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Breast cancer and response to ovarian stimulation

Background: Breast cancer is the most common cancer in the women worldwide and India is also seeing a rising trend. What is interesting is that 48% these women in India are less than 50 years of age[1]. Advances in diagnostics and treatment modalities are ensuring improved survival in these women in the developed nations and it may not be long before the same can be said about women in India. Hence issues such as quality of life and fertility potential in these women have come to the forefront. However chemotherapy which follows surgery as well as the delay in reproduction to accommodate treatment, reduces fertility prospects.

There is conflicting data regarding the response to ovarian stimulation in women with breast cancer. Lower estrogen levels due to the use of aromatase inhibitors in hormone sensitive cancers, is proposed as one of the reasons for poor response. Others have suggested a lesser starting ovarian reserve as a reason for poorer response.

Quinn et al, in their retrospective cohort analysis of 589 women over a period of 7 years have tried to evaluate the ovarian reserve and response to ovarian stimulation in women with newly diagnosed breast cancer (study group- 191) and compared these with healthy women undergoing elective oocyte cryopreservation (control group- 398).

Response to ovarian stimulation is not impacted by a breast cancer diagnosis. Quinn MM, Cakmak H, Letourneau JM, Cedars MI, Rosen MP. Hum Reprod. 2017 Jan 24.

A short review of this article is presented.

Study descriptions and results: Antagonist protocol was used for both. All controls had gonadotropins started on day 2 of stimulation. Breast cancer patients who were estrogen-sensitive (n=151) underwent stimulation with Letrozole 5 mg titrated up to 10mg daily based on the response. In

non-estrogen sensitive breast cancers (n=40), conventional stimulation was done with gonadotropins. Those breast cancer patients who did not present on day 2, random start ovarian stimulation was done.

The primary outcome was the number of mature (MII) oocytes and the secondary outcomes included- antral follicle count (AFC) , days of stimulation, total dose of gonadotropins, peak serum estradiol, follicles measuring ≥13 mm on day of trigger, oocytes retrieved, oocyte maturity rate (MII/total oocytes retrieved), mature oocyte yield (MII/AFC) and fertilization rate (2PN/MII).

Results: Ovarian reserve, measured as AFC, was found to be similar in both groups even when categorized by age. Total and mature (MII) oocytes retrieved, when adjusted for age, BMI and total gonadotropin dose, were also similar between the two groups. Letrozole use was associated with a decreased maturity rate (MII/total oocytes retrieved) compared to elective cryopreservation although the mature oocyte yield [MII/AFC] was comparable.

Key message: Breast cancer is the most common cancer in females worldwide. A good proportion of these women are in the premenopausal age-group, making fertility preservation a valid concern. Conflicting data exists about the response to ovarian stimulation in these women. This single centre study (though lacking pregnancy data) provides evidence that women with breast cancer undergoing ovarian stimulation, have ovarian reserve and response to ovarian stimulation, similar to their counterparts undergoing elective oocyte cryopreservation.

References:

1. http://www.breastcancerindia.net/statistics/stat_global.html
2. *Johnson LNC, Dillon KE, Sammel MD, Efymow BL, Mainigi MA, Dokras A, Gracia CR. Response to ovarian stimulation in patients facing gonadotoxic therapy. Reprod Biomed Online 2013;26:337–344.*

Results tables

Table II AFC by age category for breast cancer patients and women undergoing elective cryopreservation.

Age category	Elective cryopreservation AFC	Cryopreservation for Breast Cancer AFC	*P*-value[a]
18–34 years	18.3 ± 13.5 ($n = 81$)	19.1 ± 11.8 ($n = 83$)	NS
35–37 years	16.0 ± 9.5 ($n = 188$)	14.7 ± 8.2 ($n = 42$)	NS
38–40 years	13.3 ± 7.4 ($n = 101$)	11.4 ± 8.1 ($n = 45$)	NS
40–42 years	11.1 ± 6.6 ($n = 23$)	10.0 ± 7.4 ($n = 18$)	NS
≥43 years	10.2 ± 4.9 ($n = 5$)	10.3 ± 3.8 ($n = 3$)	NS

[a]t-test.
Data presented as mean ± SD.
AFC: antral follicle count.

Table III Cycle characteristics by group.

Outcome variable	Elective Cryopreservation ($n = 398$)	Breast Cancer with letrozole ($n = 151$)	Breast Cancer without letrozole ($n = 40$)	*P*-value[a]
Days of stimulation	9.7 ± 0.1	10.3 ± 0.2[b]	10.1 ± 0.3	0.001
Daily dose gonadotropin (IU)	210 ± 4	237 ± 6[b]	238 ± 13[c]	<0.001
Follicles ≥ 13 mm at trigger	11.7 ± 0.4	15.1 ± 0.7[b]	12.5 ± 1.3	0.004
Peak estradiol (pg/mL)	2842 ± 93	709 ± 34[b,d]	2472 ± 245	<0.001

[a]ANCOVA; age and BMI as co-variates.
[b]$P < 0.001$ for comparison with elective cryopreservation.
[c]$P < 0.05$ for comparison with elective cryopreservation.
[d]$P < 0.001$ for comparison with cancer without letrozole.
Data presented as mean (estimate) ± SE.

Table IV Outcomes by group for those who proceeded to retrieval.

Outcome variable	Elective cryopreservation ($n = 361$)[a]	Breast Cancer with letrozole ($n = 144$)[a]	Breast Cancer without letrozole ($n = 38$)[a]	*P*-valu
Oocytes retrieved	17.0 ± 0.5	20.1 ± 1.1[c]	16.6 ± 1.2	<0.00
MII oocytes retrieved	13.2 ± 0.4	14.1 ± 0.8	12.2 ± 1.0	0.019[d]
MII/total oocytes	0.77 ± 0.01	0.71 ± 0.01[c]	0.74 ± 0.02	0.050
MII/AFC	0.93 ± 0.03	1.01 ± 0.06	1.10 ± 0.14	NS
MII/follicle ≥ 13 mm	1.03 ± 0.02	0.94 ± 0.03	0.96 ± 0.05	NS
≤6 oocytes retrieved (*n*, %)	45, 12.5%	15, 10.4%	6, 15.8%	NS[e]
2PN/MII (ICSI, $n = 84$)	–	0.76 ± 0.02	0.82 ± 0.02	NS

[a]*n* = total number of subjects who proceeded to retrieval for each group.
[b]ANCOVA; age, BMI and total gonadotropin dose as co-variates unless otherwise indicated.
[c]$P < 0.001$ for comparison with elective cryopreservation.
[d]Pairwise comparisons between groups: NS.
[e]Chi-squared.
Data presented as mean (estimate) ± SE.
AFC: Antral Follicle Count, MII: Metaphase II (mature).

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