). The risk of ovarian cancer in these studies was increased in women with ovulatory disturbances (either lack of ovulation or reduction in the number of ovulations over one year), while according to the 'incessant ovulation' theory, these women would have been expected to have reduced risk of ovarian cancer. Moreover, Balasch 1993 critically reviewed the literature concerning follicular stimulation and ovarian cancer and concluded that even if an association between ovulation induction and ovarian cancer was found, this would not necessarily indicate an effect of ovarian stimulation. A more likely explanation is that an underlying ovulatory disorder or the absence of pregnancy predisposes the woman to cancer of the ovary (6).The gonadotrophin hypothesis - proposes a model in which persistent stimulation of gonadotrophins increases the risk of malignant changes directly, or by acting in combination with a raised concentration of oestrogen (23). Nevertheless, these data do not prove the existence of a causal relationship between iatrogenically raised serum gonadotrophin concentrations.Another hypothesis frequently suggested is that undiagnosed early ovarian cancer causes, in some manner, subfertility. This hypothesis was based upon epidemiological data that showed an increased rate of subfertility among women with ovarian cancer (10,26). Some studies suggest that the risk of ovarian tumours is not increased among women with primary infertility who do not undergo fertility treatment (4, 23, 24,30,32). However, it remains difficult to provide reassurance to subfertile women regarding their risk of developing an ovarian tumour due to exposure to fertility treatment. An evaluation of risk factors for ovarian cancer was published in a combined analysis of 12 US case - control studies of ovarian cancer diagnosed between 1956 and 1986 and conducted by the Collaborative Ovarian Cancer Group (US) (26). Only three of the 12 studies examined the association between the use of fertility drugs and invasive ovarian cancer; the others

evaluated different reproductive and menstrual risk factors. This study showed a 2.7 - fold increased risk of ovarian cancer in subfertile women who had used fertility drugs as compared to those who had not used these drugs, and a 27 - fold higher risk in subfertile women who had never been pregnant compared to subfertile women who had been treated and conceived. a large cohort study also suggested increased risk of invasive and borderline ovarian tumours among women using clomiphene citrate for 12 months or longer (24). This finding was confirmed by other studies (25,29) In contrast, several other epidemiological studies failed to confirm the above findings and showed no association between women exposed to treatment with ovulation - inducing drugs and untreated infertile women (14,15,16,24). some studies suggest that *BRCA* mutation carriers may have decreased ovarian reserve compared with women without *BRCA* mutations, as well as an earlier natural menopause (33). This may impact the fertility and reproductive health of *BRCA* mutation carriers; therefore two studies have looked at any relationship between fertility drugs and ovarian cancer in these groups of women (34; 35). At our study , out of 110 patient with different types of ovarian lesions, only two patient were with history of infertility & they received infertility drugs (1.8%) ,at which only one of them had history of ovum retrieval for icsi . (0.9%). out of 3608 cases done ovum retrieval for icsi at lamis infertility clinic over the same period seven years(January 1, 2017 to December 31, 2023.) , Also there was only one patient developed ovarian cancer (. 0.027%,), that patient was with family history of breast cancer, this is not significant .which is may be related to *BRCA* mutation carriers more than to infertility drugs.

Conclusions:

Although ,the question of whether ovarian stimulation increases the incidence of ovarian cancer, as an independent factor remains unanswered , We confirmed that ovulation induction drugs as treatment of infertility & ovum retrieval for icsi are not a risk factors for ovarian cancer, and we observed no increase incidence of ovarian cancer , Further larger studies are recommended to confirm such findings.

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