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Fertility treatments and breast cancer risk: A case control-retrospective study

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Abstract

Objective: To investigate a possible association between fertility treatments and breast cancer (BC) risk in Greek women.

Material-Methods: A series of 391 women who visited two breast clinics in Greece were studied in our case-control retrospective study. The case group comprised 238 women with BC, while the control group had 153 women without BC. All participants were examined clinically and also with breast ultrasound, while those aged over 40 years underwent digital bilateral mammography. All women answered a questionnaire about whether they had received fertility treatment.

Results: Using the Chi-square test, there appears to be no significant statistical association between fertility treatments and BC (p=0.178).

Conclusion: This study did not find a significant association between fertility treatments and BC risk. Further studies with a larger number of patients are mandatory in order to confirm this result. Women considering fertility treatments such as IVF should be informed that it does not appear to increase BC risk.

Keywords: Breast cancer; Infertility; Fertility treatments; Assisted Reproductive Technology (ART); In Vitro Fertilization (IVF); Breast cancer risk factors.

1. Introduction

Among reproductive age women worldwide, BC is the most prevalent type of malignancy **[1]**. Approximately 48.5 million couples all over the world, may have difficulties to "get pregnant", and many children especially in developing countries are born with the help of fertility treatments **[2-3]**. At least 9% of couples are predicted to encounter infertility in some way, and 56% of these couples will look into medical options for treatment **[4]**.

Nowadays, the mean maternal age at first birth is trending upwards **[5]** with the mean age approaching 30 years in several European countries and many women are delivering their first child aged 35 years or older. It is also well known that fertility in women declines with increasing age, having as a result turned to assisted reproductive technology (ART), such as in vitro fertilization (IVF) **[6]**.

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The link between infertility and BC risk is controversial. It is well-known that fertility drugs stimulate the ovaries, causing an increase in estrogen levels. Because high levels of estrogen are linked to BC risk, it has been suggested that the use of fertility drugs may also increase BC risk **[3, 7]**.

Several epidemiological studies suggest that infertility due to anovulatory disorders reduces BC risk **[8]**. However, other studies have observed either no association or a slight increase in risk associated with infertility after adjusting for other factors, such as age at first full-term pregnancy **[9]**.

As a result of the current conflicting literature, we performed a case-control retrospective study to evaluate whether there is a causal association between different fertility therapies and BC.

2. Material and methods

A series of 391 women who visited two breast clinics in Greece were studied in our case-control retrospective study. The case group comprised 238 women with BC, while the control group had 153 women without BC. All participants were examined clinically and also with breast ultrasound, while those aged over 40 years underwent digital bilateral mammography. All women answered a questionnaire about whether they had received fertility treatment.

The two different groups were assessed in the same period of time, after a written informed consent. The information regarding fertility treatment and the possible relationship with the presence or absence of BC was analyzed using SPSS 20 software. Additionally, the p-value was calculated using the Chi-square test (X^2). If the p-value was 0.05 or less, the result was deemed statistically significant.

3. Results

Of the 391 study participants, 374 (95.7%) had not undergone fertility treatment. Of these, 225 (60.2%) were patients and 149 (39.8%) were healthy. 17 of the 391 study participants (4.3%) had undergone fertility treatment. Of these, 13 (76.5%) were patients, while 4 (23.5%) were healthy.

Table 1 Number of patients who had undergone fertility treatment

Fertility treatment * CASE/CONTROL Crosstabulation					
			Case/Control		**Total**
			BC Patients	Healthy	
Fertility treatment	No	Count	225	149	374
		% within Fertility treatment	60.2%	39.8%	100.0%
		% within CASE/CONTROL	94.5%	97.4%	95.7%
		% of Total	57.5%	38.1%	95.7%
	Yes	Count	13	4	17
		% within Fertility treatment	76.5%	23.5%	100.0%
		% within CASE/CONTROL	5.5%	2.6%	4.3%
		% of Total	3.3%	1.0%	4.3%
Total		Count	238	153	391
		% within Fertility treatment	60.9%	39.1%	100.0%
		% within CASE/CONTROL	100.0%	100.0%	100.0%
		% of Total	60.9%	39.1%	100.0%

Table 2 Testing the association of fertility treatment with BC risk

Chi-Square Tests					
	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	1.816[a]	1	0.178		
Continuity Correction[b]	1.196	1	0.274		
Likelihood Ratio	1.942	1	0.163		
Fisher's Exact Test				0.212	0.136
Linear-by-Linear Association	1.811	1	0.178		
N of Valid Cases	391				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.65.					
b. Computed only for a 2x2 table					

Table 3 Percentage distribution of fertility treatment used

If yes, which fertility treatment was used?					
			CASE/CONTROL		**Total**
			BC Patients	**Healthy**	
If yes, which treatment?	**IVF with natural cycle**	Count	0	1	1
		% within If yes, which fertility treatment was used?	0.0%	100.0%	100.0%
		% within CASE/CONTROL	0.0%	25.0%	5.9%
		% of Total	0.0%	5.9%	5.9%
	IVF with ovulation induction	Count	2	1	3
		% within If yes, which fertility treatment was used?	66.7%	33.3%	100.0%
		% within CASE/CONTROL	15.4%	25.0%	17.6%
		% of Total	11.8%	5.9%	17.6%
	Insemination only	Count	5	0	5
		% within If yes, which fertility treatment was used?	100.0%	0.0%	100.0%
		% within CASE/CONTROL	38.5%	0.0%	29.4%
		% of Total	29.4%	0.0%	29.4%
	IVF and insemination	Count	2	1	3
		% within If yes, which fertility treatment was used?	66.7%	33.3%	100.0%
		% within CASE/CONTROL	15.4%	25.0%	17.6%
		% of Total	11.8%	5.9%	17.6%
	Hormonal stimulation	Count	4	1	5

		% within If yes, which fertility treatment was used?	80.0%	20.0%	100.0%
		% within CASE/CONTROL	30.8%	25.0%	29.4%
		% of Total	23.5%	5.9%	29.4%
Total		Count	13	4	17
		% within If yes, which fertility treatment was used?	76.5%	23.5%	100.0%
		% within CASE/CONTROL	100.0%	100.0%	100.0%
		% of Total	76.5%	23.5%	100.0%

In other words, of the 238 BC patients, 225 (94.5%) had not undergone fertility treatment, while 13 (5.5%) had. In addition, of the 153 healthy study participants, 149 (97.4%) had not undergone fertility treatment, while 4 (2.6%) had **[Table 1]**.

Using the Chi-square test, there appears to be no significant statistical association between fertility treatment and BC (p=0.178) **[Table 2]**.

Of the 17 patients who had undergone fertility treatment, 1 (5.9%) had undergone IVF with a natural cycle and belonged to the control group. 3 of the 17 (17.6%) underwent IVF after induction of ovulation. Of these, 2 (66.7%) were patients and 1 (33.3%) was healthy. 5 of the 17 (29.4%) underwent insemination alone. Of these, all were patients (100%). 3 of the 17 (17.6%), underwent IVF and insemination. Of these, 2 (66.7%) were patients and 1 (33.3%) was healthy. In addition, 5 of the 17 (29.4%) underwent hormonal stimulation. Of these, 4 (80%) were patients and 1 (20%) was healthy **[Table 3]**.

In other words, of the 13 BC patients who had undergone fertility treatment, 2 (15.4%) underwent IVF with induction of ovulation, 5 (38.5%) underwent insemination only, 2 (15.4%) underwent IVF and insemination and 4 (30.8%) underwent hormonal stimulation. In addition, of the 4 healthy study participants who underwent fertility treatment, 1 (25%) underwent IVF with natural cycle, 1 (25%) underwent IVF with induction of ovulation, 1 (25%) underwent IVF and insemination and 1 (25%) underwent hormonal stimulation.

4. Discussion

Several reviews have been conducted to ascertain whether there is a causal relationship between BC and fertility treatment. In 2014, a Greek systematic review and meta-analysis by Sergentanis et al. found no association between IVF and overall BC risk, but they noted that younger women who underwent IVF had somewhat worse results **[10]**.

Gennari et al.'s 2015 meta-analysis found no evidence of an enhanced risk among those who underwent IVF. On the other hand, a rise in the risk of BC cannot be ruled out with older treatment plans based on clomiphene. They also underlined that there may be an increased risk of BC with long-term administration of clomiphene and for this reason, its outside of the approved indications should be discouraged **[11]**. However, one year later, a different study found no higher risk of BC in women taking reproductive drugs after 21 years of follow-up **[12]**.

In 2017, one study after 11 years of follow-up found an increased risk only in women who had given birth and used clomiphene for fertility **[13]**.

Furthermore, a study conducted in UK in 2018, in which more than 255,000 women participated, found no additional overall BC risk with IVF, but a higher incidence of breast carcinoma in situ with more cycles **[14]**.

Additionally, a most recent meta-analysis by Cullinane et al., in 2022 found no association between reproductive treatments and an increased risk of BC **[15]**.

Although most studies as our study show that fertility treatments do not increase the risk of BC, more studies with a larger number of patients and long-term data are needed to confirm these findings. In general, nowadays, there are no

answers available about the exact effects of infertility and its treatment on BC risk, but the findings are generally reassuring **[16]**.

5. Conclusion

This study did not find a significant association between fertility treatments and BC risk. Further studies with a larger number of patients are mandatory in order to confirm this result. Women considering fertility treatments such as IVF should be informed that they do not appear to increase BC risk.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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